NORMAN W. ELLIS,		*14th JUDICIAL DISTRICT COURT
ET AL		
VS.	NO. 90-3696	*PARISH OF CALCASIEU
INSURANCE COMPANY		
OF NORTH AMERICA,		
ET AL		* STATE OF LOUISIANA

DEPOSITION OF
RICHARD D. IRONS, Ph.D.
December 17, 1991
400 Poydras, 30th Floor
New Orleans, Louisiana
Reported by:
Joyce Ann Smith, RPR, CM
Texas CSR No. 2463
Louisiana CSR No. 83083
Nell McCallum & Associates, Inc.
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Beaumont, Texas 77702

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TABLE 0 F CONTENTS

Deposition of RICHARD D. IRONS, Ph.D., a witness called by Plaintiffs on December 17, 1991, at 400 Poydras, 30th Floor, New Orleans, Louisiana, commencing at 9:20 a.m., before Joyce Ann Smith, RPR, CM, Texas CSR No. 2463, Louisiana CSR No. 83083, pursuant to the following stipulations:

COURT REPORTER: Pursuant to Notice or agreement?

MR. HOBSON: Well, I guess it's kind of both. Originally, Notice, I guess; but we have agreed to change the date.

MS. ARRAS: We never received a copy of the original Notice.

MR. HOBSON: You didn't?

MS. ARRAS: No.

MR. HOBSON: (Tendering document)

MR. BAGGETT: Can we agree that the deposition was noted - noticed for a previous date, continued by agreement, and is taken today pursuant to Notice and that all formalities are waived

except the swearing and the reading and signing and that all objections are reserved except those with reference to leading or responsiveness of the answer -- or to the form of the question, rather?
MS. ARRAS: All right. I just would like to make a statement that there was never a subpoena served on me with respect to this deposition: and in fact, this is the first time I have seen the Notice. It wasn't sent to me.
MR. HOBSON: You have never seen any of this, Dr. Irons, to bring anything with you?
THE WITNESS: (Shaking head)
MS. ARRAS: No, because I was told there was no Notice with respect to Dr. Irons; and there was certainly never a subpoena served.
(OFF-RECORD DISCUSSION)
MR. HOBSON: Any objection to Mrs. Smith, who is a Texas Notary,

administering the oath? There being none -
COURT REPORTER: May I correct you that I am not a Texas Notary, but I have my Louisiana CSR.
MR. HOBSON: I beg your pardon. So, you can administer an oath in Louisiana.
(IRONS EXHIBIT NO. 1 WAS MARKED FOR IDENTIFICATION)

RICHARD D. IRONS, Ph.D.,
having been duly sworn, testified as follows,
to wit:
EXAMINATION BY MR. HOBSON:
Q. Dr. Irons, my name is Herschel Hobson.
We've met before on several occasions: correct?
A. Yes, sir.
Q. I understand from some preliminary
discussions we have had today that you never
received any request to bring anything with you to
the deposition: is that correct?
A. That's correct.
Q. What have you brought with you to the
deposition today in regard to this case?
A. I brought a folder with articles that I
intend to rely on: and I brought a recent CV; I
have a summary that I have made of the various
cases that are involved: I have brought a
bibliography of my own on butadiene: and I have my
correspondence from Ms. Arras.
Q. Could we have the correspondence,
please.
A. (Tendering file)
MR. HOBSON: With your
permission, I will ask Mr. Baggett

to look at these while we continue,
if that's all right.
BY MR. HOBSON:
Q. May I look quickly, please, at the
articles in your bibliography?
MR. SPICER: What is that
correspondence?
MS. ARRAS: It's
correspondence with regard to this
case from my office.
BY MR. HOBSON:
Q. Are all the articles listed on your
bibliography included in the notebook?
A. No, they are really separate.
Q. Are all the articles in the notebook
included on the bibliography?
A. No, that bibliography is specifically
for butadiene: and the articles for the most part
deal with causation and with benzene.
MR. BAGGETT: Just on the
record, though, Mrs. Arras, isn't
it correct that when we had noticed
the deposition of December the 3rd
that it was changed -- the date was
changed at your request because of

some emergency or something that
the doctor could not appear on
December the 3rd?
MS. ARRAS: That's correct,
but that has nothing to do with the
subpoena issue.
MR. BAGGETT: I know that. I
just
BY MR. HOBSON:
Q. Have you brought anything else with you
to New Orleans that deals with this case that you
have not brought to the deposition today?
A. No.
Q. Have you come to the deposition today
unaccompanied by anyone, or did someone come with
you?
A. By myself.
Q. Okay. I would like to start, if I
could, you are still at the University of
Colorado?
A. Yes.
Q. And when did you go there?
A. January 1989.
Q. And you went to the University of
Colorado from CIIT?

A. Yes.
Q. What I would like to do is learn, if I could, since you have been at the University of Colorado, I would like to know all of the work that you have proposed doing and to whom it was proposed, what work actually was committed to be done at the University of Colorado, what work has been completed, and what work is ongoing that you have been involved with. I am just giving you that as a general overview and then I will start by asking you, if we could, would you tell me what work is currently going on at the University of Colorado that you have been engaged in?
MS. ARRAS: I would like to object to the word "work," and ask if you could define that with a little more specificity.
BY MR. HOBSON:
Q. Do you have trouble understanding "work," Dr. Irons?
A. I would like you to clarify in particular what you're referring to. I mean I can list everything I have done since I got to the University of Colorado, but I don't think we have enough time for that.

Q. I am not interested in every day. I am particularly interested in research projects, investigations that you have undertaken on behalf of others or investigations that you, yourself, have done. I am not interested in every day you taught class or something.
A. Okay. Could you repeat the last question?
Q. Yes, sir. I am interested in the current investigations that you're doing as a part of your work at the University of Colorado.
A. Okay. I have a research project that is funded through the American Petroleum Institute and Chemical Manufacturers Association to elucidate and characterize the mechanisms of altered stem cell regulation that are associated with exposure to benzene metabolites.
I have a grant from the Chemical Manufacturers Association to look at cell specific metabolism and stem cell regulation associated with exposure to butadiene metabolite.
I have a project funded from the National Aeronautics and Space Administration to examine potential mechanisms of toxicity and altered stem cell regulation, hematopoiesis, and

immune function that have been associated with extended space flight.
Those are currently funded projects.
Q. Since you have been at the University of Colorado, have you undertaken any investigations for others or that you have funded through some other mechanism at the University that have been completed?
A. I have had some start-up -- I had some start-up support from the State of Colorado, the University, which basically went into establishing my laboratory. I have had no other funded projects at the University up until the present time. I have projects pending and in development. The first product of the research that I have outlined for you is in submission at the present time.
Q. So, the API-CMA project has -- you have actually got it down in writing, the results, and the results have been submitted to the sponsors?
A. No, they have been submitted for publication.
Q. For publication.
A. None of these are contracts. They are grants. So, the principal product is publication

in peer-reviewed literature.
Q. Is that true for the NASA work, as well?
A. That's correct. The NASA work is part of a center grant that has been awarded to the University of Rochester and the University of Colorado from NASA.
Q. And the start-up activity is the only work that was begun by you that was paid for by others that has been completed?
A. If you want to call it completed. There really was no -- there was no product or time limit placed on it.
Q. The API-CMA project you told me about first, can you give me some idea of about when that project was begun?
A. I'm a little fuzzy, but I think it was April or May 1989.
Q. And who were your contacts with regard to those grants? Who periodically did you correspond with or meet with to review those projects as they progressed?
A. Hugh Spitzer, Ed Vernow. Those would be the two principal individuals.
Q. What is their affiliation?

A. API.
Q. Both?
A. Yes.
Q. Did you have contacts with anyone from the member companies of the API and CMA?
A. Yes. We have approximately one meeting a year to exchange information and go over progress; and at that meeting there will be usually company members from either CMA and/or API, as well as API personnel.
Q. Who do you recall has attended those meetings with regard to this project?
A. It varies. It varies dramatically from one time to another. Peter Craig from Mobil. That is the only person I can recall that would have been there for every -- every meeting. There are no doubt others, but I haven't really paid attention to the attendance.
Q. Would you give me the overall review of what it was you were trying to accomplish with this investigation, and generally speaking, what you found, sort of the executive summary sheet of the report, I guess.
A. Well, it certainly at this stage would be preliminary to outline all of the results; but

I can certainly give you some initial findings. The purpose of the project was to characterize the cell specific metabolism and mechanisms of altered regulation of growth and differentiations that are associated with exposure to bone marrow cells, benzene metabolites. My hypothesis is that the mechanism of leukemogenesis associated with benzene involves an obligate alteration in stem cell differentiation, in addition to the well-known cytotoxic effects of benzene metabolites on dividing cells. Our initial studies indicate that, in fact, benzene metabolites do alter the response of committed myeloid progenitor cells to recombinant growth factors in such a way as to stimulate their differentiation.
Q. When you say "obligates," how do you use that term?
A. Could you repeat my answer, please?
Q. I think you used it as a noun.
(PART OF THE ANSWER WAS READ BY THE REPORTER)
A. A necessary step in the overall leukemogenicity, if you will, of benzene is a requirement that there be a change in the response

or the responding stem cell pool to growth factor response. So, there is basically a shift in the size of the committed stem cell pool that is - that can serve, if you will, as a potential target for nondisjunctional events or cytotoxic events.
BY MR. HOBSON:
Q. I have had the pleasure of seeing some of the charts that you used in Virginia, although I didn't get to see you use them very much. Tell me what your view is of where we are with the stem cell in the human body.
MR. HALL: Let me object to the form of the question. It's vague and ambiguous.
A. The field of stem cell biology has changed dramatically, even in the last two years. The whole field of experimental hematology over the last 20 or 30 years has evolved from one where it's been fairly well known there was a single cell or cell type that could give rise to all the cells of the immune system, all the cells of the blood system, including the various types of red blood cells, white cells, what have you.
BY MR. HOBSON:
Q. What would we call that cell?

A. It depends upon when you look in the literature. It first was known as "the stem cell." It has gone under the aegis of pluripotential stem cell. Most recently, in order to clarify distinctions, it's gone under the term of totipotent stem cell. So, depending on who you read when, you will find these terms used: and they don't always necessarily refer to an ultimate cell that is capable of giving rise to all the various lineages. It depends upon its use and the assumptions that have gone into its use at the time that an individual chose to employ it.
Q. Do you believe that there is such a cell that exists in the human body?
A. Now, you get into the rarefied arena we now find ourselves in over the last year or two. What has happened in the last year or two is it's become clear that the various criteria we've had to approach identifying this cell, this totipotent cell, are not as reliable as we once thought and that, in fact, this cell probably represents a group of cells or a compartment that have a continuum of differentiating capabilities and are restricted in their ability to proliferate. So, we're dealing with a compartment instead of a

single cell. This is above and beyond cells that are committed to produce either lymphoid or myeloid erythroid cells. So, these cells are still uncommitted. They are capable of giving rise to either, but they are not homogeneous.
Q. Have you isolated one of those cells in the uncommitted group?
A. In several of the studies we're doing which involve enrichment, isolation, as well as looking at function, we believe we have enriched for a population that fits some of these criteria. Whether we have isolated an early or a late totipotent cell, I would say probably late: but at this point in time, I don't have sufficient data to confirm it.
Q. You think you probably have but you can't confirm it, is that what you are saying?
A. That's correct.
Q. Now, the work that you are doing for the CMA-API that we were talking about, I think you told me that that work was on committed stem cells.
A. Yes, we have been looking at the first stage of commitment associated with the production of red cells and granulocytes and macrophages and

platelets, which is the myeloid progenitor cell. Sometimes it's gone under the rubric of the myeloid stem cell. I prefer to use progenitor cell.
Q. You prefer to use the myeloid?
A. Progenitor cell.
Q. Progenitor cell.
A. Although depending upon the way in which the terms are used, you could use either.
Q. So, there is one cell, though, that's from the compartment group that we've talked about, the uncommitted, that will give rise to either the myeloid or the lymphoid lineage of cells?
A. At least one, yes.
Q. At least one. And your work for the API-CMA-is the next level down from this uncommitted?
A. It has been to date. We're beginning now to push back, but the work we've done over the last three years has been focused on that particular cell because of its importance in understanding AML and -- acute myelogenous leukemia, and it's the relative ease with which we define the system to work with.

Q. The committed stem cells of the myeloid progenitor cell that you are working with, where in the body is that cell found?
A. Bone marrow.
Q. The uncommitted stem cells that you talked about earlier that you believe are a compartment or a continuum of cells, where are they located or what is your opinion as to the best evidence as to where they are found?
A. Certainly in the human -
Q. Yes, in humans.
A. -- they are predominantly found in the bone marrow. There is evidence that they can circulate, especially under conditions of stress, to the system: but in general, certainly their functional home is the bone marrow.
Q. Is there any evidence that you have seen that the myeloid progenitor cell can circulate?
A. No. I can't speak one way or the other to that. I find it highly unlikely under normal conditions.
Q. Now, if I understood what you told me, you're looking at the effects of benzene metabolites on these myeloid progenitor cells; is

that right?
A. Yes.
Q. Which metabolites are you focusing on?
A. Phenol, hydroquinone, catecal. We have done some work with the putative metabolite trans, trans-muconaldehyde.
Q. Is your work singular when it comes to these metabolites? In other words, are you using only one metabolite; or are they being used in combination?
A. We are using them singularly and in combination. We basically have tried to create a system that will allow us to take apart or dissect the process of growth factor stimulation, stem cell differentiation, and then cell replication in the production of blood cells. Most culture systems that have been used in the past have had to use -- have had to look at this all together, and we have been using newer technology and available reagents to take this apart so we can look at it in steps. The first step we have succeeded in looking at is the recruitment or activation of this population to a defined growth factor stimulus.
Q. Okay. Could you go into some detail of

what you mean by that so I have a better feel for what you are saying your work shows in this particular regard?
A. The way in which we make blood cells is through a process of amplification, all the way from your totipotent stem cell through differentiation to committed stem or progenitor cells; and then they may be multilineage cells, capable of giving rise to several. And then there will be a cell downstream from that that may give rise to one or two different lineages.
If we're going to talk about leukemogenesis, the targets for leukemia fall into that compartment I have just described. So, cells that are downstream further are not targets for leukemogenesis. So, in order to understand what is going on in that system, we need to know how they are influenced with respect to exposure to metabolites, compounds that we are interested in determining what their influence is on either hematopoiesis or leukemogenesis.
The way in which these cells are regulated or communicated, if you will, is through growth factors, cytokines, proteins that are synthesized by either themselves or accessory

cells that they then respond to in a very cloistered environment within the marrow. Very few cells, molecules are elaborated from one cell and either directly passed to the other or it's in a very localized gradient type of environment. It's called a microenvironment. What we have been focusing on is looking at what influence benzene metabolites has on resting cells that respond to the growth factor and are, therefore, by definition committed progenitor cells: and what we have found is that depending upon the metabolite and it's interaction with other metabolites that, in fact, benzene metabolites do alter the response of resting cells to a growth factor.

Q. If I am understanding what you are telling me, then you have really focused on a portion of this development of blood or development of leukemia because the analytical techniques and the procedures that you have developed don't allow you to look at the system as a whole; so, what you have done is you have focused on a small part of this where you can get control and see the results so that you can expand this to the total system, or have I missed

something here?
A. I would say it differently. It's relatively easy to look at the whole. That's been done several times in the past, but it doesn't really provide us with any insight into what is going on.
Q. The mechanisms?
A. Right. We have disaggregated the system and we have focused on a particular portion of the system that's never been examined before. Looking at cytotoxic events is relatively straightforward and is, in fact, part of what we are proposing to do in the future: but we have elected to focus on this area of regulation first because, frankly, we think it's probably the most important for understanding the ramifications of exposure to benzene.
Q. And by "regulation," you're talking about regulation of growth and replication?
A. Yes, differentiation.
Q. And differentiation.
MS. ARRAS: Differentiation and what?
THE WITNESS: Replication.
BY MR. HOBSON:

Q. When you use the term "cytotoxic events" in connection with your studies we've been talking about, how are you using that term?
A. Well, there are two things that benzene metabolites can do. One is they can suppress growth or hematopoiesis. Bone marrow suppression is a well-known characteristic of exposure to high levels of benzene. This involves ultimately at some level effects on the stem cells or progenitor cells that give rise to blood cells.
There are two aspects to cytotoxicity. One is suppression of growth response, and the other are events that may result in genetic or transmitted errors in replicating cells. These would be nondisjunctional events, cytogenetic abnormalities that would result from nondisjunctional events.
There has been some hypotheses put forward that benzene can act through direct mutational events, but I see no evidence for that in the chemistry of benzene or its metabolites or really any data that would lead me to conclude that that's the case. So, we have been focusing on other potential mechanisms of toxicity that are known to be associated with benzene metabolites

and are also associated with certainly the cytogenetic manifestations of acute myelogenous leukemia.
Q. Now, the myeloid progenitor cell that you are working with is the only potential form of leukemia that can result from effects on the myeloid progenitor cell AML?
A. I am sorry, could you -- I'm not sure I understand the question.
Q. Are there other forms of leukemia that can result from effects on the myeloid progenitor cell that you are studying?
A. The myeloid progenitor cell is and cells downstream from it are associated with and are thought to be the predominant source for acute myelogenous leukemia and its variants, which would be any of the variants' family.
Q. But the other forms of leukemia, chronic myelogenous, acute lymphocytic, chronic lymphocytic, hairy-cell, those would come from other lineages of cells than the myeloid progenitor cell?
A. That's correct.
Q. Would you -- tell me how you do this. How is it that you capture the myeloid progenitor

cell and expose it?
A. Well, there are two -- there are two interrelated approaches. One is to partially purify bone marrow cells so that you are dealing with cells that fall into the category of any nucleated cells that don't have stroma or macrophages lying around -- stromal cells or macrophages -- and you characterize their response to recombinant growth factor.
The particular growth factor we focused on initially was called granulocyte macrophage colony stimulating factor, which is the factor that is responsible for the viability and differentiation of the myeloid progenitor. When we look at the colonies that are formed from these cells that are descended from this cell, and as in our system, the predominant colonies that are formed contain both granulocytes and macrophages, that is indicative of the fact that the cell that we are targeting is, in fact, a myeloid progenitor.
The other approach we have taken is through physical separation of cells using surface characteristics, and we can enrich functionally for that cell type using the approach that I just

described as a test.
Q. Have you been able to actually modify the development of the myeloid progenitor cell lineage chemically so that you could control the outcome?
A. Which direction it goes?
Q. Yes.
A. We have been focusing predominantly on looking at what goes on with that myeloid progenitor cell. So, our end point is, in fact, -- our principal end point is the production of mixed cell types. That appears to be the major effect of benzene metabolites in that system. The effects on other cell types like macrophages is - appears to be -- it may be -- there may be effects on macrophage development, but it doesn't appear to be of the magnitude or importance that the effects are that we have described on the early differentiation.
Q. Okay. You might have answered a different question than I asked. Has all of your work been with the benzene metabolites as opposed to any other chemicals that could alter the development?
A. No, we have looked at -- we have begun

to look at a variety of different compounds, primarily chemotherapeutic agents and their metabolites.
Q. What about any naturally produced materials within the body? In other words, have you found what it is -- how it is that the body sends the message to develop the one line or the other?
A. There is quite a lot of work on the cytokines and interleukins that precedes our studies, and this is the basis -- these are the compounds that are produced by the body that we know have some significant or biologically important effect on stem cell behavior. So, these are the compounds we are using as part of the system to examine the effects of various chemicals on the process.
Q. Do you know or do you have a clue as to the benzene metabolite mechanism now? In other words, is it direct or indirect, and if so, which one, how?
A. Well, it's very clear in my mind that the pivotal metabolite is hydroquinone. Now, again, we're talking at the level of the bone marrow, the microenvironment; and these cells have

distinct metabolic capabilities to activate hydroquinone.
Q. These cells being?
A. Stem cells. Certainly the progenitor cell population; however, the other metabolites are important for influencing the specific magnitude, the dose response, and the outcome. But in the absence of hydroquinone, along with the other metabolites of benzene, you don't see the effects that certainly we have observed.
Q. How large is your power, I guess is one way to phrase it, to determine -- to detect these differences between hydroquinone and the other metabolites?
A. Well, I guess the best way to answer that is the effects we see are equal to or greater in magnitude than the effects that are seen with the interactions of various regulatory molecules that are known to be produced endogenously to regulate the system. So, it's a fairly impressive effect and the reproducibility is very significant.
Q. What is the source of your cells, your myeloid progenitor cells? You say that they come from bone marrow, but where do you get your bone

marrow?
A. From our murine studies from mice that we have in our barrier facility. For our human studies, we're obtaining bone marrow samples either from stored transplant specimens or now we're in the process of obtaining permission to use donors.
Q. The studies that you have done to date for the CMA and API, are these studies on stem cells that come from laboratory animals?
A. Yes.
Q. Have you done any on human stem cells?
A. Yes. Very preliminary.
Q. And you say that this comes from stored bone marrow?
A. We have had access to some stored bone marrow. We are now in the process of getting a uniform source of fresh material.
Q. Was the stored bone marrow that you had access to from healthy individuals or from people who had been diseased?
A. Both.
Q. Does it seem to matter?
A. Yes, I think it does. I think if you are going to look at normal stem cell regulation,

at this stage of the game until we have developed a certain degree of clairvoyance, we need to look at normal stem cells.
Q. From healthy individuals?
A. Yes.
Q. Or people thought to be healthy?
A. Yes. At least they have no disease involving the bone marrow.
Q. How do you get your metabolites?
A. For the benzene metabolites, it's fairly easy now to purchase them. For butadiene metabolites, we are synthesizing them.
Q. When you say you purchase the benzene metabolites, are these synthetic chemicals or are they metabolites that are recovered?
A. They are synthetic.
Q. They are synthetic?
A. (Nodding head)
Q. When you mentioned hydroquinone as one of the metabolites, is there anything different about the hydroquinone produced by benzene metabolism than hydroquinone that you would buy that is reagent grade off the shelf?
A. Chemically, no, there is no difference whatsoever. In terms of administration or

modeling or attempt to reproduce the toxicity of benzene, I think there are marked differences that are associated with the complexities of pharmacokinetics, pharmacodynamics, and target organ metabolism.
Q. What do you think is the source of those differences?
A. First of all, for benzene to be toxic, it has to be metabolized. First, primary metabolism occurs predominantly in the liver. This produces the phenolic and polyphenolic metabolites, primarily phenol. Secondary metabolism of phenol leads to the production of hydroquinone and some catecal. All of these are subject to competing reactions. The most dominant competing reaction in the liver is going to be what is called conjugation, secondary metabolism elimination.
In order for toxicity to occur in the bone marrow, you have to have the metabolite, the secondary metal' s -- phenol, hydroquinone and _ catecal -- transported to the marrow: and there it appears that, again, a third level of metabolism is necessary, and our study suggests there may even be competing mechanism of conjugation and

elimination that go on there. There, the specific cell populations have totally different profiles -- it appears they have totally different profiles of enzymatic capability to deal with these compounds.
If you administer, say, hydroquinone to a whole animal, it's going to be very quickly eliminated via conjugation and excretion. Its distribution is not anything like you would expect to see. Certainly there is no evidence to suggest it would be anything like you would expect to see with benzene. In fact, although you can produce some transient bone marrow toxicity if you inject hydroquinone repeatedly into an animal, you have to go through some fairly nonphysiologic procedures to do that. If you administer phenol and hydroquinone together, you can produce greater effects on the bone marrow. Again, though, it's a fairly unphysiologic situation. And if you administer phenol exogenously by itself, you can't produce bone marrow toxicity.
Q. Have you looked at where in the body besides the liver benzene is metabolized?
A. The liver has been predominant -- it's been thought predominantly to be the major source

of benzene metabolism for years because there are a number of classic studies that show that if you hepatectomize the animal and induce metabolism in the liver that you can variously protect and alter benzene toxicity.
I would expect that the possibility for some activity in the lung exists, although you would have to characterize the specific cytochromes that are present and deal with issues like the accessibility or the transient time for benzene through the tissue. So, I would say the lung probably has some capability. The liver certainly is the major one.
We did some studies early in the eighties, very early eighties, that suggested that at the level of the bone marrow, the ability of benzene to be oxidized directly by that tissue, that is metabolized, is infinitesimally low.
Q. What about the nasal passages?
A. I doubt the nasal passages could constitute a major source of benzene metabolism.
Q. The nasal passages can metabolize some material?
A. Some things, yes. Polyphenolics certainly concentrate there. I know of no

evidence that benzene is metabolized there. There are certainly other organ systems that have demonstrated the ability to metabolize - secondary metabolism, zymbol gland is one.
Q. Not very common is humans, though?
A. Not very common in humans. An interesting model, but of questionable human value.
Q. Have you looked at human bone marrow metabolism of benzene?
A. That's on our wish list. That's one thing we very much want to do.
Q. So far, the bone marrow metabolism you have told me about has been in experimental animals?
A. It's been experimental animals. I expect that this year and into next we will either be well into or accomplish that goal, being able to compare on a cell specific basis the difference between the species. It depends on the availability of material.
Q. Material being bone marrow?
A. Bone marrow.
Q. What about the metabolites, has anyone, to your knowledge, looked at the metabolism of

benzene metabolites in human bone marrow?
A. No.
Q. Would you expect to find some unmetabolized benzene, in other words, benzene itself in the bone marrow, in humans who have had airborne exposures to benzene?
A. Whether you could detect it or not I think would be a matter of the amount to which they were exposed over some period of time: so, I wouldn't say categorically that you would be able to. But if you had an individual who was exposed to high levels for a significant period of time, I think that sensitivities are such you probably could detect benzene in the blood and you could detect benzene in the bone marrow. I think that the areas of bone marrow that are not occupied by blood, contain fat, would be under certain circumstances a source for the accumulation of benzene: but I don't think there is any evidence to suggest that that directly plays a role in benzene toxicity.
Q. In fact, there have been studies reported finding benzene in the bone marrow fat?
A. I think there are some older studies that have seen that.

Q. Have you seen any studies that show benzene in the circulating blood for people with airborne exposures to benzene?
A. The problem with those types of studies would be the levels of exposure that you would expect to find. You can't intentionally go around exposing people to high levels of benzene, and if you are going to look at -- I think you would even get into ethical questions about intentionally exposing people to low levels of benzene. But everybody is exposed to benzene. So, if you are using the most sophisticated technology available, I think you would probably be able to detect benzene levels in everything.
Q. Have you seen studies that report benzene levels in circulating blood for workers who are known to be exposed to airborne levels of benzene?
A. If I have, I don't recall.
Q. Would those be of any value to you?
A. Well, as I just said, I think except under the most extreme conditions, if you are going to monitor blood levels, it would be relatively ineffective. I don't think it would be very useful.

Q. No, I wasn't suggesting you monitor blood levels. I was suggesting -- well, I was inquiring as to whether or not that would be any use to you in looking at your models of benzene metabolism and effects on some lineage of stem cell and how they all interrelate as to whether or not -- really, what I am looking at, there is benzene in the circulating blood. Does that have any role to play in your overall research into how benzene, benzene metabolites affects these stem cells?
A. If we knew how benzene fluctuations or levels in the circulating blood related to liver metabolism, exposure, secondary metabolism in the bone marrow, and toxicity between both cell specific differences as well as species differences, then it would be a useful component. But you have to have all the components in place to really make use of that, and that ultimately is one thing we would like to see is to be able to model the process in mouse and in man so that we have an interactive system where we can begin to look at the ramifications of various exposure scenarios.
Q. And that's years down the road, you

think?
A. Yes. I think it's a lot closer than it was a few years ago. I couldn't put a time on it, but I'd say we're certainly within five years of seeing that.
Q. By the way, did you see the article in Scientific American on stem cells?
A. Yes. If you would like to discuss that, I would like to go off the record.
Q. Oh. We will talk about that off the record, then.
Getting back to the API-CMA study, what is it that you have concluded to date in your work? What have you found as far as these benzene metabolisms and how they affect the growth, replication, and differentiation of the myeloid progenitor cell?
A. In a disaggregated system, in a highly isolated and refined in vitro system, these metabolites appear to enhance the recruitment of cells from pre-commitment to the myeloid progenitor cell.
Q. How do you mean that? I didn't follow that.
A. That if you have a defined system where

you are looking at the production of colonies - actually the activity of myeloid progenitor cells to a given growth factor stimulus, that for a given stimulus you will see a range of a number of cells that will act like myeloid progenitor cells. They will respond to the growth factor and produce progeny. Benzene -- pretreatment with benzene metabolites of that pot of cells prior to stimulation with a growth factor causes a recruitment of a greater number of cells that normally would not respond to the growth factor. The interpretation that we have placed on it based on this data is that we are essentially pulling or recruiting a population that normally doesn't respond, and that is really consonant with differentiation. So, functionally, we are causing a shift in differentiation and increasing the pool of the responding myeloid progenitors.
Q. Is that the same thing as causing cancer?
A. No.
Q. How do you, if you do, make any connection between your forcing this change in differentiation with the benzene metabolites to does benzene cause cancer and how much, or can

you?
A. First of all, we start with the premise that benzene is a human leukemogen. Like several other chemotherapeutic agents, high level exposure does lead to an increased incidence of secondary acute myelogenous leukemia. I don't think there is any doubt about that. So, we're really not out to prove or disprove that benzene causes leukemia. What we're trying to do is understand not just for benzene but in a broader context how leukemogenesis occurs.
And in that realm we have a much larger body of literature than just benzene. We've got the whole chemotherapeutic experience, as well. There are no -- I am sure you are familiar with initiation promotion. There are no initiation promotion paradigms for leukemia in any experimental system, in any human system at all. Studies over the last 20 years especially have led to an appreciation that leukemogenesis is a multifactorial process, and there are several steps. If you want to get down to numbers, I don't think anybody is seriously talking less than three. There may be more.
Our focus has been to look at the

mechanism of regulation of stem cells because we feel this plays a major role in determining the potential for leukemogenesis occurring. If you look at the regulation of stem cell activation in animal systems and what data we have on man, it's incredibly tightly controlled. The number of stem progenitor cells that are known to be active at any one time is extremely restricted.
It was my hypothesis that if you influence that restriction, you influence the normal protective mechanisms that exist in the body to prevent this from happening under any conditions; and, therefore, as a step in a multifactorial process that could lead to leukemogenesis, this would be an important one to evaluate. Now, where it leads us in terms of being able to model precisely, this is a model for secondary AML, in which we have this event occurring and then this one and then we have this event and this event, we're several years away from that.
Q. The chemotherapeutic agents that you were talking about, the studies that have been done in humans, have most of those studies, if not all, been done in individuals who already have

cancer?
A. Cancer or similar diseases that require chemotherapy, yes. The vast majority are cancer patients.
Q. And they have compromised immune systems to begin with?
A. Not necessarily. It depends on the cancer type. I think you could get into long protracted arguments whether or not you have immune suppression or not. You can have a functioning immune system and host resistance in a patient who has cancer.
Q. I guess what I was wanting to ask about is that you mentioned that these are secondary acute myelogenous leukemias?
A. They are -- certainly the pattern for cytogenetic abnormalities, pattern for expression, and the target cell population appears to differ between de novo AML's for which there is no known etiology and those that are known to be due secondary to either chemotherapy or to benzene exposure.
Q. So, you would consider then in your rubric benzene-induced AML to be a secondary AML?
A. Yes.

Q. I must not have understood. I want to make sure. How do you -
A. Secondary to exposure to something. I mean you could -- I mean you could put radiation in the same category, but I think that would be misleading.
Q. Why do you say that?
A. I think mechanistically radiation is different. It targets predominantly a different cell type. Radiation is very effective at hitting resting cells. And I also don't think that whatever the -- well, this is highly speculative, but I don't think the mechanisms associated with induction of whatever events lead to leukemia with radiation are necessarily going to be the same as for chemicals that target cycling cells.
Q. Why?
A. Because, number one, you are dealing with a totally different -- you are dealing with an activated versus a quiet population, and the outcome of the insult -- I think the initial outcome is likely to be different molecularly. That -- I mean that could all be disproven a year from now. So, I mean that's speculative.
Q. I understand. I'm just trying to

understand some of your reasoning. Why do you think that there is a difference in whether these cells that are attacked or activated or not?
A. The vast majority of chemotherapeutic agents target cycling cells. Radiation doesn't require that, that they be cycling, that they be -- they be dividing.
Q. But in reality, wouldn't any human have some dividing cells of these type at any given time?
A. That's true: but as I said before, the numbers game, if you will, is very heavily restricted and controlled. If you assume that - chromosomal nondisjunctional events, which benzene metabolites are very effective in causing, and aneuploidy, cytogenetic abnormalities play a role in leukemogenesis, certainly we have evidence for the secondary leukemias that there is an overwhelming majority of them have cytogenetic aberrations. This kind of phenomenon goes on mechanically in everybody all the time. We make mistakes. Cell division is not an error-free process. It's an error-prone process.
So, the ability to restrict the number and to control growth and division in a

susceptible target cell population, I think, is a characteristic of evolution. That is to protect us. I think that system is tremendously effective and that it takes more than a slight insult to disrupt it.
If a compound or substance has the ability to alter that process in addition to or independent of producing other events, I think it must have some influence in explaining the process of leukemogenesis. But the magnitude of that influence remains to be seen. It remains to see how, to what degree I'll be able to successfully test my hypothesis.
Q. Doesn't it appear that benzene and its metabolites cannot only cause the event but affect the system, too?
A. Yes.
Q. Whereas radiation does not, is that what you are saying?
A. No, not necessarily. Radiation is certainly a complete leukemogen, there is no doubt about it. How it -- you know, what are the mechanics of how that is -- how that occurs and how is that distinguished from chemotherapeutic agents is by no means well understood. I am

simply saying that the resting cell population appears to be uniquely susceptible to radiation, in terms of certainly cytogenetic abnormalities: and whatever happens downstream from there is, again, probably a multifactorial process. Radiation plays one role or two roles or some number. I think you can say the same thing -- or I think ultimately you will be able to say the same thing for drugs and chemicals. Some can do the whole thing, some can do part of it, some can do none.
Q. You hypothesize, also, that radiation -- because of these cells being resting, radiation can actually gain access to the interior of the cell?
A. Radiation is -- yes. Yes.
Q. In a resting cell, chemically, the chemicals have no opportunity to invade the cell -
A. Well -
Q. -- but radiation can, even though the cell doesn't appear to be penetrated?
A. It's not -- I think some aspect -- I think there is some aspects of what you have suggested that may, in fact, be true. Obviously,

radiation penetrates a cell. Issues with respect to resting cell involve whether the cell has access to whatever the compound is, whether it can activate it if it requires activation, whether it's got the metabolic machinery to do so. Resting can mean many things. We normally think of it in terms of DNA synthesis but we're beginning in our laboratory to appreciate that metabolism plays a major role, too; and that's separate and distinct from whether you are producing DNA. Ostensibly all cells have the same opportunity in a given environment for exposure, whatever that is; but that does not mean they have the same susceptibility or the same machinery capability of either doing themselves harm or protecting themselves. Understanding how all those interplay is what will be necessary to really get at the crux of that. But I think susceptibility plays a major role.

Q. When you say "susceptibility," is this susceptibility of the organism, the organ?

A. The cell.

Q. The cell. You used a term awhile ago that I am not familiar with, "aneuploidy." First of all, would you spell it? Because I don't know

if we will be able to find it. Or a reasonable attempt at it?
A. A-N-E-U-P-L-O-I-D-Y.
Q. I don't know that term. Would you explain it?
A. It is an abnormal number of chromosomes, either a gain or a loss.
Q. Is anyone, to your knowledge, looking at any of the other stem cells and any effects of benzene?
A. I don't know anyone outside my laboratory who is doing these types of studies.
Q. Have you looked at any other cells besides the myeloid progenitor cell?
A. We have begun to look at -- we've just begun to do studies looking at other cytokines, stimulate other cells, and to develop systems that will allow us to look at an earlier cell in the differentiation pathway. It would be in that totipotent compartment. And also ideally, hopefully, to be able to look at lymphoid differentiation, as well.
Our first foray into this arena looking at benzene metabolites suggests, but doesn't prove, that the response is cytokine specific:

that is, it depends on the specific growth factor, and as a result of that, the responding cell is different. So, in other words, the cell that would normally respond to GMCSF appears to be affected. A cell that responds to interleukin 3, with is another growth factor thought to operate both in the myeloid and the lymphoid lineage, at least in the mouse, we have some data that suggests it is not affected by benzene metabolites in the same way.
Q. How preliminary is that?
A. Very. This has -- we have reproduced it, but I want to -- the best way to describe these studies are two or three experiments followed by 50 control experiments: and anytime we find a phenomenon that is remarkable enough to merit publication, it requires tremendous amount of work to demonstrate the rigor of the analysis and that the end points are valid. We have been able to do this with one cytokine. We are now starting on another.
Q. Which one have you used so far?
A. GMCSF, IL-3. We have looked at M-CSF, which is -- or CSF-1 macrophage colony stimulating factor, and that is the substance of the studies

that I referred to earlier when I said it doesn't look like we have as dramatic an effect on certainly macrophages downstream. But we have - I would also say there, I would have to entertain the caveat that those studies aren't completed.
Q. Do you believe there is evidence that benzene causes any of the lymphoid lineages of leukemias in humans?
A. That's more than one question: but I would say in general, no.
Q. If benzene does not cause the lymphoid lineage of leukemias, what do you expect that your experiments will show when you get into the lymphoid stem cell lineage and you do these similar tests that you have done with the myeloid progenitor cell?
MS. ARRAS: I am going to object that it calls for speculation.
A. That is just about as speculative as I think -- I think you have asked as speculative a question as you could possibly ask me.
BY MR. HOBSON:
Q. I just would like to have your answer.
MS. ARRAS: I am not sure the

doctor can answer if it's
2 speculative.
3 MR. HOBSON: Oh, I think he
4 has thought about it many times.
5 A. The problem with the lymphoid lineage,
6 is that with the exception of multiple myeloma, if
7 you look at the very tumor types that are
8 associated with lymphoid cells, the
9 differentiation process occurs outside the bone
10 marrow. Bone marrow is not a target: and, in
11 fact, if we're going to look at neoplasms like
12 NHL, we're probably looking -- several authorities
13 have suggested that we have to deal with
14 antigen-processing stimulation and a response to
15 some kind of an antigenic stimulus on the
16 periphery before we set up those conditions. So,
17 lymphoid lineage is a totally different ball of
18 wax.
19 In the myeloid, everything goes on in
20 the bone marrow. Differentiation is not a locked
21 step but it's confined to one space. It occurs
22 normally every day to provide us with the cells we
23 need for red cells and for leukocytes other than
24 lymphocytes. Lymphocytes -- the cells that leave
25 the bone marrow from the myeloid compartment are

apoptotic. They are incapable of division. They have one role in life, and this is to perform their function and die.
The prelymphocyte or lymphocyte that leaves the marrow has got the capability to divide, the capability to differentiate, the capability to invade tissues, the capability to go on and become a malignant cell. The cells of the myeloid lineage don't. So, when we talk about leukemia involving the myeloid lineage, we're talking about a bone marrow-derived event. In the case of NHL, we are most inevitably talking about an event that occurs in secondary lymphoid organs.
One exception is multiple myeloma.
BY MR. HOBSON:
Q. With respect to the bone barrow?
A. At least ostensibly, yes.
Q. Do you believe there is more evidence that benzene causes multiple myeloma than the lymphoid leukemias?
A. I would say yes, but I would also like to explain. I don't think there is sufficient evidence to indicate that benzene causes multiple myeloma. So, we are talking about grades of insufficient evidence. I believe there is no

evidence that benzene is associated with lymphoid leukemias.
Q. Would it be accurate to say that the work you have done has not addressed the lymphoid leukemias as far as benzene causation?
A. No, I wouldn't say that entirely. Certainly the work I have done for the last 20 years has included looking at lymphoid activation, the effects on signal transduction and lymphocyte response of lymphocytes to benzene metabolites. So, I think certainly in terms of cytotoxicity and the ability of benzene metabolites to alter immune function or regulation of lymphocyte differentiation, my work has contributed to that arena. Although I will -- I will quickly admit that those have been in animal systems and certain rodent systems: and certainly from the standpoint of a whole animal, we're dealing with a totally different biological model than we are man.
Q. This may be a question you won't want to answer, and that is: How good a model is the rodent? And I guess most of your work has been with rats, some with mice?
A. Rats and mice.
Q. How good a model is the rat and the

mouse for human myeloid leukemias?
A. For human myeloid leukemias, lousy.
It's a bad clinical model. It's very
controversial. It's controversial whether you
even have a malignancy.
Q. In the rat or mouse?
A. In the mouse. The rat, it's very
difficult to produce the lesions. Although
parenthetically, if you take all the studies in
aggregate that have been done in rats exposed to
high levels of benzene chronically and you compare
them to the incidence of -- increased incidence of
AML that's been seen in human populations with
high exposure to benzene, there may not be that
much difference.
Fifty years from now we may regard the
rat as an appropriate model for man because of the
numbers issue. We don't do studies with a hundred
thousand rats. We can't. It's just not
economically feasible. So, you do a study with a
thousand rats and you have equivocal results and
you can't defend them scientifically but they may,
in fact, be relatively representative.
Q. What would be a better species of
experimental animal than man for human myeloid

leukemias?
A. Man.
Q. I understand that's the best one, but that's not a model.
A. I think with all the caveats that I have said about the mouse, it's all we have got. I think that the biology of stem cell regulation is probably similar, and we are certainly in a position now where we can take it apart. So, we can ask the question "At this level is the mouse similar to man" and begin to reconstruct what is and what is not appropriate to use in the mouse. This is getting very philosophical. I think that ultimately we may end up having composite systems where we know enough about it that we can say this is relevant from this species, this is relevant from this species, and this is relevant from this species; but we are by no means there yet.
Q. What are the species that have been looked at that's a model for leukemias, the myeloid leukemias in humans?
A. Well, in the forties, fifties, and sixties, even in the seventies, there was a paradigm that was frequently used by various people doing studies. I call them a "zoo" study,

where people would look at a few of several different species. It was state of the art then. It's by no means state of the art now. I mean people have attempted to use the dog in one system or another, people have attempted to use rabbits, people have attempted to use guinea pigs, rats, mice.
Q. Pigs?
A. Yes, pigs. The problem with, for instance, pigs, which for all I know might be a decent model, is, one, we don't have the reagents to look at the biology of differentiation hematopoiesis in the pig that we do for mouse and man: and I would expect doing a study with large ends, large numbers for a species like that, even using a minipig, would just be exorbitant. People have proposed using chimpanzees or monkeys. There have been some studies looking at -- at least short-term exposure, to look at metabolism in various primate species. Again, there are tremendous problems in designing an experiment to successfully test whether you could use them as a useful model, and it hasn't been done in any -- for any compound or any system that I am aware of.

I think just to amplify that a bit, if you look at experimental clinical hematology today, the state of the art is still the mouse, even though as a clinical model it is not useful.
MR. HOBSON: Let's take a break.
(RECESS)
BY MR. HOBSON:
Q. Dr. Irons, getting back here a little bit more to your API-CMA study, has the work that you have been doing looked at changes in the DNA or the chromosomes of these cells: or have you just being looking at the chemical influence of differentiation in cell growth?
A. To date, we have been looking at the influence of chemical exposure and differentiation in cell growth. So, we've been looking at response to stimulus, gene expression. We have not been looking at effects on DNA.
Q. When do you get to that phase, if you do?
A. I am actually proposing -- in the presence of writing a proposal now for submission to NIH that will do this, and if successful, we will probably proceed with that by next year, like

the end of '92.
Q. When you propose it, or when you get funded?
A. Ideally, when we get funded if we are successful.
Q. Can you give me a feel for the magnitude of the funding from the API-CMA for this project?
A. For my laboratory, we're getting on the order of $270,000 per year.
Q. And you say for your laboratory. Do you have some collaborators?
A. Yes.
Q. Who is collaborating with you?
A. I am collaborating with Dr. David Ross in my group, who is looking at metabolism in isolated cell populations.
Q. So, all of the collaborators on this particular project are located in your department there at the University of Colorado?
A. Yes.
Q. Going on now to the CMA grant for butadiene that you mentioned earlier, would you give me an overview of that project, please?
A. That project is designed to investigate

similar phenomenon associated with the exposure of bone marrow cells to butadiene metabolites and to look at the cell specific metabolism of butadiene in bone marrow cells. It's starting from a position of -- well, there is some disadvantages and advantages there. The disadvantage is we don't know as much about the metabolism, the behavior of butadiene metabolites in the bone marrow as we do with benzene. The advantage is we can take advantage of what we have learned in developing the systems we have to look at the effects of benzene metabolites to begin to approach looking at butadiene.
Q. When was this project begun?
A. This last year.
Q. 1990?
A. '91.
Q. '91. And the early part of the year?
A. I believe, April: but I could be mistaken on that.
Q. When we started talking about the API-CMA study, you told me that one of the things -- and I'm paraphrasing now -- that was considered in organizing that study was that there was an association between benzene exposure at high

levels and the development of AML. Is that your view for butadiene, as well?
A. No.
Q. How is it, then, that you fit the butadiene work into your pattern of using this protocol that you have developed or procedures that you have developed?
A. Well, we know that butadiene will cause a megaloblastic anemia in the mouse at very high levels of exposure. We also know that butadiene influences or alters certainly early steps in lymphoid differentiation in the mouse model: and we are hoping to, by comparing and contrasting the behavior of different compounds, metabolites -- be they benzene, butadiene, or chemotherapeutic agents -- begin to segregate out what the various differences there are and the effects these compounds can have on the regulation of hematopoiesis.
Q. What is your opinion regarding whether or not benzene -- I am sorry -- butadiene is the cause of human leukemias?
A. I think the evidence is very contradictory and does not provide us with an answer to the question.

Q. Do you support IARC's recent change to suspect a human carcinogen for butadiene?
A. Well, if you look technically at the definition of the term, I have to agree that there is sufficient evidence in experimental animals and there is inconclusive evidence in man.
Q. So, by their rubric you agree with their determination?
A. Based upon the precise definition of their ranking, yes.
Q. I think you said just a moment ago that when it comes to butadiene, you're looking at lymphoid cell differentiation?
A. We hope to. Our first comparison is going to be in the same system we have because we do know that butadiene will alter the development of red cells in the mouse. That's what is - that's part and parcel of what we are talking about when we say causes a megaloblastic anemia. So, we want to examine the effects it has on regulation of stem cell behavior, as well. If you are going to understand how regulating the biology of blood formation influences bone marrow toxicity in general, this is where you have to start, whether you are

talking about leukemia or whether you are talking about anemia or anything else. So, although we obviously hope to be able to pursue lymphoid differentiation with butadiene, because that is a model that is very interesting in the mouse, we are also going to look at its effects on myelopoiesis, as well.
Q. I may have misunderstood what you said, but I thought you told me that it had been determined that butadiene affected lymphoid differentiation.
A. To the -- in vivo, it certainly appears to. It does not -- I mean obviously in the mouse it causes a T cell leukemia. It's a very complex model system, and not just for butadiene but for a variety of compounds that have been shown to cause leukemias or lymphomas in the mouse, it would be worthwhile to be able to understand that model better.
Q. You say that butadiene has produced a T cell leukemia in the mouse?
A. Yes.
Q. Is there a comparable disease in humans?
A. No, with the caveat that, of course,

there is an adult T cell leukemia in man: but it's a totally different disease.
Q. And that would be, the disease in man would be what?
A. ATL, adult T cell leukemia, HTLV1-induced leukemia. It's a viral origin.
Q. In either the mouse or the rat, can you find acute myelogenous leukemia?
A. In any system? I mean is it possible to get an acute myelogenous leukemia in the mouse or the rat, is that the question?
Q. Yes.
A. Depending on the strain, there have been reports that you can get a myelogenous type of proliferative disease in the mouse. A CBA/CA mouse is a strain of mouse that has been suggested. It is very controversial as to whether the presentation of the disease, the tissue involvement, the nature of the lesion is, in fact, a malignant disease, and how to distinguish it from a nonmalignant disease.
There are probably some hematologists who think that it is an appropriate model for leukemia. I don't, because you certainly can't distinguish between -- there are aspects of it

that clearly look like a chronic proliferative syndrome, and there are aspects of it that may look acute. I just think it is -- we don't know enough about it to use it as a model for human leukemogenesis, and certainly the major attempt that I have taken in that direction was not successful.
Q. Would it be true, then, that there certainly is no disease in mice or rats called chronic myelogenous leukemia that's known to man?
A. I would not be comfortable with using either AML or CLL to describe the types of diseases that are seen in certain mouse strains that involve the bone marrow and the myeloid lineage. There are proliferative abnormalities that roughly -- you know, that have various aspects of primarily chronic phenomena associated with them, but to distinguish clinically those disease entities as we do in man I think is not possible at the present time.
Q. For instance, the Philadelphia chromosome associated with CML, that's just not something you could do in a rat or a mouse: correct?
A. No.

Q. I am correct?
A. You are correct. The Philadelphia chromosome is a human entity. That doesn't mean that you couldn't find translocations involving a stem cell population in those species, but it has not been described.
Q. And if it were described, it would certainly be different than the Philadelphia chromosome translocation?
A. Well, since the chromosomes -- since the gene location on chromosomes in the mouse and the rat is not the same as in man, it would by definition have to be different.
Q. For humans, is the Philadelphia chromosome -- this translocation described as a Philadelphia chromosome, is that found in any other kind of disease besides CML?
A. It appears in a certain subset of ALL.
Q. Any others?
A. Precisely, I don't think so. You have to keep in mind that although we tend to talk glibly about the Philadelphia chromosome as an entity, if you want to look at the molecular rearrangements that are occurring involving the affected genes, it can occur -- there are

differences in molecular arrangements that appear to correlate with different presentations of malignancy and there can, in fact, can be rearrangements that don't have the morphological appearance of the Philadelphia chromosome.
Q. I didn't understand that.
A. Okay. The Philadelphia chromosome involves a translocation. It involves bringing one gene into a position with another. The exact place in which they come together and rearrange varies somewhat. That variation, as I recall, is important in determining -- you can tell the difference between, say, an ALL and a CML associated with that. By the same token, you can have rearrangements that can occur in the absence of complete morphologic translocation of the chromosomes that you can identify doing a chromosome analysis: and that probably represents a very small proportion of those cases that have been clinically described as Philadelphia chromosomes negative CML.
Q. Does the rat or mouse develop an equivalent disease to human multiple myeloma?
A. Not really. The same cell types are involved. I mean lymphoma by definition involves

lymphoid cells; but there are several different diseases that have different cell types, have different origins, that come under this rubric. You can say that the mouse and the rat develop lymphomas. That doesn't mean that they are -- that you can clinically take any given lymphoma in the mouse or the rat and compare it directly, clinically, to a lymphoma in man. But there are certain types of comparisons that you can make with respect to cell type, potential mechanisms, and this type of thing; but it's not a clinical model for human lymphomas.
Q. I digressed a little bit from your butadiene work, and I apologize. I would like to get back to that.
What metabolites of butadiene have you been working with?
(OFF-RECORD DISCUSSION)
A. The 1,2-buteneepoxide, the 1,2,3,4-butanediepoxide, the epoxy diol, intermediates, crotonaldehyde.
My caveat would be we are looking at metabolism and we are not at this point convinced that what we know about butadiene metabolism is, in fact, accurate.

BY MR. HOBSON:
Q. Have you actually proceeded with each of these metabolites or putative metabolites?
A. We are not in the same -- these are not being run side by side. We have developmental problems that we have had to overcome methodologically in working with these compounds and culture systems, and we have been in the process of doing that and synthesizing intermediates. For these metabolites and to follow the actual metabolism of butadiene in bone marrow cells, we need to be able to characterize the metabolites in culture and we have been in the process of developing those systems.
Q. At what level of funding is CMA providing for you, approximately?
A. On the order of a hundred thousand. There is some that's going to metabolic studies in other laboratories.
Q. Laboratories outside the University of Colorado?
A. No, in my group but different laboratories.
Q. When we talk about the University of Colorado, how much total funding would be for this

project, as best you recall?
A. I think I'm receiving about 100,000, roughly. About 35 or 40 is going into metabolic studies at the present time.
Q. The figure you gave me for the earlier study, the approximately $270,000 per year, is that all of the moneys that goes to the University of Colorado or is that just you?
A. No, that's just for my laboratory. There is overhead and there is also, as I said, Dr. Ross' participation, also.
Q. All total, how much would be to the University of Colorado per year?
A. About 350.
Q. Who is your principal contact for the butadiene study?
A. Betty Moran at CMA.
Q. Are there any member company contacts that you have had with the butadiene study?
A. Chris Bevan at Exxon.
Q. Bevan?
A. Yes, B-E-V-A-N. And I don't recall any others at the present time. There are others, but I just can't recall.

Q. Does it appear to you that you can have an exposure to benzene and then the presentation of leukemia some years later that you would say was caused by that benzene exposure?
MR. HALL: Let me object to the question as being an incomplete hypothetical.
MS. ARRAS: Right.
A. I'm not sure how that differs from the question does benzene, in fact, cause acute myelogenous leukemia. If that's what you are asking me, the answer is yes.
BY MR. HOBSON:
Q. No. I'm not trying to play games with you. Here's what I am trying to get to is in the rationale of your work should you expect to see a benzene exposure followed relatively soon by the presentation of leukemias, or is any of your work directed at looking at this lag time that appears in the literature from exposure to onset of disease? That's really where I am going.
A. Leukemia doesn't happen overnight. There is obviously lag time; and in looking at the various regulatory steps and abnormalities that can occur with time, it is an important aspect of

understanding that and how it's regulated or expressed. I don't think that you can simplify the issue of what steps occur when in the case of leukemia or assume a requirement for continuous exposure over the length of the time it takes for development.
Q. How does your work fit into those considerations, if it does? Maybe it doesn't.
A. Well, it does in the sense that if we are able to segregate out now the individual steps that are likely to occur as a function of exposure, we can determine what the influence of other factors are in the process and also determine what the probability of subsequent events will be.
Q. Can you take me beyond that? Can you tell me in more detail how your work is involved in this determination of how the lag time between exposure and manifestation of leukemia occurs?
MR. HALL: Let me just enter another objection. And I don't mean to interrupt this dialogue, but are we talking about AML or are we talking about other species of leukemias for which the doctor has

expressed an opinion?
MR. HOBSON: I am talking about his work that he is doing on the myeloid progenitor cells from -
MR. HALL: I appreciate the focus of your question but you categorized leukemia as a generic term when, in fact, we all know there are many types of leukemias, some of which may or may not be caused by exposure to benzene; and I think in fairness to the doctor you should be more specific.
BY MR. HOBSON:
Q. Do you understand what I was asking you or not? And if you want to state what you understand the question to be so that it's clear, I have no problem with that.
A. You are asking me to expand on how the work we are doing impacts on understanding the process of leukemogenesis associated with the myeloid progenitor cell?
Q. And how it fits into this apparent lag time between exposure and manifestation of

disease.
A. In the case of secondary leukemias, there is a very high proportion -- by secondary, I'm talking about AML secondary to chemical exposure or drug exposure. A very high proportion of those have specific cytogenetic abnormalities, loss of chromosomes 5 or 7, or parts of both. I don't think anybody who's really working extensively in this area would assume that that's the only thing that happens in these cells, but it's certainly a common finding.
It will be of interest to know what other steps are that are involved in this process before you get to the point where you have a cell that acts like a leukemia cell and has these cytogenetic abnormalities. We have been initially looking at the recruitment and regulation of the movement of cells into this target cell compartment. We need to finish that, characterize and compare it.
We have done this in a murine system. We now need to compare it to human and then begin to look at what other events can occur subsequent to that. If we're successful in isolating out various events, we may be able to determine what

other steps occur along the way. Heretofore, we have only been able to kind of look at the system in aggregate and not -- it's very difficult to try to distinguish what is going on. We are now trying to separate events out.
Once we have done that, if we are successful, we need to put the system back together again, which may mean no mean feat, either: but this is the first step in being able to segregate out what processes are involved in leukemogenesis, similar to what -- for AML, similar to what was done in the fifties and sixties and early seventies with respect to some of the more simplistic models of carcinogenesis, initiation and promotion, for example.
Q. You have mentioned some of the chemotherapeutic drugs. Your work, as I understand it, has involved some of those, as well?
A. Yes.
Q. When it comes to the chemotherapeutic drugs, are you talking there about work with their metabolites or the drugs themselves or both?
A. Both. It depends on -- depends on what we know about their metabolism. The object there

is -- well, eventually we may be able to say something about the individual agents but at the present time we are using those agents as probes or tools. So, I really can't say much about our characterization of individual agents other than that they are useful to allow us to compare what the effects of other chemicals or agents are on these processes.
Q. Which drugs have you used in your work?
A. We have started looking at cyclophosphamide and its metabolites. We are - we have looked at hydroxyurea and some of the Vinca alkaloids. We are in the process now of evaluating an additional tier of drugs we haven't made a decision on yet which ones to use.
Q. In what kinds of therapy or what kind of diseases are the three that you have mentioned typically used?
A. They are used for treating various leukemias or conditions associated with leukemia or lymphoma in various paradigms. Cyclophosphamide is frequently used, so is hydroxyurea and vincristine.
Q. Is it your understanding, then, that in individuals who have leukemia, these drugs are

administered and there is a different leukemia produced by the drugs?
A. No. No. I'm not following -- I'm not following that line of question.
Q. Are these drugs themselves that you are testing, the three categories you just gave me, are they capable of causing leukemia themselves or the metabolites?
A. In the particular case of the drugs we're talking about, if you look at the clinical study, cyclophosphamide is, hydroxyurea is not, and vincristine is not. At least there is no evidence that they do. They do cause -- they all cause bone marrow damage, but they do not all cause leukemia.
Q. If they couldn't cause bone marrow damage, they wouldn't be effective in treating leukemias?
A. That's correct. Benzene does the same. Benzene is a reasonably efficient myelosuppressive agent.
Q. What comparisons are you hoping to make by using these chemotherapeutic drugs?
A. By using chemotherapeutic agents that have a different spectrum of side effects,

determining what changes in cell behavior are associated with the potential to cause those side effects.
Q. How does that tie into your hypothesis regarding benzene?
A. Well, we know that benzene does cause a small but significant increase in the incidence of AML in chronically exposed populations of high concentrations. We also know that some of the chemotherapeutic agents do the same thing. Some don't. If we can dissect out at what particular level of cell these events occur and what the differences are between them, it will help us in determining what are likely to be the most important things to look at with respect to the mechanisms of leukemia.
Q. Have you gotten to that step yet? Can you now make some of these differentiations between the drugs and benzene?
A. It would be premature to comment on that now until we've really looked at all the data. We are not in a position to discuss with any degree of confidence that data base right now.
Q. The paper that's in the process of being published, I think you said it has been

submitted, can you tell me the kinds of things that you are reporting in that paper? How far are you able to report in the scientific literature with that report?
A. It characterizes the effects -- it establishes the system, characterizes the dominant effects of hydroquinone on stem cell regulation in that system. It looks at the interaction of hydroquinone with various other metabolites, their individual effects, and draws some of the conclusions that we have been discussing here with respect to the potential role of this model if, in fact, it withstands further testing.
Q. Where did you submit it?
A. Proceedings in the National Academy of Sciences.
MS. ARRAS: Just for the record, that's the CMA -- which paper is it you are referring to that's a publication with respect to?
THE WITNESS: The CMA. It's in review now. It has not been formally accepted as of yet.
BY MR. HOBSON:

Q. It has been sent to the peer reviewers for comment?
A. Yes.
Q. Have you received comment yet?
A. Some of them, yes.
Q. So, you are probably three or four months from resubmitting after all the comments are in?
A. Hard to tell.
Q. When the comments are back in, frequently the reviewers are asked to review any suggested changes they made and the responses; correct?
A. Yes. At this point -- well, it's impossible for me to tell. At this point I don't anticipate it's going to be very long.
Q. It should be in print within the next four or five months, maybe?
A. I would hope so.
Q. When did you receive funding from the NASA grant?
A. Last spring.
Q. And at what level are you funded by NASA?
A. Total budget is slightly over a hundred

thousand per year.
Q. Is that for all of the University of Colorado or just your laboratory?
A. That's just me.
Q. Is there another aspect that is funded to the University of Colorado, as in these other studies?
A. Well, the university is part of a center: and yes, the total funding is on the order of a half million dollars, or -- excuse me. It may be less than that. It may be 300 to $400,000.
Q. What work will you be doing?
A. Again, we're devising models to look at the interaction of chemicals, microgravity, and radiation on regulation of hematopoiesis and immune function. So, we are basically trying to isolate systems that allow us to look at combined influences of different things on stem cell behavior and immune function.
Q. Are you looking at ways to develop microgravities on earth, or are you going to put systems in space and see the effects?
A. I think we're going to put them up there. That is my proposal, basically to develop a system that it is compatible with space flight,

because it's my preliminary conclusion that microgravity surrogates on earth are not adequate surrogates of microgravity.
Q. Is the NASA work that's being done right now to develop the potential for this system to go into space?
A. Yes. We're using a variety of compounds that may be potential contaminants in spacecraft as a point of departure for the design of that system.
Q. Is it accurate that this is the only grant for work or funding from an outside source that you have received that did not come from the chemical refining industry?
A. At the present time, yes.
Q. Are there any chemicals that are of particular interest in the NASA grant?
A. The chemicals we are currently approaching, which is by no means -- this is not -- this project is not linked to a given chemical. It's really linked to looking at a process and evaluating the influences of various conditions on that process.
We're currently looking at some aldehyde derivatives, acrolein. We are looking at

hydrazine metabolites. Hydrazine is a rocket fuel that's been slated for extensive use in space. And we are tooling up to look at some of the pyrolysis breakdown products of teflon.
Q. So, basically, you are looking for what you might find inside a space capsule?
A. Yes.
Q. And the fuels to be used in space?
A. Yes.
Q. Are there any other projects that you have initiated since you have been at the University of Colorado we have not talked about that are of the investigative nature?
A. We have begun to look at purification schemes and culture conditions for the support and growth of human bone marrow. These are still in the initial stages, although they have been perking along now for about two years.
Q. And how do you get your funding for that work?
A. Spare time.
Q. Beg Peter to pay Paul?
A. To a certain extent. There is a great deal of interest in developing procedures for the purification of human stem cells and bone marrow

transplantation. The transplantation center is very interested in pursuing this. So, we have received support in terms of cells and time and facilities from them: and also part of what we propose to do for API and CMA involves developing analogous human systems. So, it's an above-board use of the support that we have: but we're basically diversifying our sources of funding to pursue those studies. All of these are extremely expensive types of studies.
Q. Where is your -- what is your understanding of where science is or medicine is in the isolation of these compartmentalized stem cells now? Is there enough uniformity from how things are reported in the literature that you can say I have seen this stem cell reported as opposed to this one?
A. We're dealing with two different data bases. The data bases that have evolved from looking at secondary leukemias, CML, in humans, patients, using techniques involving cytogenetics, genetic markers, have provided very sound data base on which to evaluate clonality and the general site of origin of these tumor types. That hasn't changed. What has changed is our knowledge

of the resolution or heterogeneity of the compartments where these cells reside. And in the last two years, the pluripotential stem cell compartment, the totipotential stem cell compartment has become a compartment. I can tell you characteristics of those cells. I can tell you characteristics of some of them that don't pertain to others. But we're dealing with -- what I am trying to say is we're dealing with two different sets of information and approaches to similar questions that overlap but don't detract from one another.

Q. It appears there are different cells, you just can't tell me the characteristics of each one and for sure how many there are?

A. I can tell you roughly how many there are in one compartment or another, given certain conditions. I can tell you some of their behaviors. But certainly in the murine model, the totipotent stem cell compartment has become more complicated in terms of its structure differentiationwise. The earliest cell we can find will provide long-term repopulation of an animal: but it won't provide short-term survival

from lethal radiation, for example. The spleen colony-forming cell, which has been a benchmark for looking at stem cell behavior in the mouse since the sixties, has basically been shown not to be a very good indicator of "stem cell-mess". I could go through several others, but the point is that it now appears to be much more complicated compartments than we have tended to think of it in the past.
Q. How about in humans?
A. We are -- we can't resolve it into - with the same -- we cannot look at it with the same resolution we can with the mouse. I would expect that from what we do know that it's configured similarly, if not -- it's probably not identical, but it's configured similarly. We do have markers now that allow us to enrich for certainly early cells that have the capability of reconstitution. Whether that cell is the end cell in the pyramid is anybody's guess.
Q. Does it appear that the end cell in the pyramid, as you have described it, which I think is a good description, does that cell divide without differentiating?
A. You're asking what is now one of the --

it's probably the most philosophically oriented conundrums that's facing the field. The way it's usually put is: Is the pluripotential or totipotential stem cell capable of self-renewal? For 30 years that's been the concept of what a stem cell is; and in the last two years the hypothesis has been put forward that, in fact, if the compartment is large enough and division is slow enough, you don't have to invoke self-renewal as a characteristic of any cell. So, I would say that at this point -- for 20 years that was a comfortable question to answer. It's no longer a comfortable question to answer.
Q. The comfortable answer for the last 20 years has been yes and now it's maybe not?
A. Yes. I will say that although we are having to grapple with some new biology, it really doesn't negate the overall structure of the system or our knowledge of how things have been regulated. We haven't turned the field on its head. We have just had to deal with some new concepts and dimensions that we haven't had to deal with before, but this is how science progresses.
Q. You are no doubt familiar with the

argument that materials like benzene may cause some change in chromosomes at one of the early stem cell levels, that as the cell differentiates then into the lineage of blood cells that this could result in the different kinds of leukemias and lymphomas. What I would like to know is: Has any of your work been able to address that one way or the other?
A. Well, I think we have been able to show that certainly in the murine system the target for AML is, in fact, a very interesting target with respect to the effects of benzene metabolites and that the requirements for differentiation into that compartment that would be a part and parcel of that model appears to certainly in vitro in one test appear to be valid. So, as far as linking the potential of benzene to cause AML with a model that involves the cell type that is a target for the majority of AML's, I think we have been initially successful.
Q. And I appreciate that, but I don't think that's the question -- the answer to the question I was asking.
I'm interested in going above the myeloid progenitor cell and finding out whether or

not you have done any work that would look at any genetic damage to any of those cells and how that affects the outcome of differentiation from those cells, from a leukemia or lymphoma standpoint.
MS. ARRAS: By "those cells," you are referring to myeloid cells?
MR. HOBSON: I beg your pardon?
MS. ARRAS: By damage to "those cells," are you referring to the myeloid cells?
MR. HOBSON: No, those above the myeloid cells, the undifferentiated cells.
A. I have seen no model that would adequately explain the effects of benzene or any other chemical on a resting stem cell that leads ultimately to a cytogenetic abnormality.
BY MR. HOBSON:
Q. That leads ultimately to -
A. To a cytogenetic abnormality in a replicating cell that would explain or even begin to explain the mechanism involving the pluripotential stem cell compartment. I think our data reflects the fact that the cells that -- we

may be shifting differentiation in that compartment, but the cell that's responding is no longer a totipotent cell. That's differentiation. I know of no model other than the obvious relationship between radiation exposure and CML that would involve directly a resting stem cell as a target for any agent causing a malignancy in the hematopoietic system. And there, the question I think at this point would be whether the cytogenetic abnormalities that are associated with CML, i.e., the Philadelphia chromosome, is causal step, permissive step. Whether it's initial step or a secondary event is by no means clear.
Q. The myeloid progenitor cell, can it reproduce itself without differentiation?
A. Theoretically, no. I don't think technically that is -- once you reach that level of commitment, you are going to have some change. Now, to say that we know what every little change is along the road, we don't know that. But I think it is certainly generally accepted that in a committed progenitor cell compartment, you are looking at a process in which proliferation and differentiation are linked.

Q. And the work that you are doing on the myeloid progenitor cell is a committed cell?
A. Yes, it's a multilineage -- it's a multilineage cell, but it is committed.
Q. And the compartment above the myeloid progenitor cell, those cells are not committed?
A. Those -- as far as we know, that is - that is the first demarcation that we have with respect to commitment is at that level.
Q. That level being the myeloid progenitor cell?
A. Yes.
Q. In this compartment that's above the myeloid progenitor cell, is there evidence that those cells can reproduce without differentiating?
A. The compartment obviously is able to maintain itself, but that does not mean necessarily that it has an absolute requirement for every cell in there to be able to divide without differentiating. The answer is basically nobody knows. The compartment is certainly capable of maintaining itself and that is a - it's one of the controversies that's bubbling in the field today.
Q. Where in the process of fetal

development does it appear that the totipotential stem cell develops?
A. Well, it rises in the yolk sac: and in fetal development, the liver is the first place you begin to see extensive blood cell production. It moves from the liver to the spleen to the bone marrow.
Q. Would the totipotential stem cell exist before the liver in the developing fetus?
A. Well, if you follow the model that we have a fixed number of them that evolve during embryogenesis and that that number is what we have at birth, then obviously so. That's an area right now I would say is, again, subject to considerable controversy.
Q. Has anyone looked, to your knowledge, at radiation of developing fetuses to see the effects of leukemia on the resultant fetus in order to answer that question?
A. There have been hundreds of studies done on radiation. Whether or not there have been any on in utero radiation and followed development, at this point I can't recall. I wouldn't be surprised, but I don't recall.
Q. Your CV that you brought with you

today, are there any publications that have been added in the last two years?
A. Yes.
Q. Is this CV relatively current?
A. Yes.
Q. I haven't had a chance to look at it here. Do you have an extra copy there so we can both look?
A. Yes.
Q. You went to the University of Colorado in January of 1989?
A. Yes.
Q. And, so, you have three publications that have come out since then: is that what I am seeing here?
A. In terms of standard journal articles, yes. One in submission and then two that have been published. There have been other publications, but they have either been symposium or book chapters.
Q. The one listing that says manuscript submitted, is that the one we have been talking about, the CMA-API work?
A. Yes.
Q. The two just before that, the '89 and

the '90 submissions, is that based on work that was done by you at CIIT?
,A. In large part, yes. Some of the final -- in the case of the 1990 one, I think some final changes were made while I was at Colorado.
Q. I am sorry, say that again.
A. I think some changes -- the manuscript may have been altered during that period.
Q. But the underlying research was all done at CIIT?
A. Yes.
Q. So, the only publication is the one that you have submitted here that reflects work done while you were at the University of Colorado?
A. Yes, other than, as I mentioned, symposium chapters and book chapters.
Q. Are those listed?
A. Yes.
Q. They would be under which section of your resume?
A. Let's see. "Books and Book Chapters."
Q. The recent ones would be on page 9, then?
A. 8. For Books and Book Chapters, it's reversed.

Q. I see. The most recent at the beginning?
A. Yes, the modern wonders of computer technology. I have managed to get those reversed. I haven't done it for my published articles.
Q. All right. What was your contribution in the reference with Kreiger?
A. I'm co-author. We both authored the chapter together.
Q. Which part in particular did you author, if there was a particular part?
A. We wrote it together. If there was any distribution of effort, he probably participated a little bit more heavily in looking at some of the physical characteristics of electromagnetic radiation and I focused on the clinical and biological. But we both collaborated extensively on that.
Q. Could you give me a summary of what you wrote in this article?
A. It is an extensive book chapter. I mean it covers -- it covers virtually the entire field with respect to the biology and the epidemiological data surrounding nonionizing electromagnetic radiation. I would hate to

characterize it in a sentence or even a paragraph.
Q. Is that the only work that you have published that deals with nonionizing radiation?
A. Yes.
Q. Have you done any investigations, laboratory investigations involving nonionizing electromagnetic radiation?
A. We have had some talks about looking at various aspects of this question as it relates to extended space flight, but nothing has materialized at the present time.
Q. Have you considered setting up the same sorts of investigations that you have done for the CMA and API but doing them in various strengths of electromagnetic fields?
A. As I said, we have had some discussions in this area: but I would characterize these as excruciatingly difficult experiments to design and to control. I would say most of the attempts to do so have lack -- have been lacking in very important aspects. So, the question remains on how to do them: and I have not approached that lightly. It's not something you set up on a Saturday afternoon.
Q. Have you approached the electric

utilities or their trade associations for support?
A. No.
Q. What was the benzene case study that you presented?
A. Benzene case study in that context doesn't mean what I think you would think normally as a case study. I was asked to use benzene as an example to discuss the state of the art, the advantages and disadvantages of pharmacokinetic base modeling, using benzene as an example.
Q. Do you maintain reprints of what's listed in your resume?
A. I have an incomplete set of reprints.
Q. Would you have copies of those for which you have no reprints?
A. Not all of them. I probably am lacking one or two.
Q. Would you know which ones those are?
A. Not reliably. I would have to check. I just know that some of the more -- one or more of the obscure ones when I have tried to find them I have not been successful. But they are all in the literature.
Q. Yes.
A. For the vast majority of them, I have

copies.
Q. If I wrote you, would you be kind enough to give me a copy of those I am having difficulty finding?
A. Yes.
Q. What is it that you have been asked to do in this case?
A. I have been asked to render an opinion as to whether or not the diseases of four individuals listed in this case was or could be caused by exposure to benzene, ethylene oxide, or butadiene.
Q. Have you written a report?
A. No, sir, I have not.
Q. Have you been asked to at all?
A. No.
Q. Do you depend on any of the toxicological studies in support of your opinions in this case?
MS. ARRAS: I am going to object to the broadness of the question.
BY MR. HOBSON:
Q. As opposed to epidemiological studies.
A. When I view literature as a whole, I

rely on data that comes from experimental studies, from clinical toxicology studies if they are available, as well as epidemiological literature. I don't know where I would draw the line. Could you be more specific?
Q. Sure. Can you direct me to any toxicological studies that in your view tend to rule out non-Hodgkin's lymphoma being caused by any of these three agents?
A. With respect to the specific study, no. With respect to the weight of the evidence that comes from an evaluation of the appropriateness of animal models to man, as well as the human experience, the epidemiology literature, yes.
Q. Tell me which ones of the toxicological studies you view as part of the total picture that supports your opinions.
A. Certainly the studies that look at the differences in the biology, the tumor formation, the differences in metabolism, species difference in metabolism and activation of compounds such as butadiene. And there, there are several.
Q. Could you give me specifics?
A. How about if I mark them?
Q. That would be fine. And by "them," you

are talking about the listings in your bibliography?
A. Yes.
(Marking bibliography with check marks)
Q. All right, sir. I noticed one of your other sheets that you told me about earlier is the summary of the four cases: is that right?
A. Yes.
Q. The diagnosis that you put down for each one of these gentlemen, can you tell me the source of that diagnosis?
A. It's either -- well, it's a combination of the medical summaries that I have read, as well as the medical reports and histopathology reports obtained from the medical records for each of the individuals.
Q. Are you aware of any controversy about the diagnosis of these individuals?
A. With respect to what?
Q. Has anyone come to you and said, for instance, Mr. Ellis, we have some evidence that he did not have well-differentiated small cell non-Hodgkin's lymphoma. We have evidence that perhaps he had some other disease or some other variant of this disease?

A. I think that it's obvious from his history that at the initial time of diagnosis there was some question as to whether or not the presentation was that of chronic lymphocytic leukemia or NHL: and subsequent to that, there is still some questions that could be raised but in general it appears to be much more like an NHL.
Q. Would it matter in your opinions whether it was a lymphoma or a leukemia?
MR. HALL: Let me object to the form of the question. Again it's over broad. Any leukemia or CLL?
MR. HOBSON: The one he putatively had.
A. There is some difference in the data that I would use to support my opinion. My opinion would be the same that neither are caused by exposure to benzene, but the literature would be different that I would use to support them.
BY MR. HOBSON:
Q. How about butadiene and ethylene oxide?
A. Well, it's not compound related. It's disease related; and there is nothing that's ever been demonstrated to cause CLL, not even

radiation. So, from that stand point, I would distinguish CLL from NHL. In this particular case, the prevailing diagnosis appears to be NHL.
Q. Is there any difference that you have any -- let me start over.
Some of these -- all four of these gentlemen have some form of non-Hodgkin's lymphoma: correct?
A. Yes.
Q. Where I want to go with my question is:
Some of these listed as well-differentiated small, well-differentiated diffuse, these different descriptions that proceed non-Hodgkin's lymphoma, do they play any part in your opinions at all?
A. With respect to causation?
Q. Yes, sir.
A. No.
Q. Are they the same disease?
MS. ARRAS: I object to the form of the question.
A. They all go under the rubric of non-Hodgkin's lymphoma. One of the characteristics that defines different lymphomas is the nature of the cell type and its behavior, susceptible to treatment, its rate of growth, its

ability to invade tissues, and a variety of other distinctions that are a result of the particular cell type in terms of differentiation and a variety of factors which we don't understand, as well. I think that it is important from the histopathologic and a prognostic standpoint to distinguish them one from another. That's the obvious purpose of spending so much time on differential diagnoses.
BY MR. HOBSON:
Q. Do these different variants of non-Hodgkin's lymphoma come from the same stem cell lineage?
A. Yes, but that's -- you could also ask the question: Do all the cells of the body come from the same fertilized egg?
Q. Good point. I'll withdraw the question.
Let me ask it this way: If we find -- for instance, I think you said that the myeloid progenitor cell is the differentiated cell - committed differentiated cell that develops into AML. Can you give me a similar committed differentiated stem cell that develops into non-Hodgkin's lymphoma and tell me if it's the

same for these different variants?
A. Theoretically, there is a cell that is a common lymphoid progenitor cell that ultimately is thought to give rise to both the T and the B cell lineages of the lymphoid system. But to compare that process of differentiation with the myeloid side is comparing, in the case of the myeloid, a pretty straight tract to what in the case of the lymphoid is a very labyrinthine and complicated differentiation process.
As I mentioned earlier, a major distinction between the lymphoid cells and the myeloid cells is that the vast majority of commitment, differentiation, and regulation of that compartment and cell function occurs outside the marrow. The cells that leave the marrow are capable of division and activation and a variety of processes that make them work, synthesize. So, although ultimately they may be descended from the same cell -- and there is some argument about that -- and you can obviously say that at some point they are descended from the same totipotent stem cells, the transformation process, origin in terms of their ontology is much more complicated.
Q. Could you delineate it for me? In

other words, start back at a point in time at one of these pluripotent levels where they are all common and take me through the lineage to get me to each of these variants for these gentlemen?
A. Well, I can certainly give you a paradigm that would depict what we know about differentiation for either the B or the T cell lineage. The individual lymphomas are thought to be a result of an abnormality occurring in the cell at a given stage in the differentiation process.
As I mentioned earlier, some people think that antigenic stimulation and cells responding to antigenic stimulation are, in fact, one of the sites for the evolution of a lymphoma. These cells arise in peripheral nodes, the exception, as I mentioned, being multiple myeloma; and I don't think that it's fair to classify multiple myeloma as an NHL from a biological standpoint.
If you want me to go through it, I can talk about T cell differentiation, B cell differentiation.
Q. For these four gentlemen, does it matter if it is B cell or T cell differentiation?

A. There is some discussion in the case of Mr. Lilly, I believe, as to whether or not it's a T cell origin. I'm not comfortable with that diagnosis on the basis of what I have seen. I certainly haven't seen enough to make a definitive -- to reach a definitive conclusion. I think it's more likely than not that we are looking at a poorly differentiated diffuse B cell lymphoma, although it may -- there is some argument as to whether -- histopathologically it resembled what I believe is called Lennerts. As far as taking him as a whole, I think it's more likely than not that we are looking at a series of B cell lymphomas.
MR. HOBSON: Lunch.
(LUNCH RECESS)
BY MR. HOBSON:
Q. Doctor, we're back from lunch. I'll try to get on expeditiously here. I know you have got a plane to catch.
Did you put together the list of information that's here on this yellow sheet?
A. Yes.
Q. What all did you have to draw from to gather this information on here?
A. I had the depositions of the

plaintiffs. I recall the Culver report, which I may have used; some maps that were provided me of the facility: discussions that I have had with the attorneys in this case, some of the information that's on there has been represented to me with respect to their work history: my own reading of the various reports and materials that I had available in the case. I basically am using that just to keep the individual situations separate.
Q. Under Mr. LeBlanc's entry here, there is a -- I don't know what this means. "P." something. Can you tell me what this means, please?
A. Yes. I have been told that there is personnel monitoring data from Mr. LeBlanc that is subsequent to 1977, and in that particular sample there was no benzene detected. That's what that means. ----
Q. Have you seen any personnel monitoring records other than the ones that are listed on this one sheet of paper, which I see two entries?
A. No.
Q. Have you asked for any?
A. I have inquired as to personnel monitoring data, and I am told that that's what is

available.
Q. Have you been made aware of whether or not there is any monitoring data for other individuals who did similar work to these gentlemen?
A. I can't say one way or the other. I don't know whether I have asked that question.
Q. You don't know one way or the other if any data exists?
A. No.
Q. I am correct?
A. That's correct.
Q. Would you be able to tell us at all your impressions or opinions of these gentlemen's exposure to the three chemicals that are involved here, benzene, butadiene, or ethylene oxide?
MS. ARRAS: I am going to object to the form in terms of impression. What do you mean by "impression"?
MR. HOBSON: Well, opinion.
A. I think they have all been exposed to benzene at one level or another because we all have. Basically, I think benzene is ubiquitous. So, you are talking about some level of exposure

clearly. I would like to look at my sheet, if I may.
BY MR. HOBSON:
Q. Sure (tendering document).
A. (Reviewing document) Do you have specific questions?
Q. Yes, sir. Let's talk about Mr. Ellis. Can you give me your opinion of Mr. Ellis' occupational exposure to benzene?
MR. HALL: I'm going to object to the form of the question in the sense that Dr. Irons has not been retained by us to review data or to render or form an opinion relative to qualitative or quantitative exposures to any of the chemicals with respect to any of the plaintiffs. To the extent that he has seen any information which is factual rather than opinion, he certainly is entitled to answer that; but I think that the question calls for an opinion of a person which in this instance is improper opinion testimony from a lay

witness.
MR. HOBSON: "I don't know"
will suffice, then.
MR. BAGGETT: You can go ahead
and answer the question.
A. I am not an industrial hygienist. I
rely on industrial hygiene data in reaching an
opinion. But I would -- I would not wish to
speculate on what individual exposures would be in
the absence of data to support it.
BY MR. HOBSON:
Q. Would it be fair to say that you don't
intend to offer any opinions in these cases that
we're here for today with regard to the amount of
benzene exposure that any of these gentlemen have
had?
A. That's correct.
Q. Would that be true for ethylene oxide
and butadiene, as well?
A. With regard to these individuals, yes.
Q. You were sent Nancy Culver's work in
this case, were you not?
A. Yes.
Q. Did you review that information?
A. Yes, I did.

Q. What did you glean from that information that is useful to your opinions in this case, if anything?
A. It was a useful description, general description of the facility. I found a lot of the data in it unsubstantiated with respect to -- and unqualifiable, unquantifiable in terms of degree. For instance, there were comments such as benzene present frequently in the document, as an example: and I didn't know what to make of that.
Q. Were there any obvious errors that came to light on your review of Nancy Culver's work, things where you looked at them and said I know this is wrong?
A. I don't recall. I reviewed that earlier in October, and I do not recall specifically the details.
Q. I see here that Ms. Arras provided you with other monitoring data from Cities Service. What data was that, please?
A. I have seen some monitoring data taken, I believe -- I don't recall the precise year, but I've seen -- I've seen monitoring data on the facility taken at various times and in various places.

Q. I see that you've been provided with this paper by Dr. Young from the American Journal of Industrial Medicine. Is there anything about what is said in that paper that comes to mind that you feel Dr. Young was wrong in?
MR. HALL: Let me enter an objection. First of all, it's characterizing it as a paper; and I am not certain it is a paper.
Subject to that objection, you may answer, Dr. Irons.
A. In my opinion, he has misrepresented the findings in several of the studies that he cites, and I don't believe that one in evaluating those studies necessarily comes to the same opinion that -- I certainly don't, that Dr. Young did.
MR. BAGGETT: Steve, in view of your statement that you made awhile ago, I mean it may eliminate an awful lot of questioning, but you furnished him Nancy Culver's reports and the monitoring data. Is it our understanding, for the record, that you are not going to

use him in any way as an expert concerning the plaintiffs' exposures?
MR. HALL: we can discuss this off the record or on the record, Bill, but -
MR. BAGGETT: In view of your objection, I think that it is proper for us to ask this.
MR. HALL: He is not going to render an opinion that plaintiff "X" was exposed to. levels of benzene in the amount of "Y" on a date certain or on dates certain.
MR. BAGGETT: And he is not going to rely on the monitoring data that was furnished him, it will not form any basis of his opinion?
MR. HALL: You will have to ask him that question because you are not asking me. You will have to ask the witness that question.
BY MR. HOBSON:
Q. Is the amount of exposure to benzene,

butadiene, or ethylene oxide that these gentlemen received in their occupation in any way import to the opinions that you intend to express in this case?
A. In my opinion, the diseases that these gentlemen have are not caused by benzene: and there is no evidence that the other agents caused them. To the extent that -- in that context, exposure really is in large part moot. By the same token, I don't see any evidence here that would suggest exposure certainly to benzene that would be indicative of the types of abnormalities that benzene is known to cause.
Q. Well, that brings me then back to my question that I asked before: What is the quantitative exposure for Mr. Ellis to benzene?
A. I have no -- for any of these gentlemen, I do not have any information that would lead me to any exposure data that I would find reliable to determine or to assess what their exposures were. I see no evidence that would lead me to be able to do that.
Q. So, in other words, you don't know what their exposure was to benzene occupationally?
A. I have seen no data that would allow me

to reliably conclude what their exposure was.
Q. Can you then tell me that their exposure was not high?
MR. HALL: Object to the form of the question.
A. I see no evidence to quantitate what their exposures are. I have said before that they all obviously have had some exposure to benzene. We really -- I don't see any data that would allow me to indicate for an individual or to conclude for any individual that they had high exposures to benzene.
BY MR. HOBSON:
Q. Or that they did not?
A. Or that they did not.
Q. When it comes to information that could be used for you to determine exposure levels, what have you seen so I can know the basis of your statements? We talked about Nancy Culver's report, and you have got here in this letter some documents from Ms. Arras about monitoring data. Is there anything else that you recall?
A. I have read the personal statements of the individuals.
Q. Their depositions?

A. Yes.
Q. Anything else?
A. Not that I recall.
Q. Have you been provided any documents that came from the Cities Service refinery in Lake Charles that showed any information about spills of benzene or benzene-containing materials?
A. I have seen sampling data that was associated with individual incidence, area sampling.
Q. Were you aware from reading Mr. Lilly's deposition that he washed people's clothes with benzene?
A. I recall the statement, yes.
Q. Is that a significant exposure in your mind?
A. If, in fact, one were to wash people's clothes in benzene and do it repeatedly, that would be significant exposure. I, however, find it very hard to believe, bas d on my knowledge of industry practice and benzene in general, that his description is compatible with the use of benzene.
Q. Is that the only basis for saying that you doubt what he said is true?
A. That I find it incredulous that one

would be able to work with benzene in that kind of environment without posing a hazard from explosion and a variety of other things, yes. I think it's -- it doesn't make sense.
Q. Did I understand you to say that you find that the description that Mr. Lilly gave of washing people's clothes with benzene in that era and that industrial setting is just incredible?
A. Yes. I think it's fair to say that Mr. Lilly may have washed somebody's clothes with a solvent. I think it is highly unlikely that he was using benzene.
Q. If it turns out to be true that it was benzene, would you say that the supervision at that refinery was totally negligent in allowing that to occur?
MR. HALL: Let me object to the form of the question on a couple of grounds. One, it calls for a legal conclusion: number two, it asks for an opinion outside his field of expertise: number three, it's an incomplete hypothetical.
BY MR. HOBSON:
Q. You may answer, if you can, Dr. Irons.

A. I think that the conditions and the situation are clearly undefined, and on that basis I don't think I can answer that question.
Q. Should a supervisor allow an employee that he supervises to wash clothes with benzene?
MR. HALL: Let me reiterate the same objection I just stated moments ago and make them continuing for this line of questioning.
MR. HOBSON: Fine.
MR. SPICER: We join in that objection.
BY MR. HOBSON:
Q. You may answer, if you can.
A. Could you repeat the question?
Q. Yes, sir. I want to know if you think that a supervisor should allow employees that he supervises to wash people's clothes with benzene.
MR. HALL: Same objection.
MR. HOBSON: I think we said you could ,have the continuing.
MR. HALL: I know I said it but I am always leery of it and I like to repeat myself.

A. In this particular day and age, I would find that a very improbable, if not impossible situation. Certainly if it's within somebody's power or knowledge to prevent or suggest otherwise, that would be a very intelligent thing to do.
BY MR. HOBSON:
Q. Would it have been unwise in the 1950's, as well, based on your review of the literature?
MR. HALL: Same objection.
A. In the 19 -- I don't understand exactly the frame of your question. If you are asking me if based on what was known in the 1950's would it be -- would it be unwise, I think the concern over it in the 1950's would have been a lot different than it would be today because in the 1950's it was not by any means well established that benzene was a leukemogen.
MR. BAGGETT: Was what, sir?
THE WITNESS: Was a leukemogen.
BY MR. HOBSON:
Q. You are aware, though, aren't you, that the American Petroleum Institute had published his

toxicological reviews for benzene, in which it was stated that benzene was related to leukemia?
A. Could you refer to a specific document? I don't know what you are talking about.
Q. The American Petroleum Institute toxicological review for benzene published in 1948.
A. I think that represented an opinion. I think that there are some aspects of that review itself which I don't find authoritative.
Q. But you are aware that it existed?
A. It was a comment that was made in an API document at that particular point in time, I believe that's correct.
Q. Would you agree with me that for a supervisor to allow someone to wash clothes with benzene would be an unsafe act that would be recognized in the 1950's?
MR. HALL: Let me interpose the same three objections.
MR. SPICER: We again join.
A. Chronic exposure to benzene was certainly recognized by the fifties as being associated with some bone marrow toxicity. The vast majority of cases that were available in the

literature at that time dealt with bone marrow suppression, aplastic anemia, pancytopenia, lymphocytopenia, thrombocytopenia. The number of leukemia cases on record at that point in time was an extremely small percentage of the total cases that dealt with benzene toxicity.
Certainly chronic prolonged exposure would be inadvisable, but by the same token I can see where based on our knowledge at that time that the stringent restriction of the use of benzene as a solvent for those types of procedures would not necessarily reflect our knowledge of the toxicity of benzene at that point in time.
BY MR. HOBSON:
Q. Am I hearing you say that you wouldn't jump on a supervisor who didn't stop the washing of clothes with benzene?
MR. HALL: Same objection.
Not only that, it's argumentative.
MS. ARRAS: It's also vague since it is not quantified by year.
A. Based on the state of the art at that time I would still think it reasonable to restrict the use of benzene in a chronic repeated exposure scenario, based on toxicity of the blood; but,

certainly the dangers associated with chronic benzene exposure and leukemia were not well appreciated in the fifties and, therefore, its occasional use as a solvent would not necessarily be, I think, restricted to the extent that it is today.
BY MR. HOBSON:
Q. There is a sheet here in your file that says "Index to Documents Transmitted." May I ask who prepared that?
A. I'm not certain. That was sent to me in one of the packages that I received from Ms. Arras' office.
Q. So, it was prepared at least by someone other than you or your office?
A. It was not prepared by me.
Q. Did you actually get all these things?
A. I believe so.
Q. Have you read them?
A. I have -- I have read and looked at all of them. I can't recite them from memory, but I have read them.
Q. Were you named as an expert in the Chargois case?
A. Not to my knowledge.

Q. Are you named as an expert in the Wing case?
A. Not to my knowledge.
Q. Have you had any participation in either the Chargois case or the Wing case other than reading these documents that are listed here in your packet for this case?
A. I don't believe so.
Q. There are some stapled together documents here for the four gentlemen that sort of appear to be sort of a typed-up summary, also. Can you tell me where these came from?
A. Those were provided to me by Ms. Arras.
Q. Have you verified the accuracy of what's contained in these four typed-up summaries?
A. In general, they are consistent with my own reading. I have -- I can't speak to every point on them: but in general, I recall that they are representative of my own review of the material.
Q. Would you have any idea as to what the exposures of someone working on the loading rack loading ethylene oxide would be?
A. No. I think it highly -- that would be very difficult to ascertain that without

industrial hygiene data.
Q. And you have seen no such data: is that correct?
A. Not that would allow me to reach an opinion as to what their exposures may have been.
Q. Would you have even seen any exposure data of any kind, any airborne levels to ethylene oxide or butadiene in the 1964 to '70 time period?
MS. ARRAS: I am going to object to vagueness in referring to this Cities Service plant.
BY MR. HOBSON:
Q. Anyplace, whether it's Cities Service, PCI, PCD, the world, have you ever seen any data for monitoring for ethylene oxide and butadiene loading rack operations for worker exposure in the world's literature, published or unpublished?
A. Not that I recall.
Q. Have you seen reference made to benzene being present in the waste collection system at the refinery, Cities Service refinery?
A. Yes.
Q. Are you in a position to dispute or confirm any of that information?
A. On my personal -- based on my personal

knowledge, no.
Q. How about from reviewing any records in this case, would you be able to say that that's true or not true?
A. I have seen some area sampling that was associated with the waste system that suggests for specific points in time there were measurable amounts of benzene present.
Q. There are some -- two sheets of paper typed horizontally on the page that have the style of this case in the upper left-hand corner and again appear to be some kind of a summary. Do you know who prepared these documents?
A. Again, that was given to me by Ms. Arras. I think it generally corresponds to my own notes. It's not identical.
Q. I notice that there is a reference here "Hiroshima - 1 day (1946)" for Mr. Ellis. Can you tell me where that came from?
A. Well, as I recall, he stated that he was present at Hiroshima after the fall of Japan.
Q. In your opinion, is that in any way causative of his condition of what is listed here first of all as CLL and then secondly as lymphoma?
A. No.

Q. So, the fact he was an in Hiroshima one day you don't find significant at all in causation for his disease: correct?
A. No.
Q. I am incorrect?
A. I do not see that that's relevant to the issue of causation.
Q. Are these medical records that are in your file folder all on Mr. Lilly?
A. Can I see them?
Q. Sure (tendering document).
MR. HALL: Herschel, I didn't understand your question. It's ambiguous. It could be is that all you have on Mr. Lilly, or it could be do these reports all pertain to Lilly. I am not certain which you are asking.
MR. HOBSON: I was trying to ask do they all pertain to Mr. Lilly.
MR. HALL: Thank you.
A. Some of these are some records from - this one is from Virgil Talbott.
BY MR. HOBSON:

Q. They are hard to read. I thought you could tell me rather than me trying to cipher them.
A. I just received these yesterday. I think I have copies of these already in my records, but these are -- of this, but I just received these.
Q. Are these all the medical records that you have brought with you from Colorado?
A. Yes.
Q. There is mention in here -- you pointed out Mr. Talbott's records are part of those, and I see on your summary sheet that is handwritten, you have under diagnosis, well-differentiated, diffuse non-Hodgkin's lymphoma, January '85, age 66. Then you have small cell, what appears to be, cancer of the lung.
A. Yes.
Q. 1991. What do you make of the small cell cancer of the lung in relationship to his non-Hodgkin's lymphoma?
A. It's a separate -- it's a separate disease, distinct cancer.
Q. Do you see one being related to the other at all?

A. Not -- no, not really.
Q. Are you intending to give an opinion as to which was the cause of his death?
MS. ARRAS: I object. It's outside the area of the expertise of this witness.
MR. HOBSON: All he has got to do is say no.
MR. HALL: Not only that, it assumes one or the other was and, therefore, may be an improper question.
MR. BAGGETT: Well, he knows whether he is going to testify to it or not, I think.
A. I believe he died of pneumonia. That was the diagnosis, and I would not want to or feel qualified to presume as to what the contributing causes were. I don't have enough information.
BY MR. HOBSON:
Q. Would you defer that question to the treating physician to make the call?
A. I would certainly defer it to physicians who are more experienced in that than I am.

Q. Are you in a position to say whether or not that would include his treating physician?
A. I don't know anything personally about his treating physician: so, I couldn't comment one way or the other.
Q. By the way, did you read Dr. Gore's deposition in this case?
MR. HALL: I don't think it's been transcribed yet.
MS. ARRAS: No, for the record it has not been transcribed: so, it would be physically impossible for the witness to have read it.
A. I was going to say I don't recall. If I read it, it certainly escaped me.
MR. HOBSON: A simple "no" would have sufficed for me and my simple mind, or "I don't remember." Any of those would have done fine for me.
MR. HALL: Well, something that Bill Baggett has taught me, Herschel, over the years is you never want to leave a negative inference on the record; and it

could be inferred that perhaps Dr. Irons was not doing his homework. So, that's the basis of the comment.
MR. HOBSON: Let me mark some of these so I can have them attached, please.
(OFF-RECORD DISCUSSION)
(IRONS EXHIBIT NOS. 2, 3, 4, 5, AND 6 WERE MARKED FOR IDENTIFICATION)
BY MR. HOBSON:
Q. Dr. Irons, we have marked as exhibits to your deposition your CV as No. 2; the benzene bibliography as No. 3, including the check marks that you put next to the numbers that indicated the toxicity studies.
A. It's butadiene, not benzene.
Q. I have said that wrong every time. You are right. Butadiene. And we have marked your handwritten sort of summary by plaintiff: is that right, as Exhibit No. 5? And we have marked your folder -- and how would you characterize what you keep in this folder?
A. Correspondence received from Ms. Arras

with respect to this case.
Q. All right, sir. We have marked that as Exhibit No. 4. I have got those all correct, have I not?
A. Yes.
Q. And then No. 6 here is all of your technical articles that you bound up in a little black binder for us. I don't mean to imply that that's all that there are, but these are the ones that you brought with you?
A. Yes.
MR. HOBSON: Okay. If you all want to take those, I am finished with those, I think.
(OFF-RECORD DISCUSSION)
BY MR. HOBSON:
Q. I would just kind of like to run through these articles in Exhibit No. 6. "Hematologic Effects of Benzene: A Thirty-Five Year Longitudinal Study of Rubber Workers," by Kipen, et al. Can you point to me what it is in summary fashion that you find in this article that you in some way rely upon for your opinions in this case?
A. I think it demonstrates the levels of

abnormalities that are associated with peripheral blood that have been found in workers chronically exposed to benzene in which you have some evidence of an increased incidence of AML.
Q. Anything else?
A. It points out some of the limitations in hematologic monitoring for benzene exposure.
Q. Do you know where this plant or where these plants were that are reflected in this study?
A. They are the same plants that were the subject of the Rinsky and Infante studies.
Q. The Ohio Pliofilm workers from Goodyear?
A. Yes.
MR. HALL: The record won't reflect this, but I would like it to, that Mr. Hobson is asking questions of the witness while Mr. Hobson is looking at the documents and Dr. Irons is testifying from memory. I just want the record to reflect that.
BY MR. HOBSON:
Q. If you feel like I treat you unfairly

at any time, speak up, because I will try not to be unfair to you.
A. That's fine.
Q. So, if you want to see something, don't hesitate.
A. If I wish to see the documents, I will tell you.
Q. Speak up, please.
MR. SPICER: You are referring to the documents in the black binder as Exhibit No. -
MR. HOBSON: 6.
MR. SPICER: -- 6?
MR. HOBSON: Yes.
BY MR. HOBSON:
Q. I notice in the acknowledgements here that the American Petroleum Institute provided the data and the support for this particular study. Were you aware of that?
A. Not in particular. I think it's very reasonable that if they were going to get access to the data, they probably would have to go through the industry.
Q. This was a Goodyear plant?
A. It was Pliofilm during the war. I

really can't say what the -- I'm not certain what the ownership was during the war.
Q. Would you know if Goodyear Tire & Rubber Company or any Goodyear entity has ever been a member of the American Petroleum Institute?
A. I couldn't answer that question.
Q. Is there any particular table or summary that's a part of this paper that you find particularly sets out a portion that you are relying upon?
A. I am relying on that paper in its entirety for one thing or another. I would say that the abstract certainly gives a good overview of the results and their significance.
Q. Was there an excess of any disease other than AML in this population?
A. Based on that study, as well as report from the War Production Board on these plants, there was evidence of blood dyscrasias and lost worker time due to anemia and other abnormalities.
Q. How about any other cancers?
A. Not to my knowledge other than those that have been reviewed and published in Infante and Rinsky's papers.
Q. Are you saying that Rinsky and Infante

have reported other excess cancers besides AML?
A. They have reported cases, and in the follow-up they have enlarged the size of that study.
Q. Going to the next paper here, "Benzene (Benzol) Poisoning in the Rotogravure Printing Industry in New York City," by Greenburg, et al. Can you tell me what part this study plays, if any, in supporting your opinions in this case?
A. It demonstrates the hematologic abnormalities that have been associated with high level exposure to benzene in a chronic situation. It's the first controlled study of benzene exposure in humans that I'm aware of. It characterizes the blood abnormalities and did not find any malignancies in the study group.
Q. Have you ever discussed this paper with any of the authors?
A. Yes, I have.
Q. Which one, Dr. Goldwater?
A. Dr. Goldwater, many years ago.
Q. "Disturbances in the Blood Following" -- and it appears that there has been part of the page obliterated, so I don't know if that's all the title or not.

A. I think it is.
Q. Okay. "Disturbances in the Blood Following Exposure to Benzol" by Goldwater. Is this a paper reporting on the same rotogravure workers?
A. Yes. There were two papers that came out very closely together.
Q. "Types of Leukemia in Chronic Benzene Poisoning. A study in Thirty-Four Patients" by Aksoy, et al. What in here do you find that supports your opinions in this case, if anything?
A. The predominance of acute myelogenous leukemia associated with benzene exposure.
Q. Are you aware of Dr. Aksoy reporting excesses of any other kinds of leukemia in benzene-exposed populations?
A. I am aware that Dr. Aksoy holds an opinion that, in fact, benzene may cause a variety of difficult neoplasms; but if I look at his data separately in the aggregate, I reach the conclusion that he really only has evidence to support AML.
Q. So, when you and he look at the same data you get different opinions: is that what you are saying?

A. If we took it on an individual basis, if you want to discuss that paper, we can. I would hate to have to just summarize in general what we agree on and what we disagree on.
Q. I am talking about the different kinds of leukemia that benzene can induce.
A. I think that Dr. Aksoy's data in the aggregate can support a relationship with AML and a deficit for some of the other leukemias in benzene-exposed workers.
Q. But he interprets his data differently?
A. I think it's fair to say that he interprets his data differently than I do.
Q. "Mortality of Rubber Workers with Reference to Work Experience" by -- I never can say this man's name and apologize -- Andjelkovich?
A. Well, it's a lady; and it's Andjelkovich.
Q. A lady. Well, I am even worse than I thought. I am wrong on both counts. My apologies to whoever reads this transcript.
What in this paper do you rely upon in support of your opinion, if anything?
A. If you will permit me, there is a series of papers that examine or follow the work

of the group at the University of North Carolina over the years, looking at the relationship between occupational exposure in the rubber and tire industry and lymphoid neoplasms. They begin with McMichael and Andjelkovich and continue on through Arp, Checkoway, and Wilcosky: and as a total body of work they represent, to me, an evolution in understanding and characterizing the relationship between occupational exposure in the rubber industry and lymphoid neoplasms. If you would like, I can characterize that further: but I would rather not just take a single paper.
Q. Sure, that's fine. I would accept the aggregate characterization.
A. Early studies by McMichael defined - suggested that there was possible relationship between exposure -- occupational exposure in the rubber industry and lymphoid neoplasms. There was no industrial hygiene data in that study. The surrogate for exposure was simply the assumption of which categories or workers might be exposed to benzene. Benzene formed the basis for the assumption, that benzene was associated with their findings.
In further studies, when actual

exposure measurements were made, the same finding, that is the relationship between exposure in the tire and rubber industry and lymphoid neoplasms, was confirmed: but the relationship to benzene was, in fact, disproven. The final conclusion of the group is that the relationship between occupational exposure and disease does not correlate with benzene but, in fact, there are higher associations with other solvents.
Q. Such as?
A. I think the two that were suggested were carbon disulfide and carbon tetrachloride. I don't believe that those studies provide a reliable basis for reaching that conclusion, but they certainly point out the disparity between exposure to solvents in general and benzene in particular.
Q. Are you aware of any literature that suggests that carbon disulfide or -- I have forgotten what else you said already.
A. Carbon tetrachloride.
Q. -- carbon tetrachloride can induce leukemias in humans?
A. No, I'm not. That's the only reference I know to that.

There is a study not in there simply because I couldn't put my hands on it quick enough by Monson and Fine from 1978 that independently confirms that the incidence of lymphoid neoplasms in the rubber industry appears to have been sharply reduced in the transition from a coal based -- coal tar-based solvent to petroleum-based solvent, which I think is consistent with the findings from this group.
Q. Can you attribute any chemical difference to the solvents that are coal derived versus petroleum derived?
A. I think that in order to give a responsible answer to that question, I would have to have a lot more information than I do. There are certainly major differences both in the content of benzene, as well as other compounds. Naphthas, a variety of other agents.
Q. Is there any relationship between polynuclear aromatic hydrocarbon exposures and leukemia?
A. There have been some suggestions in what I would consider to be a confusing literature base that cigarette smoking has been in at least one study associated with a slight increase in the

incidence of leukemia. In other studies, that hasn't proven to be the case. That is a source for exposure to polyaromatics in general, but it's also very complicated. Cigarette smoking is a very complicated exposure scenario. Other than that, I am not aware of individual studies looking at polyaromatics. For one reason, you don't often find in an occupational setting a defined exposure to polyaromatics.

Q. Are there sources of exposure to polyaromatics in rubber plants, such as the kind that are described in the North Carolina studies?

A. I wouldn't be surprised, but I don't have any specific hygiene information. The rubber -- rubber plants are an exceedingly complex occupational setting. Very complex. Exposure scenarios are almost impossible to define. I think it's fair to say that there is a problem with respect to occupational exposure in that setting and the development of lymphoid neoplasms, although it's by no means yet clear what the distinction amongst those are. But by the same token you cannot, I think, based on the

literature, assign or assume that causation is due to benzene.
Q. What would be the sources of PNA exposure in a synthetic rubber plant or a rubber goods manufacturing plant such as the kind studied by the University of North Carolina in these articles?
A. In coal tar-derived products, I would expect that you could find some, and certainly naphthas associate in the solvent base. In petroleum based, I don't expect you would find the same constituents.
Q. How about some?
A. Some is a relative term. I won't say as a scientist that you never can find something if you look for it. I don't know at what levels you would expect to find it.
Q. You know, of course, that the rubber solvents that have been used for the last 15, 20 years in the manufacture of tires is just a cut off of the crude still in a refinery? You know that?
A. It's a -- I think it's defined a little bit more precisely than that. Certainly the benzene content has been examined, in an effort to

reduce it or eliminate it.
Q. And there is polynuclear aromatic hydrocarbon material contained in crude oil?
A. Sure.
Q. Would you not expect, then, that in this rubber solvent cut from the simple distillation of crude oil that you would get some polynuclear aromatic hydrocarbons?
A. Again, the question is the amount and whether it's analytically measurable or biologically significant; and I am not in a position at this point to address that responsibly.
Q. Can you even tell me for sure that there is a difference in PNA content quantitatively or qualitatively between coal tar -- coal-derived solvents and petroleum-derived solvents?
A. Definitively, no. I would suspect that there are differences. I would expect to find more in the coal tar-based product.
MR. HOBSON: If you wouldn't mind, to satisfy yourself we have an accurate copy: and we will give the copy to Joyce.

BY MR. HOBSON:
Q. What other sources of polynuclear aromatic hydrocarbons would you expect it to be in a synthetic rubber plant or a tire plant such as the ones in the North Carolina study?
A. In particular, at this -- at this particular point, I can't think of any.
Q. The next article here that you have is "Hodgkin's disease and Acute Leukemia." It looks like case reports by Rosner, et al.
A. There are a series of papers there that are representative of the literature on secondary malignancies -- malignancies secondary to chemotherapy for other primary diseases: and they basically characterize what I said to you earlier today with respect to the overwhelming predisposition for AML as the secondary malignancy in these patients.
Q. Is AML the only disease that is secondary to the chemotherapeutic agents?
A. Virtually, yes.
Q. There are no reported instances of multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's disease?
A. There -- well, I can characterize -- I

can sum up certainly the opinions of some of the authors there in the context of the data you see there, as well as more recent publications such as the last edition of the text "Leukemia," that although they have been an occasional case report of one type of lymphoid neoplasm or another that they are so sporadic and uncommon that they probably are incidental and not -- coincidental and not related to chemotherapy.
Q. Meinhardt's report "Environmental epidemiologic investigation of the styrene-butadiene rubber industry." Can you tell me how this plays a part in your opinion, if it does?
A. It's one of the papers that has characterized epidemiologic exposure to butadiene. It was one that I was able to place my hands on quickly. It isn't in there because it bears any more or less weight than the others. It just happened to be one that I physically had in my hand. The others are listed in the bibliography that I gave you.
Q. I notice at the top of this article you have written "butadiene." Does Meinhardt's paper have anything to do with benzene, as well?

A. It looks at synthetic rubber plants which it's often difficult to segregate or separate out exposures: but I think that the Meinhardt study, as I recall, reflects primarily butadiene exposure. I would not expect to see very heavy benzene exposure in that setting.
Q. What do you mean by "very heavy"?
A. Significant.
Q. Would you expect there to be benzene exposure at approximately 1 part per million in the synthetic rubber plant, particularly in this plant study by Meinhardt and reported here?
A. Can I see the paper?
Q. Absolutely (tendering document).
A. (Reviewing document)
The reported detectable levels of benzene in samples in this study I take to be trivial with respect to the benzene exposure.
Q. I am sorry, would you say that again, please?
A. The exposures are extremely small. I don't think they are of biologic significance.
Q. And what level is being reported there?
A. They range between .08 and .14 ppm, with a mean of .1 ppm.

Q. And does it report there when those studies -- when those samples were made in relation to when these people actually worked there?
A. (Reviewing document) It's contemporary with the study, but it's not historical data. It was taken at the time of the study.
Q. Historical data could be much more meaningful as far as being representative than something done by a government inspector coming in after the fact?
A. I think it depends on the characterization of what was going on in the plant with respect to operations in process. If, in fact, the process hasn't changed depreciably or the conditions of use, then I think you could take it to be reasonable representation.
Q. Do you know one way or the other what was done here?
A. It does not appear to me from looking at the ingredients that are used in the process that there would have been any drastic changes, certainly over the time that we're talking about.
Q. Do you know one way or the other?
A. No.

Q. For instance, you wouldn't know if the styrene that was received at that plant at one time before it was loaded into the barges to be transported was loaded in over a benzene heel, so that the styrene became contaminated with benzene? Have you ever heard anything like that?
A. I have heard descriptions of that sort: but by the same token, you have to look at what the range of benzene concentrations were associated with styrene. In any event, if you look at the pattern of neoplasms that were seen in this facility and the results of the study in these two plants, it's not consistent with benzene exposure.
Q. More consistent with butadiene exposure?
A. Well, it's inconsistent with any causative exposure. It does not follow the pattern for benzene.
Q. All right. The next article, Dr. Downs' report and others "Mortality Among Workers at a Butadiene Facility." Do you know if workers at that facility were ever exposed to benzene?
A. Well, I have said before, everyone is

exposed to benzene in one form or another.
Q. Touche. Occupationally exposed.
A. I am not aware of that.
Q. Would it matter?
A. It would depend upon the relationship between exposure and disease, whether or not that would have any impact at all. Certainly in the case of butadiene, there is no dose dependent relationship between the clustering of lymphosarcoma and butadiene exposure. I think that's been updated recently by Divine, Barbara Divine.
Again, I didn't have that in front of me: so, I just put that one in there.
Q. Would you know if there is any butadiene exposure in a tire manufacturing plant?
A. My understanding is there is very little.
Q. What's the basis of that understanding?
A. The nature of the chemical, nature of butadiene by the time it gets into a tire, its a polymer; and the out-gassing from tire manufacture I don't think is -- as I recall, the deliberations on the workshop at Research Triangle Park on butadiene, I think it was generally accepted by

most people present that that was not a major source of butadiene exposure.
Q. So, generally speaking, you are saying that tire builders and tire workers are not exposed to butadiene occupationally?
A. The initial compounding of the rubber polymer and in the manufacture of butadiene are potential occupation sources of exposure to butadiene, but I don't think tire manufacture is a significant occupational source.
Q. I missed the very first part. Are you talking about compounders?
A. The two places where there is potential exposure to butadiene is in its obvious production and in the manufacture of the polymer. Polybutadiene, butadiene-styrene, acrylonitrile butadiene, whatever. Those are the -- I think exposure to butadiene is relatively restricted.
Q. And that's not based on any sampling, it's discussions with others?
A. Yes.
Q. And you have here "Hazardous Materials Toxicology, Clinical Principles of Environmental Health," edited by Sullivan and Kreiger. Can you give me a summary of why this is here?

A. It's a book chapter that I was asked to write in that textbook on hematotoxicity.
Q. And I don't see the second page. Do you recall the date this was published? It may be in your resume.
A. It's '91.
Q. Hot off the press.
A. Hot off the press.
Q. In the interest of time, I won't try to go through all of this chapter. Do you relate in here at what exposure level you believe to be causative of leukemia for benzene?
MR. HALL: Let me object to the form of the question. Again, Herschel, you are using a general term to describe very specific diseases.
BY MR. HOBSON:
Q. You may answer if you can, Doctor.
A. I think you will find that in there I characterize the evidence that's available with respect to levels of benzene exposure that have been associated with an increased incidence of acute myelogenous leukemia. You have asked me that question before, and I think you will find

that statement in there just recounts what I said before.
Q. Did anyone assist you with this chapter?
A. No.
Q. I notice that you list the glycol ethers in your chapter. Where do you think we are causation wise with glycol ethers and leukemia?
A. We're not there. There are a lot of issues that are discussed in that book chapter that relate to incomplete or partial data in support or against various relationships between exposure and disease. The fact that it's in there does not mean that I accept it as a proven.
Q. Do you believe that there is evidence that supports causation of leukemias by ethylene oxide?
A. I think the ethylene oxide data is contradictory and confusing. We had some relatively poorly designed studies that suggested a relationship early on. The exposures were almost causaly described. We have had studies suggesting a relationship with lymphoid neoplasms, and we have had studies suggesting no relationship for leukemia or lymphoid neoplasms. I think there

are questions you can raise about most of the studies. Certainly in the aggregate it doesn't lead you to the conclusion that ethylene oxide has been established as a human leukemogen.
MR. HOBSON: Let me give you this book for copying.
BY MR. HOBSON:
Q. Dr. Irons, let me progress onward here, hopefully. At least onward in the day.
You have said that it is your opinion that high levels of exposure to benzene are causative of AML in humans. Have I got enough qualifiers in there to make you comfortable with that?
A. I can live with that.
Q. All right. What is it that has led you to that conclusion?
A. The sum total epidemiologic and clinical history of benzene, as well as our knowledge of the relationship between bone marrow toxicity and exposure to chemotherapeutic agents and secondary AML.
Q. When you write a chapter in a book like the one we just talked about and here's ethylene oxide and you assess the data, what's the

yardstick that you use for you, Dr. Richard Irons, saying I believe this relationship is established?
A. Obviously if you have access to reliable human data, it should be certainly a primary source of information. The problem that we have there is that epidemiology studies, quantitative studies that you can rely on and hopefully draw some relationship between exposure and the incidence of disease are extremely difficult to control and to conduct properly. They are very hard to test hypotheses because you can't treat humans and manipulate them like you can animals. As a result, it's very difficult to obtain a definitive quantitative epidemiology result unless you have got an overwhelming relationship or incidence of disease to a defined exposure.
As a result, you have to look at -- I look at the pattern. We have multiple studies. Do we see a consistent pattern? Do we see a pattern between exposure and disease that allows us to arrive at a general conclusion that there is a relationship here? It's also very useful when you have questions of this nature to be able to rely on mechanistic or animal studies to at least

determine whether or not there is a basis for that relationship, and whether what you see in epidemiology studies can be supported by mechanistic data.
In the case of benzene, we have a clear pattern. We have a clear pattern for AML, and I think we have a clear pattern in the occupational rubber industry to suggest benzene is not associated with NHL.
For the other two agents we are talking about, I don't think we have a clear pattern at all. We do not have consistency in the ethylene oxide literature. We have got some major questions that suggest that in these studies there are uncontrolled variables.
We also, as I said, have confounding results. We have the same picture in the butadiene epidemiology literature where we have inconsistent results. We have inverse relationships to exposure, and I don't think that one can draw a conclusion from the data as it currently exists.
Q. So, for ethylene oxide and butadiene, you are just not prepared to take a position one way or the other to say butadiene does cause human

cancers or butadiene does not cause-human cancers?
A. Well, if you take butadiene, for example, you have studies that would suggest a potential relationship with acute myelogenous leukemia: and you have studies that suggest there is a deficit. You have studies that suggest a relationship with lymphosarcoma that is not dose responsive, and then in other studies you don't see that at all.
In the aggregate, I don't know what to draw. In order to assume that butadiene is associated with any one of those diseases, you have to assume that butadiene exposure will cause different diseases in different people, and that does not make sense. I think it's more likely that we're looking at the artifacts associated with the difficulty of designing and conducting definitive epidemiology studies.
Q. I take it that there are some relationships that you would feel comfortable with saying, "no, I am convinced this does not exist'; and you gave me an example of your view of the rubber workers and non-Hodgkin's lymphomas?
A. Yes. That relationship for benzene, not for rubber workers.

Q. Yes.
A. I am not -- in fact, I think there is a pattern present that comes through the rubber studies that suggests there is a potential problem there, but I think that the data at the same time discounts the association with benzene exposure.
Q. But if we talk about butadiene, you don't see any studies that are as convincing as benzene and non-Hodgkin's lymphoma deficit in the rubber workers or that are as convincing as benzene and AML in other workers, in refinery workers, for instance?
A. I think I agree with you, but I'm not sure that I fully comprehended the question. Can I restate it?
Q. Surely.
A. If what you are asking me is does the butadiene literature provide the same basis for saying that butadiene is not associated with these diseases as the benzene literature and the rubber literature is, no, it does not.
Q. I guess just to kind of boil it down to layman's terms, your comfort index with saying that butadiene does not cause cancer, it's just not as high as it is in saying that benzene in

rubber workers does not cause non-Hodgkin's lymphoma?
MR. HALL: I want to enter an objection to the form of the question. Cancer is much too broad a term in the context of the case that brings us here today.
A. As a scientist, I have to rely on the rigor and reliability of the data that I have to reach a conclusion. In the case of butadiene epidemiology literature, that rigor and data is not sufficient for me to render an opinion that butadiene is associated with the development of leukemia or lymphosarcoma. By the same token, there is no data that I can rely upon to say definitively that there is no relationship. The evidence is just not there to make the case.
BY MR. HOBSON:
Q. When you talk about the rigors that you apply as a scientist -- I'm talking about now you, Dr. Richard Irons -- can you quantify that for me someway?
A. As I said, if we even had a reproducible consistent pattern of disease, it would be helpful, even if the exposure data was as

poor as it is; but we don't even have that. We have inconsistency. We just don't have reproduced -- we don't have reproducible studies on which to base a conclusion that butadiene is associated with either leukemia or with lymphoid neoplasms.
Q. But don't we have some degree of inconsistency even though for benzene and AML?
A. Inconsistency in what context? If you look at -- if you look at a variety of studies in the case of benzene with AML, the one thing -- you have inconsistency with respect to the magnitude of the increased incidence from one study to another. But where you have a relatively pure play on benzene, there is not much question about what benzene does.
Q. You have a relative what? I didn't hear the term.
A. When you have a relatively pure exposure to benzene. By that I mean where you can define benzene as the predominant agent you are talking about, I think the studies are fairly consistent.
Q. But not totally? I mean if you look at workers in the shoe industry in Turkey where there were high exposures, long-term, to benzene, you

don't always find predominating AML in those groups of workers, do you?
A. If you compare the incidence of hematopoietic and lymphoid neoplasms across the board for those that were in the shoe industry and are defined as exposed compared to those that have been collected and defined in Aksoy's studies as unexposed, you do see consistency. You see an elevation in AML in the benzene. You see a deficit of lymphoid neoplasms and CML and CLL in the benzene-exposed workers compared to whatever groups of controls he has put together.
Now, those studies suffer from problems of experimental design and ability to reconstitute what the criteria were that were used; but you have to remember that Dr. Aksoy is even predisposed to consider other malignancies as being caused by benzene. And his own data will support that.
Q. When you render your opinion as to causation, such as you have in this case, such as you did in your chapter of the textbook that we looked at, is more probable than not enough for you to say this material causes this disease?
A. Given a scientific evaluation of the

data and the studies that are available, more probable than not is sufficient. But in arriving at a decision as to whether or not the evidence in a given study is reliable or can be used in that context, I may apply a different standard.
Q. So, when you look at an individual study and you evaluate that study, more likely than not is not enough? It's a higher standard for you?
A. There is a difference between using statistical methodology to determine whether or not a study has sufficient power or reliability to distinguish between an exposed and an unexposed population or a difference in incidence. That is a separate issue than whether or not based on that study one can arrive at a conclusion that it's more probable than not that this disease was caused by this exposure.
Q. I didn't know if you were finished.
A. Yes.
Q. Dr. Irons, do you, in your work, utilize a term called "scientific certainty"?
A. Yes.
Q. What does that mean to you?
A. It means a number of things. It

depends upon the definition you want to place on it. Scientific certainty in the legal context I think has a different meaning than scientists tend to use it with respect to statistical analysis in establishing the power of a study to reach a certain finding. Reasonable scientific certainty to me in a legal sense means more probable than not.

If we're going to talk about uncertainty in experimental design, then we talk about statistics, and that's a separate issue. There is a difference between something being - if a study cannot statistically -- does not have the statistical power to determine the difference between two opposing conclusions, then the study is not useful in that context. You can derive no benefit from it.

If in the case of epidemiology studies you see consistent trends, even though you don't see enough power from an individual study, you can begin to draw some conclusion as to whether or not there is any association there at all. It's just not possible to determine with confidence because the power of the studies is too low.

But in the cases we're talking about,

we're talking about inconsistent and opposing results, not trends.
Q. In talking about statistical analysis, is scientific certainty arbitrary?
A. To the extent that a scientist should at the outside -- outset of an experiment determine what level of uncertainty he will allow within his study, yes. That's the whole -- that's the premise on which statistics is based.
Q. And what number do you pick in evaluating studies that you review when you look at scientific certainty of an epidemiological nature?
MR. HALL: I object to the form of the question because I don't understand it.
Dr. Irons, if you do, you can certainly answer it.
A. I am not certain exactly what you mean.
BY MR. HOBSON:
Q. Do you require that there be some level of statistical significance before you will accept causation in an epidemiological study?
A. I think most people feel as a general rule -- and it depends upon the design of the

study -- accept a confidence interval of .05, 5 percent error as a benchmark for determining whether or not something is or is not likely to be due to chance. That's a benchmark that's used throughout the medical-scientific literature.
Q. What do you choose?
A. I think for the most part that a statistic of .05 is a reasonable figure.
Q. That number, though, is an arbitrary picking, is it not?
A. Yes.
Q. And some scientists might choose .O1?
A. Which would be much more rigorous.
Q. Yes. And some might choose .9 -- or .1 I should say.
A. .9?
Q. .1, if we are being consistent with terminology.
A. .1, I think you could get a lot of argument as to whether or not .1 would be a useful statistic for most experimental design paradigms because of the problem of random error.
Q. You say "random error." You are applying random statistics, are you not?
A. The whole -- yes, for the most part

we're talking about nonparametric statistics. There are some types of tests in which you have to use parametric statistics, and they tend to be less stringent.
Q. If data is collected in a nonrandom fashion, applying random statistics to that data will give you -- is more likely to give you error, isn't it?
A. It all depends on the experimental design. If data is collected in a nonrandom fashion, that can often bias and/or critically flaw a study.
Q. And that's a major concern of researchers and scientists, is it not, the bias that can result from nonrandom sampling?
A. The whole purpose of statistical analysis is to reduce bias and to provide some uniform evaluation of the power of a given study to say whatever it says and what it doesn't say.
Q. Can't you, as a statistician, calculate for any given set of data what the statistical significance level is for that data?
A. Depending upon what assumptions go into it, yes, and depending upon the types of analyses you are performing, that can become an extremely

complex, complicated enterprise.
Q. Don't we see these days more and more trend in epidemiological studies to report the level of significance as opposed to picking an arbitrary value of .05 or .O1 and just saying it does or does not meet this value?
A. Within a range, yes. By the same token, it depends upon how you segregate and design your study. I think you can increase the power of a test and increase the significance of a finding and completely lose track of the biologic significance by lumping, for instance, categories that are biologically different. That is a - that's been a constant controversy or problem, if you will, certainly in the hematologic field, where there is a tendency on the part of the epidemiologists to lump tumor types and there is a tendency on the part of hematologists and those of us who study the mechanisms of disease to separate them because they are biologically distinct.
Q. Or at least thought to be biologically distinct?
A. I think there is a lot of hard evidence to suggest they are.
Q. I guess in the abstract neither one of

us know what we're talking about now.
How many times have you testified this year, either in deposition or at trial? And I would like to know in what cases; so: if you could recite them as you count them, it would help.
A. I testified in Carter, Riddle, and Slueter in Roanoke, Virginia.
I think I gave a deposition in the case characterized as Chambers.
Q. Pending in Texas?
A. It settled.
Q. But I mean it was pending -
A. Yes.
Q. It was a case in Texas?
A. Yes.
I think that may be it.
Q. Two depositions or trial testimony in 1991 besides this deposition?
A. Yes.
Q. How about '90?
A. Two or three depositions in '90.
Q. Do you remember the names of the cases?
A. Buchaj.
Q. I am sorry?
A. Buchaj.

Q. With a "B"?
A. B-U-C-H-A-J.
Q. Where was that pending?
A. Los Angeles.
Little.
Q. That's a Texas case?
A. Yes. I gave a deposition in a case
Anschutz, A-N-S-C-H-U-T-Z.
Q. And where was that pending?
A. It was pending in Missouri. I think
that's it.
Q. No trial testimony in '90?
A. I testified in a case called Jones.
Q. And where was that, please?
A. New York.
I testified in a case called Mason, I
don't know what year. I think it might have
been -
Q. In Kansas?
A. Yes. It was in '90. I think it could
have been '89, end of '89.
Q. What other cases can you recall giving
depositions in or trial testimony?
A. I think we have just about exhausted
it.

Q. You were in Skeen.
A. Skeen.
Q. Any others out of that Monsanto plant that you were deposed in?
A. (Shaking head)
Q. You will need to answer orally.
A. No.
Q. Have all of these cases been benzene cases?
A. No.
Q. Which ones were not benzene cases?
A. Jones is not a benzene case, and Anschutz was not a benzene case.
Q. What was the causative agent there or putative causative agent?
A. Jones was putative agent to chlordane.
MR. HALL: I am sorry?
A. Chlordane and heptachlor. Anschutz was a civil CERCLA case.
BY MR. HOBSON:
Q. May I ask how much you were paid for your work in Carter, Slueter, and Riddle?
A. I haven't seen that yet. I don't know. I can't tell you.
Q. You don't know?

A. No.
Q. How is it that you couldn't know?
A. I haven't been paid yet. I don't recall what I have in billing.
Q. Can you give me an estimation?
A. No.
Q. Could we leave a place in your deposition and ask you to look?
A. I'll have to wait until the billings come in because I really don't know at this point.
Q. When you say you need to wait for the billings to come in, I'm not sure I understand.
A. I have billed the client for my time in that case. I have done it over a series of two or three times, and I have yet to see it all added up.
Q. Is there a time in which you expect to be paid?
A. Ideally?
MR. HALL: You took the words out of my mouth.
A. I would expect to be paid by the end of the year, but I am not clairvoyant.
BY MR. HOBSON:
Q. Have they been invoiced?

A. Yes.
Q. Would it be possible for you to add up your invoices for me and indicate the invoiced amount in your deposition when you get it to read and review?
A. To the extent that I can -- I can put that together, I could try: but I can't guarantee if it's accurate.
Q. If you could do the best you could with what you have been paid and what is invoiced but not paid, if you could give me a total figure at this point in the errata sheet, I would appreciate it.
A. I will try to.
MR. HALL: So that we're clear on the record, Herschel, "paid" has a different connotation than reimbursed. He may have invoiced travel and hotel and meals and whatnot. Do you wish to include that or not wish to include that?
MR. HOBSON: Time for services rendered.
MR. HALL: Thank you.
BY MR. HOBSON:

Q. I should -- one more thing, too. I know that you had a bunch of exhibits when you showed up at Roanoke. Were those yours or someone else's?
A. Some of them were mine: some of them, I think, are still technically the property of Monsanto.
Q. Those were used in the Skeen case?
A. Yes.
Q. Which one -- which ones of the exhibits were yours?
A. All of the photographs were mine.
Q. The microphotographs?
A. (Nodding head)
Q. Photo micrographs.
What else?
A. Some of the illustrative material is mine. The exhibits on stem cell differentiation, hematopoiesis, are the property of Monsanto.
Q. How about the bone?
A. I think I have been made a gift of the bone, although I think there is some question as to its ownership. I think it -- it certainly is in my possession. I will put it that way.
Q. can you give me an estimation of how

much time you have spent on this case to date?
A. I haven't added it up yet. I'd say that it's going to be somewhere between 20 and 40 hours.
Q. And would you give me your current billing rates?
A. $300 an hour.
Q. .Is that irrespective of what you do as far as deposition or -
A. For litigation consultation it's $300 an hour, irrespective of what I am doing.
MR. HOBSON: Take a break.
(RECESS)
BY MR. HOBSON:
Q. Dr. Irons, have you had any meetings or conversations with any other experts in this case?
A. Yes, on the 21st of November in Denver.
Q. And with whom did you meet?
A. Dr. Wallerstein, Dr. Bickers -- is that correct? Did I get that right, Bickers?
MS. ARRAS: Yes.
A. Dr. Wong, Dr. Thomas. I think that's it.
BY MR. HOBSON:
Q. Is it still your view that there need

not be a clinical manifestation of aplastic anemia or some predisposing of -- predisposing blood condition before benzene can be causative of AML?
A. I think that is a misrepresentation, to the extent that I have said repeatedly that the literature and the opinion of most hematologists is that the prevailing preservation for secondary AML, whether it's benzene or not, is almost always associated with some preleukemic phase. I have said that on the basis of mechanistic studies that it would be impossible to rule out that you couldn't have a manifestation at the level of stem regulation that might not be demonstrable or reflected in a peripheral blood abnormality. I still don't know of any evidence to suggest that it occurred, but I personally can't make a strong statement as never.
Q. Did you discuss this aspect of AML and benzene with Dr. Wallerstein?
A. I don't recall whether we talked about preleukemia or not. I don't recall. I doubt we did per se.
Q. Do you know his view?
A. Directly, no.
Q. Or indirectly.

A. Well, I wouldn't be surprised if he doesn't hold to that as certainly an important criteria.
Q. That being the establishment of a preleukemic stage before -
A. Many hematologists will tell you it's an absolute requirement. I'm just not prepared to say it's an absolute requirement, although I don't know of a single case where it hasn't been established.
Q. If you found a situation where there was a heavy exposure to benzene, by your definition, and an AML without a preleukemic stage, would you automatically rule out benzene as the cause because there was not a preleukemic stage?
A. I would not, but I also think that exposures that will lead to leukemia involving more than one individual are very likely to produce demonstrable bone marrow suppression and hematologic abnormality.
Q. Would you have any opinions regarding being cured of AML?
A. A cure?
Q. Yes. Are people cured who get AML?

A. Prognosis for AML is quite dismal.
It's not as bad as CML.' but certainly in terms of
chemotherapy, the cure of AML is only a remote
possibility. With the advent of bone marrow
transplantation techniques, there is an increase
survival rate amongst individuals who have been
successfully transplanted, whereas before,
certainly in the case of CML, prognosis was almost
defined at diagnosis.
Q. But the prospect of a cure of an AML is
not good?
A. No. None of them -- they are not
diseases you would wish to have. The prognosis
for CML is worse than AML, although the
progression is slow.
Q. What about the prognosis for NHL,
non-Hodgkin's lymphoma?
A. Its varies with the particular
histological presentation, but the prognosis in
some categories can be called good.
Q. How about for the three gentlemen who
now survive, would you render any opinion on
prognosis for these folks?
A. In the case of Mr. Lilly, I believe he
is in complete remission. From what I have read,

that may, in fact, be the case. Whether or not -- I can't -- I would have to review the data on these individuals to discuss prognosis in any greater detail.
Q. So, even though Mr. Lilly is in remission now, you cannot say what the prospects would be for him staying in remission without reviewing the records further?
A. I don't know how one is clairvoyant when someone is in remission. I mean he -- I wouldn't want to comment on prognosis without reviewing the records again. I haven't looked at them with that in mind and I haven't really considered it in sufficient detail to give a responsible answer.
Q. What was the occasion that you and the other experts met? What brought that about?
A. I think the -- well, the principal - principal of the meeting was called by Ms. Arras and colleagues: and I think we all welcomed it as an opportunity to see some of the monitoring data and see the layout of the facilities that are in question. That was the principal reason for the meeting.
Q. And about how long did it last?

A. I'd say four or five hours.
Q. Do any of your opinions that you have expressed rely upon the opinions of the other experts in this case, or do your opinions that you have expressed stand independently of theirs?
A. They stand independent.
MR. HOBSON: I appreciate your patience. That's all I have got. Thanks, Doctor.
(THE DEPOSITION WAS CONCLUDED)