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Department of Health and Human Services

October 19-20, 2000

Day One

Conference Center

Hilton Palacio del Rio

San Antonio, Texas

ATTENDANCE

Committee:

Robert W. Harrison, M.D., University of Rochester, **Chairman**

Michael A. Stoto, Ph.D., George Washington University

Michael Gough, M.D.

Robert C. Stills, Ph.D., NIEHS

Paul R. Camacho, Ph.D., University of Massachusetts-Boston

Steve Selvin, Ph.D., University of California-Berkeley

Ronald F. Coene, P.E., Deputy Director, NCTR,

Exec Sec of the Committee

Barbara Jewell, NCTR, **staff**

Air Force:

COL Harry E. Marden, M.D., Brooks Air Force Base

LTC Karen A. Fox, M.D., Brooks Air Force Base

LTC Bruce Burnham, Chief of Population Research

Dr. Joel Michalek, Principal Investigator

Attendees:

Debbie del Junco, UTSPH/Houston

Angela Garzon, UTSPH/Houston

Dr. Judson Miner, Program Management Support

Manuel A. Blanca, Program Management Support

Meghan Yeager, SAIC

William Grubbs, SAIC

MAJ Jack Spey (Ret.) Ranch Hands Vietnam Association

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P R O C E E D I N G S

[8:11 a.m.]

DR. HARRISON: Good morning. I'm Bob Harrison, chairing this session. We are missing one committee member, Mike Stoto, who like Elvis, we know is somewhere in the building -- he's been sighted.

(Laughter)

-- and we assume that he's somewhere down in the basement or subbasement, wandering around wondering where the conference rooms are. And he'll eventually ask someone and show up.

In the meantime, though, I thought we'd get started, and first of all I'd like to say how happy I am to still be a participant with the Air Force in this, what I think is one of the more interesting health studies that I'm aware of -- but then I'm relatively unaware of most things.

At the beginning, because we have a few new players I think on both sides, maybe we could start off by just a two sentence statement about ourselves; and just go around the entire table, include everyone unless you deliberately wish to remain obscure.

I'm Robert Harrison, I'm Professor of Medicine at the University of Rochester in Rochester, New York. My scientific interest is in the mechanisms of action of steroid hormones, but I do a significant amount of clinical care and clinical research.

We'll just go around this way.

DR. GOUGH: Okay, I'm Mike --

[Dr. Stoto arrives.]

DR. STOTO: I got carried away on the Riverwalk this morning.

DR. GOUGH: I'm Michael Gough. First of all, I want to say I was here for five years and when I was here before, we brought Bob Harrison on to straighten us out about the relationship between dioxin and diabetes, and I read in the minutes from the last meeting you hadn't done that yet.

(Laughter)

What's going on?

DR. HARRISON: It just shows, you can fool some of the people some of the time --

(Laughter)

DR. GOUGH: Anyway, I'm a semiretired consultant and I've been involved with Agent Orange since 1980.

DR. SILLS: My name is Robert Sills. I'm a pathologist with the National Institute of Environmental Health Sciences. My research is in carcinogenesis and toxicology studies with the National Toxicology program.

DR. CAMACHO: My name is Paul Camacho, and I'm with the William Joiner Center at the University of Massachusetts. I'm a sociologist, I'm into surveys and a lot of MIS and IS. I'm trying to do decision-making systems, computer systems.

LTC BURNHAM: I'm Bruce Burnham, a veterinarian with a Master's in Public Health, and I'm the military face on the scientific side. Generally we rotate through every three years, and I've been here for a year now.

LTC FOX: I'm Dr. Karen Fox, I'm with the Air Force, and I'm an occupational medicine physician. And I'm getting involved. I don't know if I'm representing Colonel Marden or not, because I expected him to be here, but I may be doing that. I work for him.

DR. MICHALEK: I'm Joel Michalek, Principal Investigator of the study. I have a doctorate in mathematical statistics. I've been with the study since the beginning, 1976.

DR. MINER: I'm Jay Miner, former principal investigator, been with the study since 1985; after I retired from active duty I came back to the program management side of the house, and I'm a contractor now doing acquisition support, making sure that all the science that Dr. Michalek wants gets on contract and gets done.

DR. SELVIN: I'm Steve Selvin, from the University of California at Berkeley. I'm a biostatistician-epidemiologist, and I've been on the project about 15 minutes.

(Laughter)

DR. STOTO: I've been here less than that this morning; but I'm Mike Stoto from George Washington University. I'm an epidemiologist and biostatistician as well. Before I had that job I worked at the University of Medicine and did a lot of the Agent Orange work there, too. So I'm involved with the study from that perspective.

MS. JEWELL: Barbara Jewell with FDA, and I work with the advisory committee, with Ron.

MR. COENE: I'm Ron Coene, and I'm the Deputy Director for the National Center for Toxicological Research of the Food and Drug Administration. And I serve as the Executive Secretary to this committee. For a couple of you who are new, back in '79 the Department was named to oversight this committee, oversight this study, and they passed the baton around the various components of the Department of Health and Human Services to support this function.

So that people wonder why it's I the Food and Drug Administration; well, ten years ago, eleven years ago -- eleven years ago I had a director who was on the sixth floor of the HHS building who said "Sure, we'll do it." And that's how it ended up at the National Center for Toxicological Research. So we've been at it since '89.

DR. HARRISON: How about going back down the wall this way, then?

MAJ SPEY: My name is Jack Spey, I'm a retired Major, President of the Ranch Hand Vietnam Association. I served over there for three and a half years and I've worked real closely with the members of the Air Force Health Study.

MS. YEAGER: I'm Meghan Yeager, from SAIC.

DR. GRUBBS: Bill Grubbs, SAIC. I've been supporting Dr. Michalek and the Ranch Hand Program since 1985.

DR. JACKSON: I'm Billy Jackson, a statistician who works for Dr. Michalek.

MR. BLANCAS: And I'm Manny Blancas, I'm a contractor working alongside Dr. Miner on the program management side of the house.

MR. COENE: All right. We're here, we'll be passing around, if you haven't already done so, a sign-in sheet so we duly record all of you here, as it is a public, open meeting. We don't, other than Jack -- you're the only public we have, again.

You should know you have a whole hour on the agenda tomorrow.

(Laughter)

DR. HARRISON: Well, at any rate, we're glad to have you.

MR. COENE: Thank you for showing interest and being here.

DR. HARRISON: Okay. So we're complete, we're ready?

Joel, it's in your hands.

Overview of the Air Force Health Study

[Slide]

DR. MICHALEK: Good morning, members of the committee, and friends. I'm Joel Michalek, and this is an overview of the Ranch Hands study. I estimate this will take approximately 45 minutes to an hour; and I'm expecting that people will interrupt me and ask questions, because that's the best way to present this material.

Can everyone hear me okay?

MR. COENE: You're fine, Joel.

DR. MICHALEK: I need to stop right here and talk about the opening slide a little bit. You probably ought to know this; the official name of the study and the protocol is The Air Force Health Study. However, it has another name which everyone knows, the Ranch Hands call it the Ranch Hand study; it's also called in the federal budget, the line item for this study in the federal budget is *Ranch Hand II Epidemiology Study*. So there are a number of names associated with what we do here.

And the work, by the way, there's a whole raft of people here that are supporting everything you see; they're all back at the base. Some of them are here today. We have really two parts to the organization that make this study work. We have the program managers that keep us funded and keep us legal to all of the just raft of papers associated with contracts and purchase orders and whatever else goes along with committing federal funds, and then there's the group that actually conducts the study; that's where I work. This is represented on the last two lines.

And by the way, I have handouts.

[Passing documents out] Every slide that I'm going to show is on those sheets.

And what we'd like to do when this is over is to put all these slides on our web page so you can get to them back home anytime you want to.

Here comes Colonel Marden, another investigator in the study.

What I have to do is two things: First, you have to know that what I'm trying to do here is get you to put your arms around the whole thing; and then later today and tomorrow we'll get into some topics in much greater detail. So we're going to be touching on things here very lightly just so you will see everything. And in so doing, I have to cover some things very lightly; but I'm sure you'll have questions, so you're free, of course, to stop me anytime, to make a note and get me later or send me an e-mail after this is all over with, or whatever you want to do, and we can operate that way.

[Slide]

So why are we here? We sprayed approximately 19 million gallons of herbicide in Vietnam between 1961 and 1971. That led to concern by veterans subsequent to the war; I think the key date was sometime in 1975, a claims clerk at the VA Hospital in Chicago called the newspapers to report her concern that she was seeing excess symptoms in Vietnam veterans.

That led to a lot of things, as you recall from those years; it led to in particular congressional hearings. A key hearing in 1980, attended by the Deputy Surgeon General of the Air Force, statements were made by him to be responsive and committal of Air Force resources to study the issue in the men that sprayed this material in Vietnam, the Ranch Hand veterans.

And it was from that point forward that we mark the beginning of the study. Actually, prior to that phone calls were made to Brooks Air Force Base for us to begin contemplating an Agent Orange protocol, and so we began the technical side of the issue of writing a protocol in 1976 -- but I'm getting ahead of things right here.

Here's a slide, Contents, that we're going to talk about; why are we here and where did all this come from? With an overview of Results, an overview of our publications, and the recent GAO report, recently expressed veterans frustrations that we're going to talk about, and how we can address those. And some suggestions on those frustrations right there, and some pictures of our facilities.

[Slide]

So here's the goal, of course. The epidemiologic template was applied; namely to ask the question, did we harm any of our Ranch Hand veterans in any way -- and 'any way' means health, mortality and reproductive outcomes, by means of their spraying of the herbicide which we found out, subsequent, after the war -- actually late in the war -- much of it was contaminated with dioxin, also called TCDD.

[Slide]

Here's a slide representative the key documents that launched this study. There was a letter from the White House to the Secretary of Defense, I believe, or Secretary of the Air Force directing the Department of Defense to conduct this study. And that letter is in my file, dated 16 September 1980, from Stuart Eisenstadt, Domestic Policy Counsel to the President.

Prior to that of course were the hearings that I have already described. That produced a funding element in the federal budget specifically devoted to this study; and that, by the way, is the reason why we're all here today,

that this study has dedicated funding. And we all know how hard it is to maintain funding over a long period of time in any study, but we've been fortunate in that regard.

Since then there's been a public law in 1990 to structure the committee that we see here today to allow and ensure veteran participation.

[Slide]

We have points of contact at the Pentagon in Washington and at Brooks Air Force Base regarding our contracting. And I have a pointer.

[Slide]

We have, I already talked about our program mangers; and you'll see some pictures later on. We have about 30 people, 35 people working on the study today of which ten are civil service, two active duty military, one of which is right here. Programmers, statisticians, medical coders, scanners, student aides, whatever it takes to do a study of this scope and duration.

[Slide]

It's a multifaceted operation. Here's us, here's my group right here in Brooks Air Force Base, technical side, and here's the managers you see here today. It's an enormous effort. It could not be done at Brooks Air Force Base by us; the physical examinations I'm going to talk about are done in California, those are overseen by our prime contractor, SAIC Corporation, which is right here, and those physical exams are conducted at Scripps Clinic and the interviewing is done by the National Opinion Research Center of the University of Chicago. Those are all subcontractors to Science Applications International Corporation.

Those contracts are managed by these two individuals who are sitting here today, Dr. Jay Miner and Manny Blancas, along with Major Kyle Sneddon.

Then our technical side of the study, I have myself, the other statisticians of which one is here today, the other investigators, back up here we have Program Support, it

interfaces with Congress and our money and funding at the Pentagon, and we have interface with CDC, NIH, the EPA and NIEHS, among others, and Department of Veterans Affairs, other government agencies we talk to and communicate with all the time about our study.

And we have our Advisory Committee that's sitting with us today, and other support contractors that keep us going in-house; namely our statisticians and scanners.

To date we have spent about $150 million on this study, since the beginning.

[Slide]

Well, here is the beginning. Roughly 1976, 1977 -- that was when we were asked to drop everything and begin to concentrate on writing an Agent Orange protocol. There was a peer review process that took place between 1977 and 1981, before the National Academy of Sciences, the Armed Forces Epidemiology Board, the Air Force's Scientific Advisory Board, and others during that period to refine the protocol which was made final around it, beginning of 1980-'81, and that was the basis for the first physical examination, that occurred in 1982 at Kelsey Seybold Clinic in Houston.

The protocol is available on our web page. In fact, almost everything I'm talking about today is on our web page, and the web page address is on the last slide of your handout.

Protocol, as you see, called for periodic physical examinations of the study subjects and their controls roughly every five years with a sort of break in the pattern here in '85. The pattern was '82, '87, '92, '97, and the last physical is programmed for the year 2002. Now we had an extra physical here in '85.

I think it's important and significant but often forgotten that the environment in which this study was contemplated was one of fear. The fear was that not only had we lost the war in Vietnam, that we had poisoned our own troops. That fear is represented right here.

I can't communicate very well except the following way: In 1984, we gave our first press conference at the Pentagon on our first mortality study of the Ranch Hand unit. At that time the overall Ranch Hand -- and since then, in fact, the overall mortality is nearly identical, Ranch Handers to the controls.

And we have a video of this press conference. It was a room three times this big, just packed with television crews, newspapers, lights, public, commotion, talk, and I'm up here presenting slides like I am today of the results of our first mortality study.

So to a statistician it's pure vanilla, hardly anything happening. Relative risk 1.0, back in '84. We were showing a Kaplan-Maier survival curve, which was probably too sophisticated and too detailed for that audience, but I didn't know that at the time. So I'm showing a Kaplan-Maier survival curve. The Kaplan-Maier curve has little steps, smooth, comes down. Every step is created by a death; that's how steps occur.

So someone from the audience, after I gave the results, asked: What's that little jump in the curve right there? Why does it go in those little steps? I said "Well, that's because somebody died." And as soon as I said the word die, the room fell silent. You could hear a pin drop. There was no overall effect. The relative risk was 1.0, but that's the environment we were in in 1984. That's the environment we were in in 1976 when the hearings took place that led to this study.

That's why we did this extra physical in '85. We expected the Ranch Handers to be expressing acute effects. We wanted to catch it so we could intervene and help them. That's the spirit of this pattern right here; that's where it came from.

In fact, we worry about that. How often should we have these first few physicals, to catch the effect, to intervene if we had to? [Slide]

So what do we have? We have applied the standard epidemiologic template to a problem of unprecedented scope and complication. We've had 1261 Ranch Handers who ever existed. 26 were killed in action, 50 or so had died of natural causes before the first physical examination. There were 1208 eligible for the first physical in 1982.

We had a population of Air Force veterans who were in Southeast Asia during the same time period, but had nothing to do with spraying agent Orange. They were flying C130s and servicing -- they were the air and ground crew for C130 aircraft that were used for all kinds of purposes, such as cargo, air-sea reconnaissance, air-sea rescue, whatever. The C130 was used for a lot of things. It was not used for spraying herbicides.

That's the population of 19,080 that have in our control population. We have a matched design where about 10,000 of those are matched on a one-to-many basis to these Ranch Handers. Matched on date of birth, military occupation, race.

So we have up to 8 to 10 Ranch Handers.

[Two women enter the hearing room.]

This is Debbie del Junco, University of Texas at Houston, and Angela Garzon, one of her students, who we invited.

Matched up to 8 to 10 comparisons per Ranch Hander on those variables that I've just mentioned; officer matched to officer, enlisted flyer to enlisted flyer, and so on.

In each matched set, those individuals were randomized, in random order. And after randomization in the first position, was invited to attend a physical examination in 1982, along with his respective Ranch Hander.

So at the beginning it was designed to be a 1:1 matched design. Subsequent to that, when an individual such as a control refused to come or became noncompliant, he was replaced following a strategy that's defined in the appendix of the protocol.

The idea was, we were afraid that we were going to lose a large proportion of our comparison group due to noncompliance and lack of interest. We expected -- you'll see in our protocol -- we were expected to lose 50 percent of our controls in the first few years of the study.

So with our advisory committees and with approval and through peer review, we devised a replacement strategy such that an individual who becomes noncompliant is replaced by an individual from the same matched set who has the same perception of health as the one who refused.

The refusal says I'm in excellent health; we look for another comparison in the same matched set that reports excellent health. That's the replacement strategy.

If that match can't be made, there's a scale; excellent, good, fair, poor -- then it's dichotomized: excellent to good, fair-poor. Then if we can match them on a dichotomized scale, we'll do so. If we can't match at all, we don't replace.

So it's with that strategy that we built into the protocol, we attempted to compensate for the expected losses in the control group.

Well, it turns out we didn't realize the losses that we expected; the compliance has been very good. But we still have our replacement strategy today.

DR. MINER: Once invited, always back.

DR. MICHALEK: Yes. There are more rules; we don't replace dead controls, and once a control is invited, he's always invited, for the rest of the study. Everyone is always invited back.

[Slide]

So what is the epidemiologic template? In principle it's very simple. You must define an exposed cohort and you must be thorough and you have to ascertain an exposed cohort. You don't want to take the people that walk into a clinic, for example. We have a roster. We know exactly all the Ranch Hands who ever existed. They were all identified and all living Ranch Handers were invited.

And we have a full ascertainment of our comparison group. Separately, the rest of the template is to devise an exposure index within the exposed group. What we're looking for here of course are group differences on health, and within the exposed group we're looking for a trend; we want to see the individuals with high exposure, higher risk than individuals of lower exposure.

The exposure index is the problem, of course. There was no dosimetry in Vietnam. In fact, when the herbicides were sprayed in Vietnam, we thought they were safe. We told them it was safe. No dosimetry.

The issue arose in 1976-77 after the war had ended. In other words, when you have a pattern, we have a scenario here similar to what happened with the Gulf War.

What made this study work, and what made all Agent Orange studies work, is the fact that the contaminant has a very long half life. We can measure it in the blood today, even 30 years after the exposure you can see it in the blood, because the half life is so long, it's so persistent. And it was because of that we were able to construct an exposure index that we had confidence in later on.

But at the time you wrote the protocol, the exposure index was contemplated to be based on military records and gallons sprayed in Vietnam, that I'll talk about in a minute.

The study's unprecedented scope: What was epidemiology before the Ranch Hand study? The classic example was the British article, I guess 1953, Hill and Pito, I guess. -- Hill and Dahl. It was on smoking in physicians in England.

They collected smoking information by questionnaire from physicians in England. And they looked at lung cancer. They had a well-defined exposure, they had a well-defined end point. The results were clear as a bell.

There was a significant trend; that is the classic paper. That is epidemiology. That was epidemiology before this study came along.

What do we have in this study? Number one, we don't know what we're looking for. The veterans were complaining of heart disease, of cancer, anxiety, birth defects, diabetes, skin conditions, you name it. There was a list.

It was that, the list of conditions by the way, came from the Department of Veterans Affairs. That was used to devise and design the first physical examination, to address all of those conditions. That was unprecedented.

Secondly, we didn't even know what the dose was, because we didn't have any data; except that the overall amount of herbicide spray in the whole country, we didn't have any data specific to the individual; we only had global information of the whole country of Vietnam.

So we were in unprecedented territory here. As another example of the environment in which this study was conceived, we nevertheless had the mandate to proceed, and we did. We applied the standard epidemiologic template, and as you'll see, with some great success, because of certain things that happened along the way technologically.

We had multiple endpoints, no believable exposure index at the beginning; and you'll see we applied the standard epidemiologic template for physical examinations, interviews, mortality assessments; and really an unprecedented effort to collect quality information.

[Slide]

Here are some numbers to show you what kind of compliance we've had from the beginning. Here are the number eligible, here are the number that actually complied with the physical examination on the Ranch Hand group and on the comparison group. And you'll see about 80 to 85 percent of the Ranch Hand group have been compliant, and about 75 percent of the control group have been compliant.

This is beyond our expectations when we wrote the protocol, that we would see such compliance. It also puts this study into a round of -- and you have to view a lot of studies -- this is probably one of the best studies ever done, from many points of view.

[Slide]

These men live all over the country. Right now the physical exams are done at the Scripps Clinic, California, first physical done in Houston, Texas. Our prime contractor is in Virginia and in San Diego. And our National Opinion Research Center from Chicago are here at Brooks Air Force Base.

We literally move 2300 men to California every five years. We purchase 7500 room-nights at the La Jolla Hilton every five years. It's a massive effort.

When we conduct physicals, when we move -- transport and physically examine 2300 men at Scripps Clinic, we do that over a ten month period, and we spend about $16 million doing it.

In a year in which we're not doing physicals, we're spending about $5 million on salaries and overhead to support the research activities at Brooks Air Force Base.

[Slide]

These are the words I've already said; no dosimetry, unprecedented scope. We expected great loss to follow up in compliance; that was not realized, fortunately. We have a matched design to replace strategy, and great concern about exposure excess than credibility.

One of the objects -- let's talk about this for a second. This was mentioned at the Shays hearing before the House Government Reform Committee hearing earlier this year. Another point that's important but often forgotten, one of the items on the table in 1977 and '78 was that the Air Force should not do this study, that someone else should do it.

And that was on the table in front of every advisory and overview and peer review committee until the very end, when it was decided by our peer reviewers that the Air Force should conduct the study. Why? Because it was a compelling need that this study be launched immediately and the results be obtained as soon as possible. And the Air Force had the resources and the knowledge to do that.

[Slide]

Design and analysis, there was a lot of argument at the beginning about what the control group should be; and that's still facing us today. Scientifically, of course, what you want as a control group that is the same in every way as the exposed, except for one thing; and that's the exposure, of course.

There was concern about the possibility that if we had a control group that was stationed somewhere else other than Vietnam, then we would hopelessly confound the study with effects of tropical diseases and all the rest that goes along with being stationed in a war zone in the tropics.

So the decision was, we'll use controls that were stationed in Vietnam during the same time period that the Ranch Hand unit was active, and they will be Air Force controls because of the known differences, the subtlety differences, anyway, because the different services. In other words, Army troops were out of the picture here.

So we have a control group of, like I said, Air Force veterans who were in the area during the same time. It was contemplated during that period, and on the table, by the way, to study the control groups stationed in Europe.

Now today, looking back, having attended some meetings on Gulf War, we now realize the benefit of having multiple control groups, and future studies will have multiple control groups. Such as a control group deployed and a control group non-deployed, and a civilian control group. All those things are being talked about today about future studies. When this study was designed in 1976, this was the idea.

[Slide]

We worried about all of these things on the screen here, and I'm going to talk about many of them today.

In the protocol you will see a formulation of an exposure index based on the number of flights that took place during that fellow's tour. The number of gallons sprayed, the number of days on the job, concentration of dioxin in the herbicide. That was the idea written in the protocol.

That idea was immediately discarded, as soon as the study started, because we realized that we didn't have the data. We didn't have data specific to the individual, so this was scrapped. And what we settled on was an index which was simply the number of gallons sprayed in Vietnam during that individual's tour, times the concentration of the contaminant in the herbicide, which we knew, divided by the number of persons on the job, thinking that, as we threw more men on the job, "Well, gosh, the exposure must be increasing."

Well, actually the exposure must be decreasing, because there were more men there and they'd be sharing the same amount of work. But we found out later that's a pretty lousy assumption; that what really happened on the job was when you threw more people on the job, just more people got exposed, that's all. And so by requiring that the exposure index decrease with the number of people on the job, we were probably committing a mistake.

And as you'll see later, we confirmed -- or we have data to support the idea that this is a pretty poor index.

In 1986 we were invited to a meeting at the Office of Science and Technology Policy, sponsored by OSTP, where we met CDC for the first time. Dr. Don Patterson, Larry Neil, and Eric Sampson. They had devised an assay for dioxin in human serum that was as good as and equivalent to assays that had been done before that in adipose tissue for dioxin.

We launched a pilot study; we sent 150 of our Ranch Hand veterans to three Red Cross clinics in the United States and 50 controls. And we measured, and we drew blood, and we measured dioxin in their serum. And that's published in MMWR 1988, I believe.

The study worked. We found a significant increase of dioxin body burden in the Ranch Hand veterans, which number one validates the idea that the Ranch Handers really were exposed, and as you'll see later, validates a lot of things.

So that was our first experience with the new technology, which was to measure the contaminant in the blood of these men. That was a breakthrough.

[Slide]

Here is a picture showing where the Ranch Handers stand relative to other cohorts. Now there's a lot of caveats associated with the picture, which is what I got from CDC. Here are the Ranch Handers right here in this light blue color, here are the controls, and I broke out by the five occupational categories: non-flying officers, flying officers and so on are listed non-fliers.

Here are the subgroups of the Vietnam Experience Study. The Vietnam Experience Study was intended to be a sister study to this one, based on Army troops. The study consisted of a cohort of Army troops that went to Vietnam and had opportunity for exposure, and a cohort of Army troops that didn't go to Vietnam that of course had no exposure.

They used the same physical examination, they were supposed to follow the same drill we did with repeated physicals and questionnaires. That study was stopped after the first physical in 1987. The reason being that when they assayed them for dioxin, they found background levels in both the exposed group and the controls.

Now as we see today, I regret the decision to stop that study because it has contributed to veteran frustration today. But nevertheless there they are.

[Slide]

And here are the Ranch Handers, measured at the same time approximately, 1987, as the veterans in this Vietnam Experience Study.

Here are the individuals in the NIOSH industrial cohort study. Those are men who worked in factories in the United States that made herbicide. Those men were exposed over roughly a 20 or 30 year period working in industrial factories here in the United States, in chemical plants. They actually have higher levels.

Those levels were collected from blood drawn roughly the same time period, 1987, and I have to keep telling you the time period, because remember, as an individual is dosed, he will eliminate the dioxin from his body due to first order kinetics; so the amount in your body today, if you were exposed ten years ago, is less than it was ten years ago.

And here are two other cohorts of German plant workers which are widely published, and New Zealand herbicide sprayers.

Down here are the individuals who were victims of an explosion of a chemical plant in Italy in 1976, at Seveso, where a number of individuals received up to twenty to thirty thousand parts per trillion. And by the way, the highest level in the Ranch Hand group today is about 660 parts-per-trillion. The highest level in the cohort of the NIOSH study -- well, these are medians. The highest level is further out, is about 3,000 parts-per-trillion.

A parts-per-trillion is 10^{-12}, which is equivalent to 1 second in 32,000 years or 1 dime in a stack of dimes from here to the sun. CDC can measure that level of contaminant in the body with the same level of accuracy that Scripps Clinic measures insulin; in other words, with a cv of about 9 percent. That is a tribute to the chemistry at CDC, as you'll see in a few minutes.

The caveat here is that these measurements on the Seveso victims were made from blood drawn just a few days after the accident. The caveat here is that these measurements were made from blood drawn in 1987, which is up to 15 years after exposure. So you have to remember that when you look at these slides; that these men, especially our Ranch Hand group, had an initial dose we think that ranged up to about 3,000 parts-per-trillion when they were in Vietnam. Which is still only about a tenth or less of the exposure received by the victims of the Seveso accident.

Remember also then, although the levels in Seveso are very high, the cohort is very small. There are three zones in Seveso; Zone A, B, and R. Zone A received the highest levels -- it's not labeled here, but there are a couple hundred individuals in that zone.

An acute effect of exposure to this chemical is chloracne, which is a skin condition that looks a lot like acne but has a different pattern to it. Individuals are here broken out as to whether or not they had chloracne; and there's no well-defined cut point based on dioxin body burden to determine who will get chloracne and who won't.

[Slide]

So what does dioxin distribution look like in the Ranch Hand group? Now here I'm showing the histogram in raw units, which doesn't look very pretty, because it it's so highly skewed, of the distribution on the Ranch Hand side and on the control side. The controls, 99 percent of the controls have less than 10 parts-per-trillion, currently.

This is published in -- and I'll show you some citations on that -- the median or mean is about 5 parts-per-trillion. All of us in this room have about 5 parts-per-trillion in our blood. We get it from breathing smoke from burning trash, from eating certain fish and seafoods; that's the primary source of uptake in the United States, is diet. And you get it primarily in your diet from seafood and from dairy products, and from meat. Anything that has fat in it.

You can also get trace amounts from plastics and paper products. Just by touching a styrofoam cup, you're getting a tiny amount of dioxin in your body. What happens is that all of us are experiencing constant uptake of a tiny amount every day, and at the same time we're experiencing whole body elimination. So we're at kind of a steady state.

Our body burden is going to fluctuate for the rest of our lives; it will gradually increase, and that's published in 1998, showing the data from our control group. In the Ranch Hands group, of course, you see that decreased. Here it is in log units, which is our favorite transformation in statistics, which shows a nice, approximately normal distribution in the Ranch Hand group and control group.

In the Ranch Hand group, the median is 12 parts per trillion.

DR. CAMACHO: Joel, could you go back to the previous slide, please?

Out there in the Ranch Hand population, the people out there at 600 --

DR. MICHALEK: Right.

DR. CAMACHO: What's the end for that?

DR. MICHALEK: Okay, I'll give you some numbers on the Ranch Hand side. The median is 12; 50 percent have less than 12. In other words, half of the Ranch Hand group look like controls as regards their current body burden, which is not a nice fact to have to face statistically, if you're worried about exposure --.

The percentiles, don't have those memorized. There's one individual with 660 parts-per-trillion. I can get you that a little bit later.

DR. CAMACHO: But that's only one or two people.

DR. MICHALEK: One or two people, right.

I'll give you another number: 98 percentile in the control group is 200. Almost all of them are less than 200, in the Ranch Hand group.

I don't have the other percentiles memorized, but I can get those for you.

DR. HARRISON: Joel, what's the molarity of 12 parts-per-trillion?

(Laughter)

DR. MICHALEK: That's a good question. I have a slide on converting whole weight to liquid weight dioxin, but I don't have a slide converting parts per trillion to molarity. But we can get that. Can't get it for you instantly.

DR. HARRISON: You know, I ask that every meeting.

DR. MICHALEK: Sorry, I don't have that conversion memorized.

DR. MINER: You did that, though.

DR. MICHALEK: No, I didn't do that one.

DR. MINER: I gave you that last time.

DR. HARRISON: Just to put this in for one more time, the argument that I have with environmental assessments is that they assume a relationship between the toxin all the way to zero. Whereas in my world, there's a concentration of active material below which you don't see anything.

LTC BURNHAM: You're seeing a threshold.

DR. HARRISON: And I know the EPA's position is that 1 trillionth is just one trillionth as bad as 1. But in my world, one trillionth is the same as zero.

Jay, you say you know what 12 parts per trillion is?

DR. MINER: No, I said -- I copied some conversion factors and brought them to you last time, but I don't have with me now.

DR. MICHALEK: We can get that.

DR. CAMACHO: On the noncompliant and the people who dropped out of the study, is there any standard like survey done to see if they had anything.

DR. MICHALEK: Yes; they're given a noncompliant questionnaire: Why didn't you want to come? No time, no interest, too sick, whatever.

DR. CAMACHO: And they were spread all over the place.

DR. MICHALEK: Yes, they're spread all over, and the are groups equivalent on that. However, that's an important point, in that when the individual says "I can't come, I'm too sick" we pay attention. When we start to see -- one of two things can happen that would make us very worried.

If a great proportion of them couldn't come because they're too sick to come, or if one group was unbalanced with regard to the other in that direction, that statistic is very important to us and we're watching that. It's only a few percent, one or two percent that can't come because they're too ill. But we have ways to find out about them, too, by means of medical record collection.

So we're on to that, yes, and that's all in our reports.

DR. SILLS: Joel, I have one question. Can you go back to the last slide -- the slide before this. You know when you talk about chloracne with the Italy study, I was just wondering, in terms of your Ranch Hand population, did you see any chloracne?

DR. MICHALEK: We have found no chloracne. That's published in the Archives of Environmental Health, 1998.

And that paper took five years to get published. What we did was we went back to medical records that were collected while they were in Vietnam, on every Ranch Hander, and we studied every record. We found only one individual that had any annotation on his record that he was having a skin problem. And we reported that in the article.

So the article then talks about acne. The intent of the article was chloracne, but the study is affirmant because we didn't have any chloracne to study. So no, we didn't see any.

DR. STOTO: It wouldn't possible, though, if you had an 18 year old man with acne that he wouldn't think it was exceptional enough to --

DR. MICHALEK: Absolutely, yes.

Of course, remember, that in Vietnam at the time that the doctor didn't know; he was told the stuff was safe. And probably the whole concept of chloracne wasn't at the top of his mind at that time, in 1963, '64 when this stuff was being sprayed.

Yes, Jack?

MAJ SPEY: I would just make a comment about that. All the flight crew received annual physicals. We were all in the area, in the general age bracket of between 24 and 28 years old. Had any of us started coming down with acne at 28, 24 years old or 18 or 20 years old, I would have been brought to the attention of the flight surgeons; they wouldn't have recognized the difference between chloracne and ordinary acne because it takes a specially-trained dermatologist to be able to make that determination; but it certainly would have been indicated in part of our health records, and it wasn't.

DR. MICHALEK: And we have all those records.

MS. del JUNCO: Joel, in the group of troops that was the Army, the first group that you guys didn't follow anymore, how many dioxin body parts and samples did you analyze?

DR. MICHALEK: Would you say that again, please.

MS. del JUNCO: In the first group, the one before the Ranch Hands, the ground troop veterans, the ones that included the Army and was discontinued, do you have any samples?

LTC BURNHAM: The Vietnam Experience Study.

DR. MICHALEK: Oh, the Vietnam Experience Study. Yes.

MS. del JUNCO: Okay, the Vietnam Experience Study, as you call it. Do you have any actual dioxin --

DR. MICHALEK: Yes.

MS. del JUNCO: How many samples did you analyze in that group?

DR. MICHALEK: I didn't analyze those. Those were done at CDC and those were published.

DR. GOUGH: There were 600 people from Vietnam, and 80 or 100 non-Vietnam comparisons.

MS. del JUNCO: And these were Army and Marines?

DR. GOUGH: No. All Army. The low, medium and high was categorized by the relationship of the reported positions of the Army units to the Agent Orange spraying missions, which is just subject to all kinds of misclassifications.

But the prediction, from the spray missions, is that the Army troops would not have been exposed, because they weren't very close, they were sprayed only rarely, and there's a lot of diffusion of Agent Orange before it got to the ground.

So those results are consistent with the estimates of what the exposure would have been.

DR. HARRISON: And of course, if you're comparing the effects of dioxin, there were other defoliants used by the Army that contain dioxin; so the actual dioxin exposure is probably not easily estimated.

There's something, when I was looking at the minutes last night that I thought about, Joel, and I guess I might as well ask it now.

There was a small population of men who died before the study began. If you were looking for an acute effect of dioxin, those might have been the ones acutely affected. I know you looked at it. I know you looked at it. I'm just asking you, how did you look and what did you find?

DR. MICHALEK: That was published in JAMA in 1990, the very first mortality study. There aren't any group differences, by cause of death. And that's all we can do; we didn't have dioxin levels at the time.

DR. HARRISON: Let me ask it this way: were most of those deaths cardiovascular? Cardiovascular and renal, let's say.

DR. MICHALEK: We saw that effect later. In 1988-'89, we saw an increased risk of cardiovascular death in the enlisted ground crew, which gets our attention, because they have the highest levels.

Didn't see that, we didn't even know to look so carefully in the early years, but I don't remember and we'd have to check that.

DR. HARRISON: Okay.

DR. STOTO: Weren't they mainly automobile accidents and things like that?

DR. MICHALEK: There was some evidence of increased risk of, external-caused events, deaths; yes, in the first few years after Vietnam.

DR. GOUGH: Which has been observed in other veterans of Vietnam --

DR. MICHALEK: Remember, both groups are Vietnam veterans in this case.

DR. GOUGH: And Korea and World War II.

DR. MICHALEK: True, but both -- our control group was in Vietnam, too.

But it wasn't significant, I don't believe. I don't remember. I have to check.

DR. STOTO: My recollection is that a lot of the deaths were of that sort.

DR. MICHALEK: Oh, yes.

DR. STOTO: That's what you would expect for men of that age.

DR. MICHALEK: Yes. At that time many of the deaths were externally caused.

[Slide]

Okay, how good is this dioxin measurement? Well, fortunately we had this pilot study where we sent them to the clinics.

A few months later they were invited to the 1987 physical at Scripps Clinic in California; and at that point they invited everybody to give blood for dioxin. But we still had this cohort that had been to the clinics. 47 of them volunteered again, so we had paired measurements, within a few months apart, on 47 people; which we used to do a standard, a measure of reliability, and the original units or individuals 11 parts, up to 50 parts per trillion, and the coefficient of reliability is 87 percent.

On the log scale -- because that's the unit we use in all of our analyses -- the coefficient of reliability is 96 percent on a scale of 0 to 100, which means 96 percent of the variability in the measurement is due to true differences between people, and only about 4 percent is due to the noise. Which is very good, considering the scale on which CDC is operated on a part per trillion scale.

DR. STOTO: That's reliability with respect to what the persons' dioxin level was at that time.

DR. MICHALEK: Yes.

DR. STOTO: And if you try to extrapolate back, those numbers would be somewhat different.

DR. MICHALEK: I have some things to show you later that I'm so excited about it's hard for me to tell you.

(Laughter)

Fortunately, we have another meeting in December, and I have some data which combines Seveso half-life studies and the Ranch Hand half-life studies that will address what you just said.

Anyway, here we have, in log units, the classic picture that you want to see, this is what you see in textbooks; you expect to see a 45 degree line. When you plot the dioxin level in the pilot study versus the dioxin level measured at Scripps Clinic, or cut from blood from Scripps Clinic, and it's just very tightly in log units, scattered around a 45 degree line, which gives us great confidence in the measurement.

And here it is in original raw units, and you see a pretty good, tight scatter around here, less than 50 parts per trillion, which is the reason for our statement about less than 50 and greater than that is pretty noisy. But we don't analyze original units anyway; we always analyze in log units, so we're happy about that.

[Slide]

What does this measurement have to do with what actually happened in Vietnam on the job? That was the next question, and the very first question at the tops of our mind is at the time. To address that, we sent a quantity to all enlisted Ranch Handers -- there's about 500 of them -- and we questioned them about on the job activities in Vietnam. And we found out what they did in Vietnam by interviewing two Ranch Hand crew chiefs who happened to live in Texas.

Someone had to get in the tank, it was a thousand gallon tank in the back of the plane, it had a dump valve. Someone had to get in the bank, get down on his hands and knees, and grease the valve. And as I was told, the bank is never completely empty.

Some of them used herbicide as a hand cleaner, because they were told it was safe, and because it actually does a very good job of removing grease and oil from your hands.

Some of them got sprayed in the face and torso as they were standing on landers behind the trailing edge of the wing, sticking coat hangers and screwdrivers into the nozzles, to clear the nozzles. Because the herbicide would dissolve rubber, and so there were little bits of rubber and other crap in the line, it would clog up the nozzle.

They were in tropical heat. This was on the job exposure. And of course they would get herbicide on their clothing. This is a different scenario from the flyers, who didn't receive this kind of exposure because you didn't work in the tanks and fill the tanks like the enlisted; is that true?

MAJ SPEY: Can a make a point?

DR. MICHALEK: Yes.

MAJ SPEY: Just a simple observation. when a flight crew member, a pilot, preflighted his airplane, he walked around the exterior of course; and then when you walk through the cargo compartment, you'd grab a pressure line, you'd touch the tank, you'd check to make sure that the tank cap was on tight. You had scudge on your hands, and then you might wipe the sweat off your face or scratch your eye --

(Laughter)

-- helmet on, or some of us, you know did this. The material was everywhere. I mean, it wasn't wasted, it wasn't flowing across the cargo compartment of the airplane, but anyone that went on that airplane; passenger, crew member or whatever, came in physical contact with the material.

DR. HARRISON: You know, that's something I hadn't thought about, but this stuff is somewhat volatile, isn't it?

DR. MICHALEK: I don't know what that statistic is. The vapor pressure of the herbicide?

DR. HARRISON: In other words --

LTC BURNHAM: You can smell it.

DR. HARRISON: How much did you breathe?

DR. MICHALEK: I don't know those numbers.

DR. HARRISON: And that would be good absorption.

MAJ SPEY: I'm not sure if protocol allows me to answer questions.

DR. HARRISON: It doesn't, but why don't you go ahead, sir?

MAJ SPEY: The air flow in the C-123 -- we flew with the open troop jump doors -- the troop jump doors open so that the flight engineer could pull a pin on a smoke grenade and throw it out to mark the position of ground fire. The front windows in the cockpit were open to prevent shattered plexiglas from injuring us, should a bullet hit that window. Plus, it was our air conditioning system.

(Laughter)

The air flow came in, the troop jump doors in the rear of the aircraft, the odor, et cetera, et cetera, came forward across the inboard side of the face of the pilot and copilot and out that window. You were smelling it all the time. And you know, it smells terrible.

DR. MICHALEK: In retrospect, we should have given that questionnaire to the flyers, but we didn't, to the officers. We only gave the questionnaire to the enlisted. That was because the data at the time showed the enlisted had much higher levels. So that's why we did what we did.

DR. STILLS: Joel, I have one question: In terms of, you mentioned that 66 parts per trillion was the highest exposure that you --

DR. MICHALEK: We saw it in the Ranch Hand group.

DR. SILLS: -- that you saw in this study.

Did you have a nice correlation when you looked at, for example, it's the 66 parts per trillion, was that observed in the men entering the spray tank? Is that where you saw most of --

DR. MICHALEK: We're getting to the next slide, yes.

[Slide]

So here are the activities that were reported to us and which were included in the questionnaire. Here are the results.

We actually looked at the questionnaire and we scored the total number of days of skin exposure, and across the vertical we have dioxin levels in log units -- this is the right hand side; all of the individuals are here. And then we broke the cohort down into categories.

We didn't administer a questionnaire to controls. We included the controls here as a reference. So these are enlisted controls. We have the same experience as the Ranch Hand group, they're the same rank, same activities, but they weren't spraying herbicide.

Then we took this cohort that received the questionnaire, and we broke them out into five categories. Some of them reported being administrators, which meant they sat in an office in the command section, and weren't out on the flight line.

Some of them reported no exposure whatsoever: "I never touched it" and they'd leave their questionnaire blank. And then after that we had the group that reported exposure by means of all the methods you saw in the previous slide.

We broke those out into tertiles, by the number of days of skin exposure. And we looked at that versus their dioxin body burden measured in 1987. I want to use the word "awesome" but this is a technical discussion, so I won't.

This is it. This is the connection between what we measure today and what actually happened in Vietnam. We see this. This validates the dioxin body burden as a measure. It's not perfect, because you see we have individuals here -- that one is almost zero parts per trillion, who had, according to the questionnaire, very high skin exposure.

DR. GOUGH: Are they very skinny?

DR. MICHALEK: Yes. There was a range of percent body fats, percent body fat in Vietnam. And that turns out to be a very important predictor of a lot of things, which I'll talk about in a few minutes. You couldn't be too heavy, because you had to get in the tank, and it was an 18 inch hatch.

Here we look at the flight engineers who operated equipment in flight, and this is the ground crew that filled the tanks, and this is everybody.

This was published in the Journal of Exposure Analysis, 1996 I believe. Somewhere in the Nineties.

[Slide]

Here it is again; here I've simply created a few categories; the administrators, the enlisted flight engineers, enlisted ground crew, showing the high correlation between activities in Vietnam and subsequent body burden of dioxin in log units.

[Slide]

And if the officers were here, by the way, if I had included officers in the slide, they would be right there, right in between the controls and the administrators.

As part of the study, we have focused a lot of attention on the way in which people eliminate dioxin from their bodies, because that's an important consideration when trying to estimate the initial dose. For that purpose, in 1987 we identified all Ranch Handers that had body burdens above 10 parts per trillion, which is by the way the

98th percentile of the control group. We identified about 500; there were about 500 in that category to be selected for repeated measurement for the rest of study to observe their full body elimination of dioxin.

So that led to estimates of the elimination rate which were at the beginning, and which we realized right away were hopelessly biased because the response variable

that we're measuring was based on a truncated dataset, that we were selecting individuals because they were high. That's a standard environment for an artifact in statistics called regression to the mean.

Well, during that period, the 1990s, we devised a way to force the SAS PROC GLM to produce unbiased estimates even in the presence of a biasing effect of selecting individuals for being high. This is the same effect you see when you give students a test and you select individuals that score high on the test and then you test them again a few weeks later, you'll be just a little bit disappointed. You'll find that they have regressed towards the mean. That's an effect that you see whenever you select individuals for being high or low on a continuous variable.

DR. CAMACHO: Isn't there something about a fallacy of regression involved in this? There's going to be a little football around the line, it's spread, it's going to look like a football.

DR. MICHALEK: Exactly.

DR. CAMACHO: If you do it later, it always looks like the bottom came up and the top came down.

DR. MICHALEK: That's regression to the mean.

DR. CAMACHO: That's what you're referring to now.

DR. MICHALEK: That's right.

DR. CAMACHO: All right.

DR. STOTO: But they're only looking at the top half of it, so. You see the top coming down but not the bottom going up.

DR. MICHALEK: This algorithm was published several times during the period, and it's used in all of our recent papers on estimating the half life of dioxin in the Ranch Hand cohort.

The latest estimate is that the half life of dioxin in Ranch Hand veterans is about 7.6 years at a 95 percent confidence interval.

[Slide]

Here's a picture of the log units, the dioxin level is decreasing in the right chamber over the four repeated measurements of the -- roughly 300 individuals have repeated measurements across all four study cycles.

Remember, we took the first measure in '87, then we went back to the freezers and extracted serum from our freezers and measured the serum that was collected in 1982. And we continued that up to 1997. Our most recently published paper concluded that we should not continue the pharmacokinetic study because so many individuals were getting into background levels, the variance of the estimate was actually increasing rather than decreasing with increased repeated measures. So there was no statistical gain to continuing that study.

[Slide]

Here you see the increased body fat over time in this cohort that was in the pharmacokinetic study, our study.

There is a strong relationship between the body fat and the elimination rate. Heavier individuals hold onto their dioxin longer. They have a smaller elimination rate. And here you see the elimination rate plotted against the body fat measured in 1982, and we see a downward trend.

That's an important consideration in all of our statistical analyses. In all of our reports we adjust for body fat for this reason, because we're trying to accommodate the known variation in the elimination rate with body fat.

DR. HARRISON: that doesn't look very -- What's the R-value for that thing, Joel?

DR. MICHALEK: It doesn't look very pretty, does it? But remember, this is an uncontrolled study and that's the way it is.

DR. HARRISON: Wait a minute, though. Where did that line come from?

DR. MICHALEK: The line is a least squares line from the analysis to produce the elimination rate.

DR. STOTO: It actually looks quite high, if you would drop out that one point with the negative elimination rate.

DR. MICHALEK: Now this guy we can talk about. Why does he have a negative elimination rate? That's because his dioxin level went up. And the reason it went up is he went to work for a utility company in Kentucky between 1992 and 1997 and he was handling transformers and electrical equipment. We think that's where he got his dioxin from.

Remember, these are free-living individuals, they're all exposed to dioxin in the United States, just like all of us in their job and in their leisure activities. So what we got is an exposure that took place many years ago, and overlaid on that we have some noise; from exposures that were experienced here in the U.S.

DR. HARRISON: That R is like .35, right? That R is like .4, right?

DR. MICHALEK: Possibly. Yes, I can find out.

DR. STOTO: But if you took out that guy in Kentucky, it would be substantially higher than that.

DR. MICHALEK: Probably less, yes.

DR. GOUGH: The R would be higher, or the slope of the line would be more acute?

DR. MICHALEK: I don't expect that -- that's not the influential point on the slope. This one's influential, but that one is probably not.

DR. HARRISON: It almost looks like something is tethering it around that 10 percent mark.

DR. MICHALEK: We called him up to talk to him; his levels were coming down nicely. They are like 80 parts per trillion, 60, 50, 90. "Where were you? What did you do between 1992 and --" "Oh, yeah, I got this job."

So things happen, and that's just a reminder that these are not animals, these are people, and we can't control what they do.

DR. HARRISON: How was that assessed?

DR. MICHALEK: How was what?

DR. HARRISON: How was the percent body fat assessed? I forget.

DR. MICHALEK: That's simply the body mass index times -- a later function of the body mass index, weight over height squared, in metric units.

DR. HARRISON: Has that assessment throughout that study ever been -- you know, I went to the Bills-Chargers football game last week, and I saw literally a ton of individuals who had body mass indexes in the obese range, but who literally had no body fat. You know, those are highly trained athletes, highly muscled athletes.

At the other end of the spectrum, there's something referred to as the sarcopenic female. That's a woman who has a more or less normal body weight because she doesn't eat much, but who has more than normal body fat because she doesn't exercise much. So she has a normal body weight but she has a high percent body fat.

DR. MICHALEK: The body fat measurement was discussed many times through the study. The current method is being used for a lot of reasons. The gold standard, I believe, is the immersion method in a tank of water?

DR. HARRISON: Sure, but you've got bioconductance, which is a pretty convenient way and is reasonably close to -- I just wonder if you have -- for instance, if this were a prison population, you'd be overestimating body fat because those guys have nothing to do but work out all day. I just wonder.

DR. MICHALEK: Since the study began, there are new and better ways to measure body fat. In fact, we have a clinical study of insulin sensitivity happening right now in Little Rock, Arkansas. There they're using something called a bod-pod, which is a chamber in which you sit and then you displace air. And of course that has its own limitations, but that might be better -- I don't know; I haven't seen any literature on that.

But there are probably higher technology ways of measuring body fat today that didn't exist in 1976, which is when the original concept of body fat, where weight over height squared was specified.

DR. HARRISON: I just wonder, Joel, if you could even say that in this population there was greater variability or less variability using the BMI, that would at least allow you to comment on the scatter that you see.

DR. MICHALEK: I can tell you the BMI is widely used in our studies; it was used in the Vietnam Experience Study, it was used in the NIOSH study.

DR. HARRISON: Well, the BMI is -- that's the standard.

DR. MICHALEK: I know. It's the standard, and not only that, it's noninvasive. I'm not arguing that there may be better technological ways to measure body fat, and those should be considered for the next physical.

DR. HARRISON: Heck, you can go to Brookstone and get one of these little things, you hold it in your hand like that, and it does bioconductance.

DR. STOTO: Well, two things. One is that if the BMI is an imperfect measure, presumably the R-square would go up if you had a better measure, in this discussion here.

DR. HARRISON: Right.

DR. STOTO: And I guess the second thing -- we should think about this tomorrow. You know, is it worth trying to do some of these other, more precise measures?

DR. MICHALEK: At this stage of the game.

DR. STOTO: Yes. I don't know what the answer is, but I think it's worth talking about.

DR. HARRISON: My question was had it ever been done, and your answer is no, you've not ever correlated the BMI in your study population with any other more precise measurement of body fat.

DR. MICHALEK: No, we have not.

DR. GOUGH: Didn't you do some immersion studies on a --?

DR. MICHALEK: We thought about it, but we gave that up. Because it's not a very pleasant experience for an older gentleman to be put into a tank and told to exhale and stay completely exhaled until some technician says, "Okay, you can breathe now."

DR. GOUGH: Or you sink to the bottom.

DR. MICHALEK: It's not fun.

Oh, you just thought about it.

LTC BURNHAM: Our oldest subject is 80 years old --.

DR. MICHALEK: I did it once. I would not like to do it again.

Yes, so that's an issue. Body fat is an issue.

MS. del JUNCO; 92.

[Slide]

DR. MICHALEK: Here's a comparison with some other studies on half life. Here is the Ranch Hand study 57.6 years. There was a study of individual adults in Italy in the Seveso accident done by CDC, and another study of -- you saw the previous slide of those observing the industrial workers; these are smaller studies based on paired measurements and our study is based on up to four measurements per subject. Roughly the same ballpark, which gives us confidence that we're working in the right arena.

[Slide]

Here are some Ranch Handers at a museum in Hurlburt Field, a Ranch Hand aircraft.

Do you want to say a word about that airplane? Do you happen to know anything about this particular aircraft?

MAJ SPEY: It was not a spray airplane, sir; when it was moved to the airpark, why we convinced them to put spray booms on it just for fun. It was an airlift airplane in Vietnam.

LTC BURNHAM: Is the one over at Lackland originally a spray air? There's one outside the gate at --

MAJ SPEY: I'm not sure.

DR. MICHALEK: Here you see a representation of the spread of conditions that were being reported by Vietnam veterans; and those form the structure for our study.

I'm now going to run you through, show you an overview of findings, and this will be layered. In other words, today I'm going to show you an arm's length view of everything, and then we're going to focus down to some particular areas such as diabetes and peripheral neuropathy.

We have produced about 20,000 pages of reports, almost all of which have been written by Science Applications International Corporation, by means of a study design and statistical analysis plan, which is based on these statistical models.

We have four approaches to analyzing data in the study. In the first approach, we don't use dioxin measurements at all. We just compare all Ranch Handers with all controls. And then within these three occupational categories, we compare Ranch Hand officer with control officers, and so on. It's about a one.

Separately, the next three models use the dioxin body burden. In those Ranch Handers that have high levels today, that means more than 10, we extrapolate back to Vietnam, and ask whether the initial extrapolated dose is related to current health. That's called the

Initial Dioxin Analysis, or Model 2.

Separately, we categorize individuals into four bins; with controls, and then we take the Ranch Handers and break them up into three parts: Those that have background levels today and then those that are above background where we break them out to low and high. And we compare each of those three Ranch Hand strata with the controls. That's called our Dioxin Category Analysis. That's the way you'll see it primarily in all our published papers.

And then finally we ask: Is there a connection between today's dioxin body burden and your health? No matter how much you had in Vietnam or where you got it from, is there any connection at all between today's dioxin body burden and health? And that's our Model 4.

These are the four models that were used in our 1997 report, which is on the web page. In our 1992 report, we used six models, where we added two more dioxin level analysis at the bottom here that I'll talk about later.

[Slide]

Here are some sample sizes of the numbers of people that came to a physical exam that were in the strata used in the first model. See number of officers, enlisted flyers and ground.

370 Ranch Handers came to the physical, and 1251 controls. We have about an equal number of enlisted ground as we did officers.

[Slide]

Here's dioxin category numbers, and here are those four bins I was telling you about. Here are the comparisons, and in the comparison group we eliminated the one percent or so of the comparisons that had greater than 10. Because some of those, we believe, received high levels here in the United States, by means of their occupation.

So because of our philosophy of wanting to study exposures that occurred during the war, we wanted one to focus on war-related exposures, and that's why they excluded the top 1 percent of our comparison group.

And by the way, even if you put those people in, the analysis results generally don't change.

Here you see the three categories in the Ranch Hand analysis. The low and high categories were defined by their initial dose in Vietnam, the median level that 94 parts per trillion. That's the split that broke this group up into parts of roughly equal size.

The analysis drill is to compare each of these, and their health, with the comparisons.

[Slide]

This is a thumbnail sketch of what we saw, not just in the last report, but in all available data. In the area of general health, I guess the finding that I remember most is that we see a significant, adverse relation between reported health and dioxin body burden. Reported health on a scale of excellent-good-fair-poor. We see an increased risk of reporting fair-poor health in the high dioxin-exposed category, in our dioxin category analysis.

That was a point of discussion at our previous meeting, and I have some slides on that. In October of last year, why are we seeing this and why did we see it in previous reports? What does this mean? What does the general assessment of health mean?

Since then we have looked and we have found that that particular assessment is significantly related to diabetic status. Meaning that, at least part of what they're recording is their diabetes, which is interesting. Because that thread of thought will prevail through many of the findings in the study.

We see so far no relationship, or no significant relationship between any measure of exposure and cancer. However, that's certainly an issue we look at very carefully. That's been looked at of course in all of our reports, but it's recently published in the American Journal of Epidemiology, 1999.

The latest report from SAIC, just recently released in January of this year, we see a 6 percent increase in cancer in the whole group; which is of course not significant. About 16 percent of all Ranch Handers and comparisons have one or more tumors, at this point.

So we have very good statistical power to detect relative risk of 2. We have no statistical power to detect a relative risk of 1.06.

In neurology, because of our work with the National Institutes of Health and the National Institute of Dental Research, we have collaborated with a physician at the University of Michigan to measure peripheral neuropathy in the most thorough way that we have ever done, and we have found a significant and adverse relationship be peripheral neuropathy and dioxin body burden, and that is in submission to a journal, and I'll tell you more about that in a separate talk on that.

In psychology we're seeing generally no relationship between any measure of exposure and any measure of psychological health except -- that means the MMPI, the SCL90R, and all the measures we've given to the

study. If you look at our web page and click on our reports, you can look at the cite chapter and you will see all the different instruments we've given since the beginning.

However in 1982 we gave, in addition to questions about anxiety and depression, we administered the Wexsler memory scale and the Wechsler adult intelligence scale, and the Wechsler reading achievement test, the RAT. Those results are recently now analyzed and are in submission to a journal. We see a significant and adverse relationship between short term memory and dioxin body burden that we had not seen before, because only now have we gone back to analyze data in 1982 cognitive function.

That data is interesting because it's consistent with results seen in babies of women who were exposed to PCBs in studies done in Amsterdam, in Holland. And those are recently published.

MS. GOVAN: Joel, when you're identifying positive versus negative findings, are the findings that are positive mean that it had to fit that monotonic, linear relationship from low to high? And if it's negative, there could have been an association, but it would fit that linear pattern?

DR. MICHALEK: Certainly the first thing is true; If it's a positive, that means there's a significant adverse relationship there, a positive trend with dioxin body burden. If it's negative that means we're unable to find any pattern there that made any sense.

I have a separate talk on cancer where I actually show you the data. What happened on cancer was, that we see an increased risk of cancer in the low group but not the high. In fact, we saw a decreased risk in the high group. Difficult to interpret. So we interpret that as negative.

DR. CAMACHO: Are the numbers in the cells in all of this --

DR. MICHALEK: 300, roughly. We have small numbers. Certainly this study has no ability to study rare diseases such as a particular sarcoma. It has good -- we're getting into another talk.

This physical power to study all cancers combined -- in the area of gastrointestinal, we look at history of liver disease -- and by the way, all diseases are verified by medical record review, 100 percent. So we looked at liver disease, we looked at liver enzymes and liver function. And we see a consistent and adverse relationship between certain liver enzymes such as UDT and dioxin body burden, but no evidence of a relation between liver disease and dioxin body burden; and that's currently in submission to a journal. That's also been described in our reports.

DR. HARRISON: What about gastrointestinal functioning?

DR. MICHALEK: In what regard.

DR. HARRISON: What about, let's say the incidence of patients taking medication used to treat peptic ulcer disease, taking medication used to treat gastric motility problems?

DR. MICHALEK: Have not studied those endpoints. We've studied ulcers, we have not studied medication as an endpoint.

DR. HARRISON: For instance, patients with diabetes will at some point, or can at some point have difficulty with gastric emptying. So you'd expect to see, if you had a big enough population, you might expect to see some evidence of that.

DR. MICHALEK: Well, that idea is certainly captured in the minutes, and we'll--

DR. HARRISON: And it would go along with your positive peripheral neuropathy because these are all neuropathic problems, and the more you tie those together, Joel, the tighter you make the story.

DR. MICHALEK: The picture.

Cardiovascular, we're seeing an overall 25 percent increase in cardiovascular disease in the Ranch Hand group. Again, all verified by medical record review. That's separate from cardiovascular mortality.

We are talking about here the health effects we see in the veterans who've come to Scripps Clinic.

However the patterns after that are not completely clear. We see --

DR. GOUGH: Joel, did you say 35 percent?

DR. MICHALEK: 25 percent.

Yes?

MS. GOVAN: Could you describe a little bit about -- that's such a big, broad brush.

DR. MICHALEK: I know. I have a separate talk on that, too.

DR. HARRISON: Ma'am, this is basically an overview to try and get the committee up to speed on what has happened overall.

DR. MICHALEK: There is a wide range of ICD codes that cover that definition, and I'll have to address that separately.

[Slide]

Hematology, we're seeing a significant and adverse -- I couldn't call it adverse, because I believe people know what's adverse here. But we're seeing changes in platelet count and mean volumes with dioxin body burden; and that's in submission to Archives of Environmental Health. The meaning of that is unclear or unknown.

In endocrinology, of course we're seeing the significant -- we have a lot to say about diabetes today. We're seeing a relationship between diabetes and dioxin.

Immunology, published in the American Journal of Epidemiology, 1999, we see no detectable adverse relation between any measure of exposure and immune function.

In pulmonary we primarily no relation except among officers we saw an adverse relation between -- bronchial obstruction. There was a finding in our 1997 report, and that's the reason for the plus-minus.

In dermatology we've seen, as I said, no evidence of chloracne with the caveats that we stated.

And in renal, no relationship between any regular exposure and renal function early in disease. Not expected, either, in renal.

[Slide]

Here are some numbers showing you what the demographics were in 1995 after Cycle 4, the fourth physical, of what the ages were, all of the categories of our dioxin exposure

index. You see the individuals in the high category are slightly younger, and the individuals in the background are slightly older than controls. That reflects the fact that most of the individuals in the high category were enlisted, and most of the individuals in the background category were officers, and officers are generally older.

[Slide]

Here you see that the pattern in body fat parallels the pattern I just described by occupation.

Here you see the percentages by military occupation in the high category are 2 percent for officers, whereas in the background category, 61 percent are officers. Which is an important adjustment in our analysis, because officers are generally college-educated and enlisted are not. So we have to be careful to make these variables part of our statistical modeling.

[Slide]

Here you see what diabetes looked like in 1995, which was a pattern of increased relative risk from background, low/high, .7, 1.3, 1.5, and that 1.5 was significant, and there's a lot to say about that during our meetings today.

Here's what it looked like in 1998, the same increase, the prevalences are increased. Back up here you see a 20 percent diabetic in the high category and here 23, almost 24 percent diabetic in the high category.

[Slide]

Here's what cancer looked like in the study. This is what I was telling Debbie about just a few minutes ago. We see a pattern of increased risk here, but not here. After adjustment for many covariates. This is all cancers.

Heart disease, we see a pattern here which is not very exciting statistically. We see a relative risk of 1.0 and not a category; that's what I meant, the cardiovascular findings are a puzzle. We see an increased risk overall, in all Ranch Hand groups. We see this one, we do a dioxin category, but we see an increased risk of, evidence of prior myocardial infarction when we look at the initial dioxin body burden in Vietnam.

Yes.

DR. HARRISON: Dr. Sills knows more about this than I do. But patients with diabetes don't have clinical heart attacks, but they do have subclinical heart attacks, and they have more of them. They're smaller.

Part of the mechanistic explanation for that is that they have more atherosclerosis, they have more partial obstruction, and so they produce more bypasses on their own, so that when they do finally knock one off, they knock of a smaller, more localized piece and frequently just don't have chest pain and don't have any symptoms and go about their business.

So depending on what -- see, if what you're calling heart disease is the medical record that this patient had a myocardial infarction, then that should well be different from, if you did EKGs on everyone and found this puzzling observation, that a lot more of the high group had abnormal EKGs.

DR. MICHALEK: Which we do find.

DR. HARRISON: Do you agree, Dr. Sills?

DR. STILLS: I just want to point out I'm a veterinary pathologist.

But I agree with what you say.

DR. GOUGH: Joel, before we leave the slide, if you do the comparison between Ranch Hands and comparisons, is there a difference? Non-stratified.

DR. MICHALEK: Yes. We see a 25 percent increase.

DR. GOUGH: Is it statistical significant? I mean, those numbers aren't.

DR. MICHALEK: I wouldn't be surprised. You know why? Because the prevalence is 65 percent. 65 percent of both groups had some condition which counted towards our definition; so we have very high prevalence and we have very power. We probably did have significance or borderline significance on that 25 percent.

DR. GOUGH: Well, this is a strange dose response.

DR. MICHALEK: It is. It certainly is. But there's a lot of complications here, as mentioned by Dr. Harrison. And there's --

DR. GOUGH: But see, I ignore Bob's complications. I can never understand them.

DR. MICHALEK: There could be a problem with our definition

DR. HARRISON: Let the record show that the Chair has been dis'd.

DR. MICHALEK: There's literature out there to suggest that dioxin destroys vascular tissue, and that we may be just looking at the date incorrectly. There's a lot of ways to look at this data, and that's why we're having this meeting.

DR. GOUGH: But to follow up on something Bob said, you have EKGs on everybody, right?

DR. MICHALEK: Yes, we do, and that's one of our endpoints.

DR. GOUGH: So that's factored into this?

DR. MICHALEK: No, this is a definition by -- by ICD code, there was a definition of heart disease --

DR. GOUGH: Oh, okay.

LTC BURNHAM: Is carotid thickness in here, too?

DR. MICHALEK: No, carotid thickness is a separate analysis which is being done by Billy.

DR. GOUGH: Okay.

DR. MICHALEK: Not part of the SAIC report.

[Photo]

Now we're going to talk about mortality. This is a moment to the Ranch Hand killed in action at Hurlburt Field. We did the standard breakout by unaligned cause of death. These are the same categories used in many other studies.

Overall, through 1993, we see -- relatively we see nothing. We see an observed 118 deaths in the Ranch Hand group after Vietnam, and expected 120, both risks less than one.

However, when we look by cause of death, here we see a finding, we first noticed in 1988 increased risk of death from cardiovascular disease in the enlisted ground crew. And that has persisted ever since. And all the other areas we see no evidence of an effect of any note; especially in cancer the relative risk is .9.

Remember, what we're talking about in mortality is a comparison between the observed and the expected number of deaths in Ranch Hands as compared to the death rates in the 19,000 in our control population. We do not have dioxin levels on 19,000 controls. We are not able to adjust here for dioxin body burden. We are only able to adjust for date of birth, race, and military occupation. That's all we've got in the way of covariates.

That causes us to be concerned about this digestive death relative risk of 1.7, which is significant. We know that many of these deaths were due to alcohol abuse. We're unable to adjust for alcohol consumption in these mortality analyses. We're also unable to adjust in the cardiovascular area, for example, for cardiovascular disease in the family, which is a risk factor. We're unable to adjust for smoking, which is a risk factor. We're unable to adjust for any of the standard risk factors that we're able to do when we look at data coming out of Scripps Clinic.

Bill Grubbs and SAIC have access to all the covariates; we do not have those covariates with mortality.

Yes.

DR. HARRISON: What about the increased risk in infection?

DR. MICHALEK: Those are small numbers. Two individuals here in 1.3, I'll find out what those were and tell you what they were; I have to look at the records.

DR. HARRISON: I'm sorry; I see. Okay.

DR. MICHALEK: Small numbers.

DR. HARRISON: I agree.

DR. MICHALEK: The other arm of the study is reproductive outcomes.

We have identified all children, live births, 8,100 children. We have identified and verified their lineage -- their existence, their lineage and their health up to the age of 18, by means of medical record retrieval and review.

We have identified all 10,000 conceptions that were produced by these men over their entire life, by medical record review of the records of the mother, primarily.

Separately, we have measured sperm parameters on the men themselves, and certain gonadotropins such as testosterone and FSH and LSH.

And here are the endpoints we studied. I think I have a slide. We primarily see no result when we ask whether there's a relation between any of these conditions and any measure of exposure. There's a few exceptions.

In the area of hormones. In testosterone, if you study levels of abnormally high testosterone -- as we did in a published paper in 1996, I believe -- you'll see no relation between abnormally high testosterone or abnormally low testosterone and dioxin body burden. However, if you look at testosterone mean, averages of testosterone, you'll see a significant decrease, a slight decrease which is statistically significant, because we have enormous statistical power when studying averages. And that's published in Epidemiology.

In the area of birth defects, we see no pattern which was considered meaningful or suggestive by CDC. With the exception of spina bifida, we saw in our dioxin exposure analysis zero cases in the control group; zero in the background category of the Ranch Hand group; one in the low group and two in the high group. That pattern of 0 1 2 was declared suggestive by the National Academy of Sciences, and that led to compensation to all Vietnam veterans of spina bifida in their children.

So that is the reproductive finding so far that has been recognized: The pattern of increased risk of spina bifida. We couldn't handle that statistically because the numbers were too small.

[Slide]

And here is a description of the check mark pattern. We have a picture of that, and I'll show you that in a second.

The pattern is represented simply by a trend in the Ranch Hand group, from background-low-high, and yet an overall relative risk of approximately 1.0. What that will be realized as, relative risk of less than one among individuals in the background category, and a relative risk of greater than one in individuals in the high category.

That was first interpreted in 1992, as possibly an artifact of reverse causation. And it's been talked about in the National Academy of Sciences books on Agent Orange in Vietnam veterans.

During the last decade, we have devised a simple misclassification model to explain the pattern.

[Slide]

But things have changed in the last couple of days, and I need to tell you about that. And here's a picture of the histogram again I showed you earlier, and here's a statistical model of the back up. Here's the normal distribution of the Ranch Hand group and the control group, and here's a statistical model, there's the rent control distribution, there's the Ranch Hand distribution today, and there was the Ranch Hand distribution as we think it should have been many years ago, before they lost their body burden, before it decreased.

Here's the picture we see today in diabetes. That is, up until about 3 o'clock yesterday.

Up until 3 o'clock yesterday -- this is what I want Mike Stoto to hear -- we have been analyzing diabetes with logistic regression adjusted for body fat, age, family history, and other covariates. And we consistently see this pattern.

What has happened in the interim is that we have written software to match, one-to-one, Ranch Handers to Comparisons on body fat when they were in Vietnam to within three percent. Family history of diabetes in the parents, brother or sister, perfectly. And date of birth -- nearly perfectly. And race. And military occupation.

DR. STOTO: This is not the regular --

DR. MICHALEK: No, this is super-matching.

DR. STOTO: -- standard match; this is new matching.

DR. HARRISON: Super matching.

DR. MICHALEK: I'm setting you up. Are you ready?

DR. HARRISON: Did you say super match or super magic?

DR. MICHALEK: This is super matching. This is maximal. And what's great about it is that body fat was measured before they were even exposed.

There's no issue here about reverse causation, about dioxin body burden changing your body fat. That body fat was measured in Vietnam.

We did matched pair analysis. The new relative risk in the background category is one. The new relative risk in that median is higher; it's about 1.2. And the highest, 1.5. And overall the relative risk is 1.2, significant.

DR. STOTO: I'm sorry?

DR. MICHALEK: I'm losing you.

DR. STOTO: Yes.

DR. MICHALEK: What happened was,

first of all, the check mark pattern went away, when we do a matched analysis, highly matched, the way I said.

You see this? We don't see this anymore. This is what we've been seeing for the last --

DR. STOTO: What are the three graphs corresponding to?

DR. MICHALEK: See, I'm so excited, I can't even tell you.

(Laughter)

DR. HARRISON: Are you saying that that right graph is the supermatched groups?

DR. MICHALEK: Yes. Up until 3 o'clock yesterday, this was a graph showing what we expected to see according to the statistical model that these slides were supposed to talk about. What I'm saying is, we don't need that statistical model anymore; dump it. I'm telling you that with this supermatching that I just described, this is what we see in the real data.

We don't see this anymore. This is what we saw using old-fashioned logistic regression. This is what we see when we do very careful matching.

That means that this diabetes as a disease is very sensitive to these factors, and that your body fat when you're young is very predictive.

COL MARDEN: Which way?

DR. MICHALEK: Adversely related.

COL MARDEN: So more body fat means more absorption.

DR. MICHALEK: Higher fat individuals have an increased risk of diabetes.

Yes.

COL MARDEN: So more body fat, more absorption and body burden, more diabetes.

DR. MICHALEK: yes.

DR. GOUGH: When you say body fat, you just mean height and weight, right?

DR. MICHALEK: Yes, it's basically BMI.

Now of course this is brand new. It isn't even out of the -- so everything I'm telling you today is going to be checked out over the next several weeks. Yes.

DR. GRUBBS: Joel, the additional adjustment factors here, to summarize, are?

DR. MICHALEK: Family history, body fat in Vietnam.

DR. GRUBBS: Okay, body fat before exposure.

DR. STOTO: Let me see if I can restate what I understood you to say.

When you control in this new improved way for the known risk factors for diabetes, the relationship between exposure to dioxin and diabetes is strong and the check mark problem goes away.

DR. MICHALEK: Exactly.

DR. STOTO: Okay. That is pretty important.

(Simultaneous conversation)

DR. MICHALEK: In other words, the pattern we see becomes sharper. The picture comes clearer.

DR. GOUGH: What do those symbols

above the second and third box mean? Exposure, or respective --

DR. MICHALEK: This is that statistical model I'm talking about. This is the distance separating the distributions. We back up one.

You see this distribution, Mahalanova's distance units. This is the controls today and that's the Ranch Handers today. The distance in Mahalanova's distance units is the difference of the means over the standard deviation. That's about 1.5 today.

If you imagine what the Ranch Handers looked like years ago, they were probably out here. Now the Mahalanova's distance is 2.5.

I'm able to statistically model this pattern in terms of that single parameter called Mahalanova's distance. I can make the pattern go away and I can make it come back. I can make it go away by making a bigger distance, and I can make it come back by making it a smaller distance.

Here is the observed pattern and here is the expected pattern. This is what we see today and this is what is predicted by the model. And I can make the model go away by moving those distributions apart.

But I can dump all this now. Forget it, we don't need it anymore. The purpose of this was to think, well, maybe this check mark pattern was due to misclassification. You know, we're being misled. The day is fuzzy and they're far apart and they're closer together now than they used to be, and our statistics are all screwed up because of it. Dump it. We just did this matching, we don't need this anymore.

DR. GOUGH: Well, the other thing that is really striking to me is that, I thought in the past, when comparing Ranch Hands versus Comparisons, that the incidence of diabetes between the two groups is essentially the same.

DR. MICHALEK: That's not true anymore.

DR. GOUGH: Well, that's what I asked about.

DR. MICHALEK: Because that's unadjusted. Yes, unadjusted, the overall is about 17 percent in both groups. But that's unadjusted.

DR. GOUGH: But when you adjust on the basis of family history, obesity and race?

DR. MICHALEK: Obesity in Vietnam, race, family history, and military occupation, I don't have the percentages. But now the relative risk is 1.2. There's a 20 percent in the Ranch Hand group, and the confidence interval does not include 1.0.

DR. GOUGH: This is distressing to me, but a clearer picture is emerging, for sure.

DR. MICHALEK: Well, we're going to have a meeting in December. I'll have a separate talk on this in December.

DR. CAMACHO: So in plain English--

DR. MICHALEK: In plain English, there's an increased risk of diabetes --

DR. CAMACHO: If you have two guys in Vietnam, both of them enlisted and one's chubby and one's thin. They both get the same exposure. The guy who's chubby has a higher--

DR. MICHALEK: Higher risk of diabetes.

DR. CAMACHO: -- risk of diabetes. Okay.

DR. MICHALEK: As he was exposed, and another chubby person in Vietnam who didn't get exposed.

DR. CAMACHO: Who didn't get exposed.

DR. STOTO: I think that supports original check mark theory, by the way.

DR. MICHALEK: Yes, it does, by the way. It supports everything that's happened in the last few months. That there is a relationship between diabetes and dioxin.

DR. HARRISON: How many people in the Ranch Hand group with diabetes? In other words--

DR. MICHALEK: About 16 percent out of 1000 --

DR. HARRISON: So you're saying there's 150 to 200. So what you have is 150 to 200 on this side, and then you picked 150 to 200 exact matches on this side.

DR. MICHALEK: No, no, we didn't match them. You're talking case control. We matched cohort. We took every Ranch Hander, whether they had diabetes or not, and we matched them perfectly to a control.

DR. HARRISON: Oh, okay.

DR. MICHALEK: And then we looked at differences on diabetes. And we stratified by dioxin body burden, and we see this.

COL MARDEN: And this check mark was in over 50 different analyses.

DR. MICHALEK: Oh, yes. We saw it in body fat --

COL MARDEN: So it does make you think that it was the statistical analysis rather than something specific to diabetes.

DR. HARRISON: It's always statistical analysis.

(Laughter)

COL MARDEN: This is true.

DR. MICHALEK: So we're going to go back, we're going to check to see if we can make some other check mark patterns go away with this careful matching.

MS. del JUNCO: Joel, and the results were significant for both groups?

DR. MICHALEK: Say that again, please?

MS. del JUNCO: The results were significant, the confidence intervals were significant for both groups for diabetes?

DR. MICHALEK: The results. Yes, the relative risk is significantly increased overall, and is significantly increased in the high category.

[Slide]

This is an overall, thumbnail sketch of the whole study. We've talked about all these things. And we've made a lot of reports, and they're all available on our web page.

This is just a quick overview of all the papers we've published. I know I'm running out of time, so what should we do? We were supposed to stop at ten.

And Jay hasn't done his slides yet.

I can stop here.

DR. STOTO: Can I just report that on this, we talked about whether the heart disease would be significant if you lumped all the Ranch Hands together? I think that the answer is yes.

DR. MICHALEK: I think we needed to check that.

DR. STOTO: I just tried to do -- I think the answer is yes.

DR. MICHALEK: It is?

DR. STOTO: Yes. Not adjusting for anything else, obviously.

DR. HARRISON: Well, we started a little late, so why don't we plan to go until 10:15, and then we'll take our break. Is that enough --?

DR. MICHALEK: In other words, I should finish up, and --?

DR. MINER: Yes. Go ahead, Joel.

DR. STILLS: Can I ask one quick question? In terms of the neuropathy and the cardiovascular disease, are you only seeing that in your group that is significant diabetes?

DR. MICHALEK: Yes, I have a talk on that, too. Of course peripheral neuropathy is highly related to diabetes. In fact, the relative risk of having peripheral neuropathy is about 30. Diabetics have about 30 times the risk of peripheral neuropathy of non-diabetics.

So in our analysis of that variable we had to be obviously very careful about diabetes. Are we seeing simply another reflection of diabetes or not? The end analysis was done with diabetes in the dataset, with diabetics in the cohort included, and then as a covariate, and it was also done with diabetics excluded. And we still saw a significant increase in risk of peripheral neuropathy.

But when we went back and looked at the medical records of every case of individuals that were diagnosed as having peripheral neuropathy, there was always some mention in the record of glucose. Even though they aren't called diabetic yet. It's interesting that the physicians wrote, "something to do with glucose or insulin" in their record.

DR. HARRISON: Well, that may be a self-fulfilling prophecy. I mean, if I see someone with peripheral neuropathy, I'm going to write in my notes that I have to rule out diabetes. So if you're just scanning, that's -- phhh.

DR. MICHALEK: Yes. But the point is well made that the two outcomes are highly related and they were addressed in our analysis.

So we have written many different papers, and these are the areas that we've published:

[Slide]

Statistical methodology, health endpoints, pharmacokinetics and dioxin levels. And many of those are published, of course, and some are in submission and some are out right now.

I want to emphasize here, something we failed to emphasize when we talked to GAO. GAO said in their report we didn't start publishing until 1990. That's not true. We actually launched our research immediately; and this first paper, published in 1980 -- actually, as you know, you write these things; they take years to write and get published. We began that work in 1977.

So we had papers published initially in Statistical Methodology because we were told that we would be working on a large cohort study using matched analysis; and the primary emphasis at that time was survival analysis. So were studying linear rank procedures and the Cox model and logistic regression and things like that during the period in the '80s, before we published our first health paper in JAMA in 1990.

And remember that the JAMA papers published in 1990 actually began in 1985. When we started to write those JAMA papers, we initially wrote them to include data from the Cycle 2 physical. But then working on the papers, the Cycle 3 data came. And so we updated the article to include only Cycle 3, or 1987 data.

So the activity of publishing began in the middle '80s; it didn't begin in 1990. That's all this is about. More papers on hypothesis testing, discriminative analysis, reliability theory -- these were all coauthored with visiting faculty that were working with us at the time. Published in Biometrica, Biometrics, Statistics in Medicine and other journals like that.

[Slide]

And we've continued up to the present day; we're still writing methodology papers in statistics. We have a paper in progress; we had a paper on calculating P-value that sounds fairly -- why are we doing that? Well, there was always a disconnect between the P-value and the confidence interval and the SMR, which we fixed, and published in the American Journal of Epidemiology in 1998. And recently writing papers on estimating new parameters in epidemiology such as lethality, and we'll talk about that later.

[Slide]

Now the first health paper was published in JAMA in 1990. As I said, the work actually began in '85.

And diabetes was first mentioned, the first published mention of it occurred because of the talk in 1991 or '92 in Helsinki, Finland at the International Dioxin Conference. And that was published in their proceedings, in work on halogen compounds.

Subsequent to that we had papers published in epidemiology and gonadotropins and diabetes. This is the primary diabetes paper which led to a talk earlier this year to the National Academy of Sciences, which I'll tell you about.

And this is the paper on chloracne that I already mentioned, and we have an interesting paper, I'm showing a strong relation between insulin and sex hormone b_globulin and dioxin in the Journal of Endocrinology and Metabolism.

A paper on cancer and immunology,

1999, American Journal of Epidemiology. And another paper on diabetes in Epidemiology showing a relationship between dioxin body burden and dioxin in our control group, which was reported by -- first authored by Matt Longnecker and that was reported to the National Academy of Sciences this year.

And papers on mortality and a letter to the editor on the possibility of differential binding of dioxin to lipids in serum in 1998.

[Slide]

In Reproductive Outcomes, all of our data on reproductive outcomes has been published in one form or another, except for fertility, and that's an article that we -- we went to lunch with Debbie del Junco, and she is with us here today.

Primary birth defects, a paper published in 1995. The work on it actually began in 1984 when we began to verify all health outcomes, all birth defects among all children followed by these men, by medical record review.

Sex of children is an issue. In the Seveso cohort it is shown that children born to families who, for whom the mother and father have experienced high dioxin levels and were all girls. So we repeated the analysis in our data and found no relation to the sex of the children and their father's dioxin body burden.

Here's the paper on testosterone (inaudible) published in 1997.

[Slide]

In Pharmacokinetics we had a number of papers published on the cohort with repeated dioxin body burdens and half life, appearing

primarily in the Journal of Toxicology and Environmental Health. The very first one appearing in 1989. And the very latest in 1999, and that's a statistic I quoted earlier, half life of 7.6 years.

[Slide]

Dioxin levels, the very first results from our pilot study at the Red Cross clinics was published in MMR, WR in 1988. And subsequent to that we have our paper on the skin exposure by questionnaire to the enlisted data I already showed you, showing a relation between on the job exposure in Vietnam and today's current dioxin body burden, and the reliability data I showed you was published in 1996; and we have a paper on the comparison group showing the data, the dioxin body burden comparisons published in 1998, and we have -- in the year 2000, which has just recently been accepted, we have shown a significant decrease in the dioxin body

burdens in the control group with time, which parallels a decrease seen in cohorts in Germany and other parts of Europe, that cohort body burdens are decreasing; the speculation is that that's due to regulation of industry.

[Slide]

DR. CAMACHO: I think we're missing a page.

DR. MICHALEK: Oh.

DR. STOTO: I think that page 11 of the handout is missing.

DR. MICHALEK: Oh, I'm sorry. Is a page missing?

DR. CAMACHO: I believe so.

DR. MICHALEK: Okay, I can fix that. We have the originals here.

DR. MICHALEK: In submission, this is the paper I was telling you about, into the neurotoxicology . We have some very dull papers in psychology that show absolutely no relation between the MMPI and dioxin, which would be very difficult to publish; but this is in submission to the Journal of Consulting Clinical Psychology. It's been with them now about a year, but before that it was submitted to other journals and bounced immediately, or said 'rejected' -- so this may -- we may never get this published. That's our paper showing no relation at all between the MMPI and any measure of exposure.

This paper is close, it's been reviewed and sent back to the journal. We've responded to the referees; this is showing the relationship between liver enzymes and dioxin body burden.

Hematology, this one is very, very close. It's been reviewed several times by the Archives of Environmental Health, and we've responded once more to the referees and sent it back. We expect acceptance very soon.

Peripheral neuropathy was submitted to the American Journal of Epidemiology, we got a very glowing letter back telling us what a great paper it was, and they rejected it. So we are responding to the referees right now, and we're going to resubmit to Neural Toxicology. That's the paper showing the relationship between dioxin body burden and peripheral neuropathy.

[Slide]

In this, a meta analysis of -- relating dioxin body burden and diabetes with dioxin body burden and diabetes in the NIOSH cohort, and that's in submission to Epidemiology. That gives the expected result; mainly -- you see a trend in the Ranch Hand group and you see a fairly wimpy trend, so to speak, in the NIOSH group, and it won't go away; it causes an interaction and prevents a meta analysis. It was not a very interesting paper.

And finally there was a paper on dioxin and diet which shows no relation between any measure of exposure to dioxin or any aspect of diet, and it's collected from the diet questionnaire given to our study subjects in 1997, I believe.

Is that when we did the diet questionnaire?

DR. MINER: '92.

[Slide]

DR. MICHALEK: In progress right now we have a measure of the carotid artery wall thickness. It was done by Dr. James Dwyer at the University of California, and he has shared that -- of course he's part of our team and he's been working with Billy Jackson, and we're relating that to dioxin body burden. That's one part of a two-part paper on cardiovascular disease and dioxin body burden.

We're seeing a relationship that is puzzling, between carotid wall thickness and dioxin body burden. We have a paper on medical symptoms. These individuals fill out a checklist of up to 30 symptoms at every physical. "I have aches and pains, I can't sleep, I urinate too much" all kinds of things; and those symptoms have never been described as related to exposure, and we're attempting to write a paper on that with CDC. That paper is in the works.

We have a paper on thyroid function with Dr. Arnold Schechter which is just about to start. And a paper on fertility with Ann Sweeney and Debbie del Junco and Kanazi {ph} University of California-Berkeley, which is just about to start. Although here we realize we have to clean up our datasets.

And there's the paper on check mark pattern which has been blown away by the result I just told you about; and dioxin body burden and elimination which I have a talk on that to give you later.

[Slide]

Days in Vietnam was an issue brought up by our advisory committee last year. Forget dioxin; number of days in the country, did that have anything to do with your health? And we have a statistician working on that problem right now. And we have other papers in progress -- others here that I will not read to you.

[Slide]

We have many reports; all of them are available on our web page. We were audited by the GAO, all of calendar year 2000 -- In 1999, sorry, and they released their report in 2000 with three recommendations: Release all of our data, improve our communication, and improve the advisory committee outreach; and all of those things are being done or have been done.

[Slide]

The data release. We are literally releasing everything that we've got to the public by means of CD-ROMs that we send to the Government Printing Office and by means of our web page. You can download datasets that we used in all of our reports. They're there in two formats: in SAS and in flat files. You can point and click and download those.

There's up to 12 clinical datasets for every physical exam. There's one for general health, dermatology, cancer, heart disease, diabetes, endocrinology. All of those are on our web page, all of the laboratory datasets are there, and everything to do with reproductive outcomes, and all of our mortality datasets.

Now we're just about to release all the data collected in 1985 and by the end of the year, we will release everything collected at baseline in 1982.

[Slide]

Limitations are clear; we know these, we've known them when we wrote the protocol. Cannot establish causality. There was a paper published later by Bross in Biometrics which clearly shows epidemiology studies cannot establish safety and cannot clearly say the ____ derivative is one, we don't have sample size to do that.

We don't have the power for rare conditions. All of these things are there, we've known about them. More recently it has been emphasized to us by the veterans that, "Gosh, why did we use a Vietnam veteran cohort for our control group? I wish we had used a non-deployed control group."

Well, that was the thinking back in '77, '78 and that's what we've got. And why did we use Air Force veterans? They wanted to see an Army study, which makes me regret that CDC stopped the Vietnam Experience study.

In accordance, the veterans are saying, we're asking the wrong question looking at Air Force veterans; why aren't we looking at Army troops? That was the Vietnam Experience study, which was stopped.

[Slide]

A suggestion would be, and this was brought up at a meeting at the VA a few weeks ago, to restart the Vietnam Experience study. After all, they received a physical and questionnaire just like the Ranch Handers did back in 1987, and the records are still there, they're in boxes. The study subjects are all identified and all the data is available to do a final examination.

So that idea is being discussed. Another study that has been sitting there and has not been fully published is the twin study. It's a study of about 4,000 individuals who didn't go to Vietnam; it had a twin brother who did go to Vietnam. And that study is being conducted by Dr. Seth Izin at the VA Hospital in St. Louis.

We have the dataset and we've been tracking their mortality along with the Ranch Handers controls, and we're about to give him a dataset so that he can look at mortality, anyway, comparing his ultimately matched study of twins.

DR. HARRISON: Were they raised together?

DR. MICHALEK: What.

DR. HARRISON: These were twins that were raised together?

DR. MICHALEK: Well, I assume they were raised -- I don't know. They're twins.

DR. GOUGH: They separate out the ones who were raised together from the ones who weren't.

DR. MICHALEK: They were born from the same womb at the same time.

DR. GOUGH: They've been doing this since World War II.

DR. HARRISON: Okay. Okay.

DR. MICHALEK: I can tell you more about that later.

Secondly, there's the idea of constructing a new control group for this study, which is certainly a possibility. For example, if there was another large cohort study out there with diabetes for example, we could pass -- and that cohort is good follow up on diabetes, as we do in this study; and if it was a large enough dataset and we could

find such a study, we could simply hand them a diskette and say "Here, please match your controls to our Ranch Handers" and it lets you look again at diabetes. That's a possibility.

DR. STOTO: Joel, on the Vietnam Experience study, my recollection was that there were two studies, one comparing Vietnam vets to other people who served in the military, maybe the Army at the same time but not in Vietnam. And that was in fact done, results were published from that.

Then there was a second study which would have compared people who served in the Army in Vietnam in trying to establish high and low exposures and compare those to one another. But the OTA, with Mike's guidance, said "don't do that one."

DR. GOUGH: No, no, no. No, no.

We did say that, but we were ignored.

DR. STOTO: But -- that study didn't get done. That's the one that didn't get done.

DR. GOUGH: No, no, no. That was the study that was done with the 600 people, the 600 men in Vietnam, 100 or so out, and there was no evidence for dioxin exposure.

So that study was dropped because you couldn't find people -- there was no power to find people who were exposed.

Yes, the Vietnam Experience study was just simply, "Did you go to Vietnam, did you not go to Vietnam?" Those results were published, and I don't know -- I don't even know if that was discontinued. The reason for discontinuing the dioxin study is pretty clear; because we couldn't find any evidence for --.

DR. MICHALEK: We're just saying that the idea is that this would address veteran frustration.

DR. STOTO: I'm not sure which one you're talking about revising.

DR. MICHALEK: I'm not sure, either. Although we need to talk about that.

DR. GOUGH: No, but the guys who had the dioxin measurements were not participants were not participants in the Vietnam Experience study, as I recall. They did not go and have the physicals and things.

DR. STOTO: Right. That's my recollection, too. But I'm not sure about that.

DR. MICHALEK: We didn't know those details, but we can check it out.

Almost done. Yes?

DR. HARRISON: No -- I'm just saying.

DR. MICHALEK: Okay. Go.

[Photo]

Here we are, these are our buildings. Don't look very fancy, but they're very nice inside. Each one cost $300,000, and lots of high tech stuff in there. A good computer system, lots of smart people.

[Slide]

Here's one of coders. By the way, we have triple-entry quality control. Everything is coded independently and blindly by two medical coders, and then adjudicated by a third. This is unprecedented quality control in this study. Everything in this study is checked 100 percent, layers of quality control in every aspect of the study, and that's what this slide is about.

[Slide]

Here are the freezers; this is an issue. We have collected over 50,000 specimens of urine, serum, adipose tissue, and semen, and they are in the freezers. They were collected, under informed consent, through IRB approval, to address the Agent Orange issue, and we still have them in our freezers today; and that's a point of discussion for later today.

[Slide]

Our LAN, new computer equipment which makes life very efficient for us; and our new shelving for medical records, we have collected over 4 million documents on the individuals through their repeated physical examinations and their medical records that they bring to us from their family physician when they attend every physical because we ask them, plus the corresponding records on all of their children and their girlfriends and their wives that produce babies. They're all in those folders.

And all of their military health records and military records showing where they were and when during their military career.

[Slide]

And we're scanning the entire pile of paper into a system so that you can reach any document on any subject with point and click, with really great resolution. And that's what this slide is about.

DR. HARRISON: So this is all OCR?

DR. MICHALEK: No; some of it's OCR and some isn't. Many of these documents don't lend themselves to OCR because they are a doctor's scribble on a notepad. Or they were mimeographed in 1956 and they're fuzzy. But many of the reports, very clear printed reports, are OCR.

DR. HARRISON: So some of it, though, in order to actually use the data, the person getting this is going to have to sit down and transcribe it, so there's going to be an ultimate layer of errors that you don't have any control over.

DR. MICHALEK: There are many layers of information here. The physical exam --

DR. HARRISON: I'm saying your information is pristine; --

DR. MICHALEK: Yes.

DR. HARRISON: I'm just commenting--

DR. MICHALEK: Yes, with the future. What the future brings.

What you've got, if you -- maintain the only release of this study would be what's on the web page. If you have now divorced the squeaky-clean electronic data, which was used on our reports, from the patient folders, that limits the ability of anyone to do research. Because now you will see, well this kid had a defect. What was it? What did the doctor say? Well, to do that, you need to open the report.

You've got to have -- and you need to open the folder. So you have to have access to the folder, but the folder's private, because there's this privacy and confidentiality; so we have some enormous problems here with regard to preservation of confidentiality, adherence to the IRB rules about confidentiality and about the release of data and privacy.

So all of that needs to be discussed separately. Thank you very much.

DR. HARRISON: Thank you.

Any questions?

DR. GOUGH: Yes, and a couple of comments.

Joel, I found one of the slides -- I assume the slides are for technical audiences, but when you give the morbidity results, with a plus/minus, I think for a lay audience the pluses are a little misleading. Because when it says cardiovascular plus, it's --

DR. MICHALEK: I know, it's hard.

DR. GOUGH: Well, it may sound good, but the problem is, it doesn't encompass --

DR. MICHALEK: All the caveats and all the --.

DR. GOUGH: Yes.

DR. MICHALEK: The cardiovascular plus is a very complicated picture.

DR. GOUGH: Yes. That's the only thing. I mean minuses are clear, but the pluses are complicated. That's only technical.

DR. HARRISON: In Joel's defense, though; what he said at the beginning was that because of the number of new members on the committee and everything, he wanted to give an overview.

DR. GOUGH: Yes. I agree.

DR. HARRISON: I find that this is considerably lacking in Joel's usual detailed -- (Laughter)

I might have even said welcomely lacking -- (Laughter) -- detailed.

DR. GOUGH: The other thing was, I was on the committee in 1990 when we urged the Air Force to begin publishing the results; and I think that everybody associated with the study deserves commendation for that, because although now I have this feeling to "be careful about what you ask for because you'll get it" because there's such an outpouring of information. And I am also very pleased that the Air Force has made its data so accessible, and is continuing to make its data accessible.

DR. HARRISON: I think that's an outstanding accomplishment.

MEMBERS: I agree.

DR. GOUGH: And particularly when there are people who, for various reasons, don't release data.

DR. MICHALEK: I know. If I were to tell you in detail the whole study, we would be here a long time.

(Laughter)

DR. BLANCAS: Okay, don't start.

DR. MICHALEK: For example, I gave this overview --

(Laughter)

DR. HARRISON: -- in detail, we went 2 hours and 20 minutes. I gave it in detail in the same time; 2 hours and a half to the Senate Veterans Affairs Committee. I gave it at great speed to the London School of Hygiene and Tropical Medicine in England in January. They gave me one hour.

So we cannot do justice to this study with this kind of presentation. I'm only trying to give you a watercolor sketch. So now you want to know detail, we've got detail ready for you, which you'll see in a few minutes.

DR. STILLS: Joel, I really want to say that we really appreciate this overview. I thought it was very informative; gave me a really broad overview as to the depth and all the factors that are involved in this study, and how critical, that you have addressed these issues.

This was extremely informative, as a new member of the committee.

DR. MICHALEK: Thank you very much.

DR. HARRISON: All right.

DR. MICHALEK: That means I succeeded. Thank you very much.

DR. MINER: Take a break.

DR. HARRISON: Why don't we --

DR. MINER: You want to press on.

DR. HARRISON: No. What's the committee's will? Maybe 10 minutes?

MAJ SPEY: Smoke break.

DR. HARRISON: Smoke break, yeah. A 15-minute smoke break.

MR. COENE: Okay, 10:30.

DR. HARRISON: 10:30 we'll start back.

[Recess]

DR. HARRISON: Have a go, Jay.

DR. MINER: All right.

Contracting/Program Management Overview

DR. MINER: good morning, I'm Jay Miner. I work with the program management in the Human Systems Program Office, and I would like to recognize Mr. Richard Overshoch who is in the Assistance Program Office, and the program management function is in that organization on Brooks Air Force Base.

I might say that one of my biggest activities during my active duty time was to limit the number of cups of coffee that Dr. Michalek consumed before he would give his talk.

(Laughter)

We really appreciate Joel's enthusiasm, and that carries over into the science an articles that he does, and that's great.

I thought, though, for all the new members, it might be important if we spent just a few minutes talking about program management and contracting specifically because there are two pieces of things going on. There is a technical side, that Dr. Michalek works, and then a program management side. The study was in fact designed that way to free the scientists first so they could do science; and secondly, to kind of limit the impression that management has control over what the scientists are saying. Because as was stated earlier, back in 1980 there was a very big concern that the Air Force was investigating itself and they would not find anything, and "Oh, gee, if a federal investigator found something, management would say 'no, no, no, you can't do that.'" So those were separated out specifically.

[Slide]

We'll talk a little bit about some program management, some acquisition strategy activities. Over view there, you can read down through those. Our program manager, Major Snedden, is not here today; he's up in St. Louis working on another program. He has several programs that he manages.

[Slide]

The program management concept specifically, we work the requirements side of the house, we take them from protocol, statement of work, schedule requirements -- Dr. Michalek says we are going to do this every five years no matter what, right on the button; and the budget and then incorporate any suggestions back to the technical side into the contract.

We do then manage the prime contractor, Science Applications International Corporation has been our prime contractor since 1985. We have quarterly management reviews with them, and specifically address the status of the contract, status of the program, milestones, we look at finances, we look at what data items are being delivered, what datasets, what reports; and we have a technical interchange then as well, we develop action items at these quarterly meetings and keep the program on track.

We also monitor the contract deliverables so all those wonderful chapters that you've got to review not too long ago, or some you got to review not too long ago, those are end items and we monitor the delivery of those.

Support contractor management, I am your support contractor; I work for Operational Technologies. You've noticed on the slide that Joel showed with the number of personnel, there were a lot of contractors on there. When this study started there were not many in-house contractors; I don't think there were any. But as the Air Force and Department of Defense have drawn down positions, we have had to give up civil service and active duty positions, and those have been replaced by contractors, onsite contractors. There's about 25 or 27, depending on who's working which day, that assist with our program.

[Slide]

Our in-house activities as well, team meetings -- we have a staff meeting every week -- is to make sure that the technical side of the house, that their needs are being met.

Well, as I said, this is a contracting effort, and here's how we're going to try and do this. We want to accomplish Cycle 6 by contracting for all of these things. And you may be aware of something called the Federal Acquisition Regulations. We are a government agency, we have to abide by those, and they put sometimes some timeline restrictions on when we can do things.

So specifically, that's why we're talking statement of work activities right now, because it takes a long time to go through the milestones and requirements to meet the FAR.

[Slide]

Just as a little bit of background, again for the new people, Cycle 1, 1982, this went as full and open competition. We had multiple contracts, Kelsey Seybold in Houston; we did have, Lou Marris was our organization; we did have a research center that actually wrote a portion of the questionnaire; but the Air Force served as the integrator, and we tried to run all these things.

And that didn't work quite as well.

Cycle 2 and 3, with Mr. Obershock's guidance, we said we want to have a single, private contractor, let them run all the subs, and we want a final product. That was awarded as a single contract, a full and open competition. We had three bidders, basically: Science Applications, Westat, and the Marsfield Clinic.

Cycle 4 we also went full and open competition, but only SAIC bid. So in Cycle 5 we went out with an advanced sources sought synopsis looking for people to do this study, under the guise of full and open competition, but no one responded.

So I went out and conducted a market survey on any firms that had ever provided any interest in doing a study. And usually their first question was, "Oh, well, yes we saw the solicitation notice. Are you unhappy with Science Applications International Corporation?" We said "Well, no."

They said "Well, why should we spend twenty to thirty thousand dollars putting together a proposal? They've been doing this for X number of years."

Only one firm, then, seemed to be interested. And we then went to the FAR, and it does allow for a sole source award if there are a limited number of sources. So we have obtained a justification and authorization -- that's what a J&A is -- to go sole source with SAIC for Cycle 5. And I'll talk more about that later.

Of course what we're looking for in a contractor is past performance; they won't read the bullets particularly, and current capabilities. We want the contractor to do an outstanding job.

[Slide]

We also want to do some streamlining initiatives. Specifically, a statement of work scrub, and again that's part of the purpose that we're doing here. We also look at our contract data requirements list, and see what type of data that we really need to do the study. And this is not only quality control data, but some management data as well; quarterly reports, monthly reports, what type of study plans do we need. Do we really need a biomedical test plan? Yeah, I think we do. Do you really need a statistical plan? Yes, we do. But we look at those each time in great detail to make sure that we're not asking a contractor to give us too much data. Why? Because every piece of data we ask for costs dollars. And we want to make efficient use of our dollars because there are limited funds.

We also like early contractor involvement. And we stay involved with our contractors on a technical basis even though the report has been written for Cycle 5, we're still talking and still doing bits and pieces on how to make it better for Cycle 6, a lessons learned.

And then our specification and authorization does allow for possible sole source award for Cycle 6. Like I said, we do have the advanced sources sought out on the street right now. Depending on the response for that, we may be able to go sole source again.

Now, with contractors sitting in the room here, I can't say "Yeah, we're going to go sole source" but -- okay.

[Slide]

Now again, why are we doing this statement of work stuff now? This doesn't happen until 2002. Well, here's the time line basically that's required by the Federal Acquisition Regulation; we start with the issuance of an advance sources sought synopsis, which asks for firms to let us know if they are interested and what their capabilities of conducting the study are. That went out this past week.

We have to make an acquisition plan, and this says it's a formal document, that we then present to an acquisition strategy panel -- that's a formal committee composed of contracting individuals on the Air Force - DoD side of the house. If that gets approved, up to higher headquarters, so on and so forth.

Lots of stuff going on here, but I want to point out a real important piece right here. When we release the Request for Proposal out to a contractor or out to contractors, that's when the statement of work gets locked in. If we don't have a real good handle on it, a real good statement of work, and we have to go back and make a number of changes, every change we make costs dollars. We award this as a firm, fixed price contract with one reimbursable line item on it, for the logistics and per diem that we pay our participants. But otherwise it's firm, fixed price.

So again, every time we change, that costs dollars. And that's why at the end of this, when we're talking about format of the final report, during our last committee meetings there were some members that said "Well, can't you present the data a little differently? Let's have it look like this, or let's change it to look like this. Or let's change it to look like this."

We could do that, except that costs big dollars and causes delays. So if you have format considerations, now is the time to get them out, and that's why we're going on this route.

We are looking for a contract award in June of 2001. This is a little bit earlier than we've done in the past. That's primarily to give Science Applications and Scripps Clinic a little more prep time. Usually if we awarded at the end of September, there are sometimes physical modifications to the Scripps Clinic, and getting forms

printed and so forth; then lots of leg work needs to get done, lots of things need to happen to pull this off by the spring of 2002.

So we're going to try to give the contractor a little more lead time in doing that.

LTC BURNHAM: Whoever that might be.

DR. MINER: Whoever that might be.

Questions?

DR. GOUGH: When will the exams start, provided that all this goes on?

DR. MINER: We're looking for a May 2002 start date, I think.

DR. CAMACHO: I'm real new. So you're asking us for our input for something you want to kick out the door by June?

DR. MINER: Actually, I want to kick it out the door by April.

LTC BURNHAM: What we really want is another meeting in December, two months from now, and that's when we want your input.

DR. MINER: Right. This is an orientation; bring ideas.

DR. CAMACHO: So we get a sketch of what your game plan is now? To critique --

LTC BURNHAM: Right, that's what -- we'll be going over that.

DR. STOTO: The last item in the briefing book was, I thought, a draft statement of work. Oh, no, that's the old one.

DR. MICHALEK: That is, we put the old statement of work in the book so you get an idea what they look like.

DR. STOTO: I see.

DR. MICHALEK: Then what we're going to do is modify that one.

DR. STOTO: But on the agenda for tomorrow is it discussed?

DR. MICHALEK: Yes.

DR. MINER: Yes, we will discuss in greater detail the statement of work. But I just wanted to go over the contracting process, especially for the new members, why we're having to do it now, and what that means.

DR. HARRISON: Any other questions?

DR. STOTO: When did it become Ranch Hand II as opposed to Ranch Hand I?

DR. MINER: That is the name of the program element in the DoD budget.

DR. STOTO: So the study has been Ranch Hand II since the beginning.

The operation in Vietnam was Ranch Hand I.

DR. MINER: Well, there was just operation Ranch Hand, in Vietnam.

DR. GOUGH: Mike, that's a parallel study we don't know about.

(Laughter)

VOICE: A parallel universe.

DR. HARRISON: Let's try to move on here.

What do we do next?

DR. MICHALEK: Are we ready for the next?

DR. HARRISON: Okay. No other questions.

Review of Minutes

The next order of business is to go over the minutes. Since I'm the only one that was here -- no, I'm the only one that was here for the whole meeting, Dr. Stoto just showed up for --

DR. STOTO: You know, it said I was missing at the beginning but didn't say when I showed up. Other than that, I thought it was okay.

DR. HARRISON: I tried to figure out how many pages of minutes there were before you got to the meeting and after you got to the meeting, and I couldn't make that correlation.

Does anyone have corrections to make to the minutes?

MS. JEWELL: You don't have any, Bob?

DR. HARRISON: I have a -- of course.

Actually, not -- on page 3, and this is trivial, really. It's the fifth line from the top, not counting the header. It says that I said that obesity causes diabetes; and maybe I said that, but that wasn't quite what I meant.

COL MARDEN: Contributes.

DR. HARRISON: Yes; could we say that obesity is a strong contributor to diabetes or something like that?

MR. COENE: Done.

On page 4, second -- actually third paragraph -- that paragraph just didn't make -- actually, that relates to something that I mentioned, Joel, to you earlier this morning about trying to make the relationship, that the perivascular disease didn't make sense; but it might actually make sense if you analyzed the endpoints that you'd expect to be associated with an increased occurrence of diabetes and metabolic disturbance.

So I guess that's not a correction. At the bottom of the page, though, it says that Dr. Check had prepared copies of her summary and tables, and since those tables were referred to in these minutes, I wonder if we shouldn't incorporate those tables in the minutes.

Just a question, Joel, on page 10, second paragraph from the bottom. I'm not sure if this makes a whole lot of sense to me, either; but it says that I noted that the labeling of subjects as having Type II diabetes in the study is not supported well enough in the report. And you said that you were going to add additional data to the chapter.

DR. MICHALEK: The additional data was, there was one individual with Type I diabetes. And that was stated.

DR. HARRISON: Okay. all right.

And on the last page -- actually, that's not really a correction to the minutes anyway. Forget it.

Page 17, I know this is trivial. But paragraph 3, it's Wolf-Parkinson, not -sons. It's Wolf-Parkinson-White. They were the three physicians to describe that particular -- it's not Wolf Parkinson light. That sounds like a beer made in Massachusetts.

So it's called Wolf-Parkinson-White syndrome.

That's all I have.

DR. MICHALEK: Well, I had some slides to summarize what happened at the last meeting and how we responded, so I suggest that --

DR. HARRISON: Okay.

DR. MICHALEK: October 1999 --

DR. HARRISON: Oh, do we have to accept these minutes?

MR. COENE: Yes, as amended.

DR. STOTO: So moved.

DR. SILLS: Second.

DR. HARRISON: It's been so moved by Dr. Stoto and seconded by Dr. Sills; and we accept the minutes as corrected.

Anyone opposed?

[No response.]

All in favor? Just say aye.

[Chorus of ayes.]

Okay, that's done. Let's go.

Action Items from Last Meeting

DR. MICHALEK: This is the same meeting, the meeting for what you just saw the notes. It was October '99. At that point the committee was doing its final review of a report, the report summarizing the 1997 physical, which was subsequently released to the public in the early part of this year; I believe February of the year 2000.

And here I'm just summarizing statements made by members of the committee regarding the study. Dr. Camp, for example, suggesting that these two procedures, sigmoidoscopy and treadmill be conducted perhaps the next physical.

There's a slide talking about these items later in this presentation.

Dr. Trewyn was concerned about other herbicides may or may not contain dioxin, and Favata was interested in residential history, and Dr. Stoto were talking about tables, where we would indicate nonsignificance with an NS, for example.

Dr. Miner just pointed out, wanting to change the format of the report at the end stage, which is very expensive in a fixed price contract, and that's why we're resistant to that.

DR. STOTO: But it's something we should talk about for the next --

DR. MICHALEK: For the next cycle.

DR. MINER: Yes.

DR. MICHALEK: And that's why we're here today, is to firm up what we're going to do in the next report and the next physical.

And again Dr. Favata mentioning some things about the questionnaire. Dr. Camp wondering what the relation of reported health was, and I just told you it is related to, among other things, diabetes.

[Slide]

And some items there mentioned by the members of the committee. One item brought up by Dr. Trewyn was the actual location, where are these men? And in particular, where were the controls; suggesting that perhaps our control group was affected by the locations of their tour.

This is not an easy question to answer thoroughly, because our dataset doesn't have the necessary detail even today; but the caveats here and the complications were that these men had multiple tours of variable lengths, and they were in different locations and sometimes the actual location of the individual isn't precisely represented on the record. What might be represented on the record is the particular place for a unit, but the unit might have been moved during his tour to somewhere else.

So this takes research, and we're talking about over a thousand people here in many tours, so it's quite a lot of work, and it's ongoing right now to improve our --

DR. STOTO: Are you talking about the controls here?

DR. MICHALEK: Yes.

DR. STOTO: This is about the controls?

DR. MICHALEK: These are controls, right. That was Dr. Trewyn's idea.

So what we're doing is we're completely revamping our tour dataset to include the precise location of every single tour of all Ranch Handers and all controls. And that's not finished yet; we're still doing that.

[Slide]

This is just a display of the complications of the data --

DR. GOUGH: Excuse me. That issue came up because of what? Concern that some of the comparisons had been exposed?

DR. MICHALEK: Either that, or that the comparison group may not be -- there may be some adjustments that we're missing here when we compare Ranch Handers with controls.

LTC BURNHAM: If I remember right, it was something to do with the fact that Dr. Trewyn was concerned that maybe around the bases themselves where these guys were stationed there may have been spraying for fields of fire and that sort of thing.

DR. MICHALEK: So here is a table showing the -- we have what's called the qualifying tour. That's the one where you actually located the -- with some level of detail but not completely -- where they were. That's the tour that enabled them to be a Ranch Hander, or enabled them to be a control. They had to be in a certain unit at a certain time and a certain place. And that is what we searched for in the military record to determine whether a particular Air Force veteran was a control or not, or a Ranch Hander. And these are just the locations of where they were without regard to group.

[Slide]

Here are some days in Republic of Vietnam in the comparison group who went to at least one physical, and there you see the distribution is highly skewed. A lot of people were there less than 100 days, 457, and -- I'm sorry, a lot of people were there less than a day -- and a lot of our controls didn't spend a lot of time in Vietnam at all. They were in Thailand or Cambodia or somewhere else.

They were in Southeast Asia. Didn't necessarily mean they were in Vietnam.

DR. STOTO: What about the herbicide use in those places? Do we know that --

DR. MICHALEK: That's an issue. There was some spraying, we found out just recently, in Thailand.

[Slide]

So where did this reference cohort come from? The point was, this was defined in our protocol in 1977. That's where it came from, and why are we using other control groups? Well, I went through some of the description of that, those discussions that took place in 1978. Well, why didn't we use the U.S. male population or other control groups? And today we're still thinking about that.

[Slide]

Here is a description of the Vietnam Experience study relative to the Air Force Health Study, and who was in the comparison group and who was in the reference group.

[Slide]

Then there was an issue of, where do these normal ranges come from that we use at Scripps Clinic? When Scripps decides who was abnormal and who isn't. On insulin, for example, where do they get their normal ranges from?

Well, generally they come from a package insert that came with the laboratory kit that did the insulin measurement in the lab. And those measurements and those normal ranges come from who knows where; they could be hospital populations or outpatient clinics, or whatever.

So many times we analyzed the data using Scripps normal ranges, but we also sometimes analyze using percentiles of our own control group. And you will get different results depending on which normal range you use. And we take that into account in many of our analyses.

[Loud noises from adjoining room]

[Slide]

Here's a summary of the different herbicides that were sprayed in Vietnam -- showing all the different concentrations of dioxin and 245T. It was the phenoxy group size that contained TCDD, or dioxin.

It happens that blue had no 245T and therefore contained no dioxin. But only a very small percentage of all herbicide spray was herbicide blue; it was only 3/100ths of a percent. The question was, what was the percent content of 24D in some of these service sizes, and here I'm summarizing that. Blue, green, and pink didn't contain any 24D, whereas purple was 50-50.

And here's a summary of the 245T and dioxin in orange, white and blue. And there you see the great majority of all herbicide spray was Agent Orange. However, 27 percent was white, and white contained no dioxin at all.

[Slide]

And that's the percent of the herbicide that was 24D.

[Slide]

This is just emphasizing the point that when we compare all Ranch Handers versus all control, we are now addressing any exposure whatsoever, to any kind of herbicide.

Yes.

DR. STOTO: Can I ask about the previous thing, was that herbicides that were used in Vietnam or sprayed by the Ranch Hand folks?

DR. MICHALEK: Yes, sprayed by Ranch Handers in Vietnam.

[Slide]

Whereas, you see here with the first model, we had four statistical models. The first model addresses any exposure to any herbicide, because there is no dioxin measurement in the analysis. Whereas the other models involve various ways to use the dioxin measurement; but there you should realize that the dioxin concentration in the body is not only a measure of dioxin concentration; it's also a measure of exposure to herbicides, period.

So we believe -- that's our hypothesis -- that individuals who have the high dioxin levels also have high exposure, not only to Agent Orange but to other herbicides, too; although we can't measure that.

[Slide]

There was an issue raised by Dr. Favata of the possibility that individuals who live near hot spots in the United States may be confounding our results. And so she wanted to know what was the residential history and what's the story on the exposures in the United States.

Well, we have the entire residential history of their entire life in a dataset showing not only the location by residential address, but by latitude and longitude, too. So we know where they've lived.

But we don't have, not made an attempt yet to relate that to existing EPA datasets of hot spots in the United States, such as the Vertac Hercules Superfund site in Arkansas, for example.

There are places where individuals could simply live within a few miles of a certain factory will have high blood levels simply because they live there. Because of pollution. So that's an issue and it's still something we want to do and have done that yet.

Then there's the issue of a more detailed look at employment history. We do have the entire employment history of every individual, every job ever held for more than three months; the start date and the stop date and every job coded into a standard coding system so we know where they have worked and what they did, and the idea is to use that data to try to resolve some of our findings; have not done that yet, but we could.

Then there are these other procedures that were mentioned. We see some of these as evasive and risky and logistically difficult because we're walking the 2000 men through a clinic over a ten month period; they're there like three days and they have many other procedures to do.

Yes?

DR. HARRISON: If I recall correctly, though, Dr. Camp was saying --

DR. MICHALEK: I know. I misinterpreted Camp. He's suggesting these be done on a case-by-case basis.

DR. HARRISON: No. What happened was, that some of the men who were evaluated at Scripps were told that they should have sigmoidoscopies done. And that they should go back to their primary care doctor and have a sigmoidoscopy, because they had either -- I don't know, positive blood in their stool or this, that or the other.

COL MARDEN: Yes, it was a medically-indicated follow up kind of thing.

DR. HARRISON: And Dr. Camp was questioning whether that shouldn't be the responsibility of the study.

COL MARDEN: To pay for it.

DR. HARRISON: Yes. And I'm just going to add that I'm not sure that Dr. Camp's right; and I can see reason to disagree with him; but that was I think -- his question was basically, in this aging population, as you find what you think are non-related problems, where does your responsibility end in actually performing a procedure like this?

DR. MICHALEK: I'm sorry I missed that point. That's right, you're correct.

DR. MINER: Some of them did elect to have the sigmoidoscopies at Scripps and paid for it with their insurance. But I see where you're going with that.

DR. MICHALEK: And isn't it true that Scripps offers the procedures --

DR. HARRISON: In terms of clinical studies, in general what a consent form says is, that "if we make you sick from the study, we'll take care of you." But if you just happen to get sick while you're being studied, you're on your own.

COL MARDEN: We discovered that you're sick.

DR. HARRISON: Yes. So as I said, I'm not sure I agree with Dr. Camp, but that was his issue.

DR. STOTO: To what degree do veterans benefits cover things like this?

LTC BURNHAM: Only if it's service-connected.

DR. HARRISON: There are also income issues, though, right? So if you're poor and you're a veteran, then you may still qualify for care even if it's not service-connected; isn't that right?

LTC BURNHAM: Although the VA would generally say, would be done at our facility. I'm aware --.

DR. STOTO: But having the option to do that would be better than nobody.

DR. HARRISON: Well, and I'm not sure that you might not think of this as a -- and your IRB would probably have to deal with this -- as an inducement to continued participation.

LTC BURNHAM: We might find out something we're interested in, also.

DR. HARRISON: Well, that's --

DR. STOTO: That's a different issue. I think the issue here is that in the course of the research, you're providing screening which is beneficial.

DR. HARRISON: And a very comprehensive screening. I mean, you wouldn't get this kind of screening anywhere else.

DR. STOTO: It's beneficial, but it's only beneficial if people have the ability to follow up on it.

DR. HARRISON: Exactly.

DR. CAMACHO: I would be suspicious of somebody getting those tests as they went back to the VA, to be certain that that really happened. But your idea about keeping people in, reducing the dropout rate, it's an incentive, a big incentive.

DR. HARRISON: Yes. But see, the IRB would have to deal with that, though, see; because you don't want -- you can't be coercive in a clinical trial. You can't set it up so that the person can't afford not to participate. And that might be an issue.

DR. MICHALEK: Dr. Camacho, you should realize that, as they depart the clinic, they are outbriefed by a diagnostician over the entire three days or two days they've been there on what their findings are.

They are given a letter describing all the abnormalities and recommending, if necessary, that they see their doctor. And subsequent to that our staff calls them up to make sure they see their doctor and remind them.

They get intensive follow up by our staff, continually; everyone who ever went to Scripps, we continually track these people. So they are reminded to see their doctor.

DR. HARRISON: So let's say, Joel, for those people for whom it was recommended that they have sigmoidoscopies -- I'll be impressed if you know this, but how many had that recommendation made and how many actually got their sigmoidoscopies?

DR. MICHALEK: No, no but we can certainly answer the question later today.

DR. HARRISON: Yes.

LTC BURNHAM: I did get a letter this year from an individual who did follow up and was thankful because it was present -- his physician said it's lucky you got this, because we need to remove it. He felt like the study saved his life.

DR. HARRISON: You know, from a public relations standpoint, what you're doing is good, and I'm just repeating again, I don't think that Dr. Camp is exactly correct that this is an obligation for the study to perform.

Go ahead.

DR. STOTO: Do you do a PSA test on these people?

DR. MICHALEK: Yes.

DR. STOTO: That is a beneficial thing as well.

DR. HARRISON: Oh, yes.

VOICE: Also has lots of false positives.

DR. MICHALEK: Also, we did skin biopsies for cancer, because they're examined by a dermatologist; and any suspicious lesions are noted.

DR. HARRISON: They're not biopsied as a part of the study, are they?

DR. MICHALEK: Do we pay for the biopsy?

MS. YEAGER: Yes.

DR. MINER: Yes, we do.

DR. MICHALEK: You're kidding me?

DR. MINER: We do.

DR. HARRISON: So you do ultrasound?

DR. MICHALEK: No, skin biopsy.

DR. HARRISON: Oh, a skin biopsy. I thought you were doing prostate.

DR. MICHALEK: No.

DR. MINER: No, no, no.

DR. MICHALEK: We do a punch biopsy on the skin.

Somebody raised the idea of treadmill testing.

CAPI questionnaires, we talked about that. We changed our questionnaire methodology in 1997 to a laptop, menu-driven questionnaire. And the answers are then entered real time, on the keyboard. The questionnaire has built-in range checks and logic checks; that's new. In the early parts of the study it was a hard copy questionnaire, being filled out in pencil by an individual.

And it's a nice thing, but we didn't realize that we needed to have a nicely formatted printout so we could read it; what we got from NORC was dataset results, which are very handy, but you ought to know what was the question and what was the answer. So we're getting NORC to fix that through SAIC, provided nicely formatted output.

[Slide]

The baseline questionnaire is a point you need to know, that in 1982 we gave a very extensive questionnaire, covering their entire life up to that point plus all occupational exposures and bad habits such as smoking and drinking and family history. That's the baseline questionnaire which is different from the interval questionnaire.

There are questions on baseline that are asked only once, and then at interval we ask you, "Since the last interview has a doctor told you that you had diabetes?" for example. In other words, it's an interview bounded by the five year previous to the previous physical.

Well, everyone gets the basic questionnaire of course at baseline, but any new participant gets it also. So we have that questionnaire, separate from the interval questionnaire that we did. And we have not changed that on purpose, because we want to be able to have consistent data across study subjects on that instrument.

[Slide]

There are questions about drug use. We have addressed that in our questionnaire using our randomized response method, and we might want to refine that for the next study cycle. Now we ask them about marijuana and heroin and cocaine and other things like that.

It's only a small percentage of this group that use those illicit drugs; but still, it's an important issue.

[Slide]

Here's a discussion of residential exposures and possible use of ATSDR exposure history questionnaires. So we might want to consider that for the next physical.

You should also know that, I believe, if it's not in your loose-leaf, if you go to our web page, on our last cycle report there's a schedule that shows what happens while they're there at the clinic. You know, they get an hour for psychological testing, they get two hours for interview, they get -- and then they go to the different physical exam components.

So there is a certain window of time at the clinic where they're interviewed. So we don't have an unlimited amount of time to apply questionnaire-ing. So that's an issue, and that has to be traded off with other things, probably.

[Slide]

And health status. Of course we've already partially answered the question here that there is a relationship between reported health and diabetes.

[Slide]

And the ESR erythrocyte sedimentation rate, someone suggested that we move that from the general health chapter into the hematology chapter. So that's possible certainly to do in the next cycle report, now that we're in the planning stages for that.

[Slide]

There were questions about how was the dioxin handled, and they answered that by showing the CDC protocol.

[Slide]

And the changes in dioxin level with time; in fact, our most recent paper shows that in the control group, and we've shown that in our papers on half life.

There was another issue, we found a relations between other neuroses and other liver disorders with dioxin body burden in our latest report, but that was a conglomeration of ICD codes. There were many conditions that went into that variable called "other neuroses". There were many conditions that went into a variable called "other liver disorders."

So separately, we asked SAIC to take that apart and dissect those outcomes, and they did that and they delivered a report, and that's going to be on our web page very soon.

And the answer is, if you take it all apart and look at the individual pieces, you don't see anything -- which happens a lot in statistics. When you conglomerate you see a pattern, but when you try to take it apart and see it, it's gone.

So there's no outstanding piece of these that seems to be driving the finding, as I recall.

DR. HARRISON: That wasn't a part of the original --

DR. MICHALEK: No, it was not part of the original report.

DR. MICHALEK: No, it was not part of the original report.

DR. HARRISON: So that's an add on?

DR. MINER: Yes.

DR. MICHALEK: That's an add-on.

DR. GOUGH: It costs money.

DR. MINER: That's an add-on, that's right.

DR. MICHALEK: And we're to reconsider the use of NS tables in the report, as I said earlier today. And there were some questions about immunology, and those changes were made according to Dr. Check's review. And that's it. That's what happened in October of last year.

DR. HARRISON: In the report, did insulin-dependent get changed to insulin-requiring?

DR. MICHALEK: Yes.

DR. GRUBBS: Yes, many times.

DR. HARRISON: Okay.

Does anybody have any questions?

[No response.]

Okay, we're just zooming along here now. So what is this heading, Institute of Medicine and Environmental Protection Agency reports?

DR. MICHALEK: Well, somebody considered that important to know how we relate to the IOM in their recent review of diabetes and dioxin.

DR. HARRISON: I saw a newspaper article on that.

DR. MICHALEK: And how are these findings and this study related to EPA's dioxin reassessment, and that's what these slides are about.

Let me just flip through them so I am reminded of what these slides are about.

[Pause]

DR. MICHALEK: I wanted to get my mind clear on what we're doing here. A second.

This is another way to look at the Ranch Hand study, from its interface with the Institute of Medicine and its interface with EPA.

Now separately, during this meeting today, I have a very detailed talk on diabetes and dioxin to show you; I guess it comes next after this. So we're touching on diabetes and dioxin here, but then you're going to see it again in great detail in a little while.

[Slide]

So what has happened is that -- certainly Mike Stoto can talk in great detail, too -- but the IOM recently released a report: Veterans and Agent Orange. It's a new installment to their series of books on Veterans and Agent Orange, which is a biannual review of the entire issue, animal and human studies, all studies ever done in the world on dioxin in humans or dioxin in animals are reviewed by the National Academy in a book every two years.

That includes us. All of our reports and articles are mentioned in one way or another in that book. And that book is designed to render an opinion about certain conditions and to -- to be useful for Congress and the Department of Veterans Affairs to make decisions about compensation.

Well, recently the issue of diabetes and dioxin has become a centerpiece, and that has led to a new installment, particularly just on that issue.

Now the eight IOM books cover all health conditions in general, but this particular installment had only to do with diabetes. It was released just a few days ago on 11 October. It has the same format as their books. And the emphasis on the interpretation has to do with statistical association and not causality. That's the point made throughout the interpretations.

Now there's four categories of IOM interpretations, and I'm listing them here, telling you what conditions have already been assigned to the particular categories by the IOM, as reported in their latest text.

The strongest category of data is that called *sufficient evidence of an association*. And in that category they have assigned soft tissue sarcoma, non-Hodgkins lymphoma and chloracne, to date.

The second strongest is called *limited suggestive evidence of an association*, and that list includes these conditions you see on the screen. Spina bifida, that's the finding I described earlier, based on -- the basis for that decision was the data coming from this study. Spina bifida in children of Vietnam veterans.

DR. STOTO: Can I make just one point about this? It says 'association' which you mention. But the other thing is that --

DR. MICHALEK: But cannot rule out.

DR. STOTO: Well, no. The other point is that the threshold for making it into this category is very low, compared to what scientists would normally do. It's because both the congressional staff and the VA staff were quite insistent that that was the appropriate standard that they had to use.

LTC BURNHAM: David Butler gave a briefing on this in Dioxin 2000, and he mentioned the criteria for this is one good study that does a good job of controlling for chance, bias, and confounding. That's it; one study that does those things.

DR. MICHALEK: But of course I believe you're still looking for consistency. If you saw one good study that showed an association and then you found out a bunch of other studies that were all pointing in the opposite direction --

DR. STOTO: And were good studies.

DR. MICHALEK: -- you might change your mind about that.

DR. STOTO: Yes. I think it's a little bit different than that. But the key point is that's a very low threshold. And at a congressional hearing about spina bifida, we had Joel asked the question, does this establish causality? And he said No.

And we had the guys from CDC say "Did their studies establish causality?" And they said no. And then we had to say, "Why do your studies differ?" and it was because, first of all it's not causality and secondly because we have a very low threshold that the Congress asked for.

DR. HARRISON: Sort of like "possibly, probably, and surely."

DR. STOTO: Right.

DR. HARRISON: This falls into the "possibly."

DR. MICHALEK: So this is the state of affairs right now.

DR. STOTO: You can't rule out as another way of --

DR. MICHALEK: Yes. Inadequate or insufficient evidence. There you see the list.

The list is long, actually; quite a lot of conditions on that list. Inadequate or insufficient evidence, and you have -- I have handouts for this.

MS. YEAGER: We have them.

DR. MICHALEK: Limited evidence of no association --.

[Slide]

So then the issue is diabetes. To give you the bottom line, diabetes was put in the 'limited suggested' category. It was based on several articles, and there's a two page slide here showing the list of articles it was based on.

To describe these two quickly, Calvert et al., 1999, is a study of diabetes by self-report in the NIOSH study, and relating that to dioxin body burden. They saw a very weak relationship between diabetes and dioxin category, similar to our dioxin category analysis in this study.

The caveats are that they didn't have medical record review like we had. They had self-report of diabetes. They didn't have medical follow up, they didn't have repeated measurements of, repeated physical examinations. They didn't have all the covariates that are present in this study.

So there are differences of strength of these studies, and there are complications in interpretation. But certainly this one was an important study, because that NIOSH cohort had much higher dioxin levels than the Ranch Handers did, let's face it. And you saw the slide earlier when I showed you those bar charts.

Steenland was another analysis of the NIOSH cohort strictly from the point of view of mortality. All us in epidemiology know that that's a very unhappy to analyze diabetes, because diabetes generally doesn't show up on death certificates. So the prevalence of diabetes is usually much higher than what's indicated on death certificates.

And he found a relative risk of something like 1.05, which is certainly not significant.

And Vena, et al., was another -- I believe a mortality study of the IR cohort. The IR cohort is a conglomeration, a meta-analysis of industrial cohorts from all around the world, which include the NIOSH cohort, and was used by the International Agency for Research on Cancer to conclude that dioxin is a carcinogen. But it was based on a huge collection of over 20,000 workers who had demonstrated exposure to dioxin.

And they used that cohort to study diabetes, and with as many caveats as the Steenland paper, found an increased relative risk, but not significant.

And Calvert, et al., looked at glucose and insulin, but Calvert, et al. in 1996 looked at glucose and insulin, much like we do, against dioxin body burden, and found a suggestive but not significant increases.

[Pause]

That was the mortality study. Steenland '99 was death with diabetes. I guess these were two very similar papers on Steenland '99 and Steenland '92 were both mortality studies looking for death with diabetes mentioned on the death certificate. Both relative risks were small and not significant.

Cranmer was interesting because it's getting closer to the Ranch Hand-type analysis. Cranmer, he went to the Vertac Hercules Superfund site cohort, which are men who worked in the herbicide plants in Arkansas and isolated 77 individuals were nondiabetic, and you had demonstrated -- he only had dioxin body burdens measured, just like Ranch Handers do -- and he broke those out into low and high; less than 15 parts per trillion or greater than 15, and he looked at insulin. And he found a significant increase in insulin levels, just like we do in the Ranch Hand non-diabetics.

Yes.

MAJ SPEY: Sir, how many of these studies that you've annotated here are based on blood measurement of dioxin?

DR. MICHALEK: So far -- the Calvert paper is based on blood measurements. The Cranmer paper is based on blood measurements. Pesatori is based on blood measurements -- that's from the Seveso study. Pesatori found an increased risk of diabetes in women at Seveso but not the men.

And the rest of these are all based on -- of course those are all our papers; those are all based on blood measurements.

The papers that were not based on blood measurements are -- well, I don't know. I wouldn't be surprised if the Steenland papers did, because they measured dioxin in the NIOSH cohort.

DR. STOTO: I think they were not, Joel. I think they were in the full cohort.

DR. MICHALEK: Right. Yes.

Some of these did not include dioxin measurements, but many of them did.

So what we've got is a mixed picture of certainly -- and here you see, you already saw the effects of -- I'll have more to tell you on diabetes in a few minutes. You saw the pattern in the Ranch Hand study, the increased risk, and Longnecker just recently showed a relation, statistical relation anyway, between dioxin and diabetes in our control group.

Now even there, we had controls with up to 10 parts per trillion all at background levels; there's in evidence a suggestion of a statistical association. And here was the paper showing, Michalek '99, et al., is the -- in nondiabetic Ranch Handers we see significant increase in insulin with increased dioxin levels, which is consistent with Cranmer.

So that's the basis for -- not finished. Then the Australian study of Vietnam veterans compared the prevalence of diabetes in the Vietnam veteran cohort against national rates of diabetes in the general population, and they found more diabetes than expected in the Australian cohort. And there was no mention of statistical significance there. I don't remember that, whether it was significant or not, but it was an increase.

And Henriksen N87 is our diabetes paper.

DR. GOUGH: Joel, I didn't hear -- the Seveso result was, there was an increase in women?

DR. MICHALEK: As I recall with Seveso, there was an increase in the women but not the men, in zone A.

Sorry, Seveso was a 15 year morality study and it found a relative risk of 1.2 in the females in zone R. The results were significant.

[Slide]

So the conclusion of IOM was that there's a limited suggested evidence of an association.

LTC BURNHAM: And again, the importance here is that the VA uses this report for compensation. In the past, all the others that have gotten this designation have been compensated.

DR. CAMACHO: Which report are they using?

LTC BURNHAM: This report, this IOM report, the VA uses to make recommendations on compensation.

DR. MICHALEK: Now as part of their review of the diabetes issue, I presented a talk before the IOM on June 9th of this year. That talk, together with improvements that were made subsequent to questioning that I received during that presentation is the talk I will give to you today, to show you what I showed to IOM and how that talk, with embellishments or expansion to include responses to their questions.

[Slide]

Separately, the EPA is currently conducting a dioxin reassessment from the point of view of regulatory activity in the United States. They have a report which is several thousand pages; it's in three volumes, many chapters. In particular we were interested in the epidemiology data of both cancer and non-cancer effects. We were also interested in their overall conclusions.

So we as a group proofread their report over the last couple of months. And we sent them a line-by-line critique of their chapters 7, A, B, and their integrated summary in Volume III, and we delivered that and they very graciously accepted that and now are making changes in their report.

What we found were many errors in coding our papers or things that they missed, but none of which would change the conclusions of their report. You know, they may have misspelled a name or they may have gotten a citation incorrect or one of their sentences may be slightly misleading, in our opinion, so we asked them to change; things like that.

If you'd like to see that, I can get that for you, our point-by-point response to EPA's dioxin assessment. But we have delivered that, and I am planning to attend their advisory committee review of their document, which will occur on November 1 and 2 of this year, in Washington, in Arlington, Virginia. And I believe Ron Tredy may attend that, too, and Mike Gough.

DR. GOUGH: Will you make a presentation?

DR. MICHALEK: No. Only if they say something wrong.

DR. GOUGH: Okay, but your comments went to the SAB as well as to the --?

DR. MICHALEK: Yes. I'll tell you, they went to EPA. I don't know if they sent them to the SAB, but they did say that they would now -- they have written us in as contributors to the report, because they have accepted our edits.

DR. GOUGH: All right.

MR. COENE: That's their science advisory board.

DR. MICHALEK: What is the bottom line of their report? That is that TCDD is a human carcinogen, and that's stated explicitly in Section 2214, part 3. And that, what is their statement about diabetes? That's in part 3, Section 225, mainly that recent studies suggest biological plausibility regarding a relation to diabetes and dioxin.

Actually, at that June 9th meeting in Washington in front of the IOM, Bill Farland was there, and so he heard my presentation on the Ranch Hand data.

DR. STOTO: What do they mean by that second point there? Is that relying on the epidemiological data, or?

DR. MICHALEK: That's relying on the epidemiology data and the animal data, primarily by Matsumari, on glucose transporters. Well, that was primarily on animal data, I believe.

DR. STOTO: Yes, because normally when you say biological plausibility.

I wonder, what are the implications of saying it has biological plausibility without going further to say that, like the first statement, it causes diabetes, or?

DR. MICHALEK: I don't know, that's all they said. In other words, they made this statement in the report, they didn't claim that dioxin causes diabetes at the same level as they said dioxin causes cancer. They only said that the relation is biologically plausible; that's all they said.

DR. STOTO: One implication may be that if you establish that it causes one disease, that's enough to regulate it. I don't know, maybe in terms of cost-benefit calculations, you'd like to know about everything that --

DR. MICHALEK: I suggest that you go to that meeting, too.

DR. HARRISON: Is the Matsumura data published?

LTC BURNHAM: No.

DR. MICHALEK: Is what published?

LTC BURNHAM: Matsumura data.

DR. MICHALEK: Matsumura, by the way, we have a relation with the University of California at Davis; and Professor Matsumura, who is analyzing adipose tissue specimens taken from 313 of our study subjects at the last physical to assess the relation between dioxin body burden and glucose transporters and P-pargamma {ph} and TNF-alpha.

DR. HARRISON: What I'm asking is, is the second point here by the EPA based on his unpublished data?

DR. MICHALEK: I believe it's based on published data by Matsumura. As I recall on that particular page, there are several articles of Matsumura that are cited.

DR. HARRISON: Okay.

DR. GRUBBS: Joel, in the first statement, TCDD is a human carcinogen. Is that end of sentence, period? Or is it with any caveats with it?

DR. MICHALEK: Oh, I'm sure --.

DR. GOUGH: The human evidence is not convincing. That's what they say. But the combination of suggestive hemadotus {ph} plus the animal evidence, plus what they say is a common mechanism of action which is based entirely on the idea that dioxin interacts the AH receptors, convinces them it should be classified as a human carcinogen.

DR. MICHALEK: In fact, here are the reasons. My next slide. Here are the reasons: Why do they call it a human carcinogen? And there are four reasons.

There is a consistency across occupational epidemiologic studies of association. They see extensive carcinogenicity and multiple animal species, and they have general agreement dioxin is a -- the mechanism is AH receptor-dependent across animal species, and they see consistent relationships between animals and humans in roughly equivalent body burdens. These are the reasons cited in their report.

Now there's an interesting sideline to this thought of dioxin being a carcinogen. Why aren't we seeing it in this study? We have a relative risk of 1.06. We have patterns that we don't understand. We have a relative risk of 1 in the high exposure category and 1.5 in the lower dioxin category. We don't understand that.

With some members of the EPA staff, we have computed the -- I don't know how to say it. I actually shouldn't be talking about it because it's brand new and I can't talk. I'll tell you that later.

That's the end.

So what we've got is an interface with the IOM on diabetes and dioxin that authority I will describe to you in greater detail in a few minutes. And we have an Air Force proofread of the dioxin, EPA assessment.

DR. HARRISON: Questions? Mike.

DR. GOUGH: I'd like to comment. I think that the reason there's no cancer in the Ranch Hand population, perhaps, is that -- one argument of course is that it's too small to pick up some of these tumors that are reported.

The other is, it's by far the best study that's been done, it's the best information about exposure. And the fact that it's negative is the truth, or closer to the truth than these other studies where they're very poor measures of exposure. And gross generalizations based on years of exposure and things like that.

Also, the cancers in the NIOSH study are limited to people exposed 20 years. So no Ranch Hand was ever exposed occupationally for 20 years.

DR. MICHALEK: One year. On the average, about one year.

DR. HARRISON: It always worries me when people use the word "truth."

DR. GOUGH: I hate to use it, too; but it --

DR. HARRISON: Maybe "reproducible"?

DR. GOUGH: No, I think truth. I've changed my mind. You know, truth is a thing that eats -- is a fish that eats Darwin

DR. STOTO: And causality is either truth or not truth. The association is a little more complicated to talk about in those regards.

DR. HARRISON: Other questions or comments?

[No response.]

Okay, moving right along.

DR. CAMACHO: When you said size, you meant population size.

DR. GOUGH: Yes. Yes.

DR. CAMACHO: And are we back to that small number in cells again? That problem where the error rate can grow.

DR. GOUGH: Yes.

DR. HARRISON: What was your question, Dr. Camacho?

DR. CAMACHO: The size. He mentioned the word size, because our size was too small. I'm back to that notion of errors in cells, when the number starts to drop.

DR. GOUGH: Formerly, there had been a great deal of interest in relatively rare tumors like soft tissue sarcomas, and I don't know, you would expect one or two in the Ranch Hands. In fact there is one, I think. But they're just too small.

DR. CAMACHO: Sample size.

DR. GOUGH: Sample size, yes.

DR. MICHALEK: So it's always nice to acknowledge what you can't say about a study.

Thanks, Joel.

(Laughter)

Institute of Medicine and

Environmental Protection Agency Reports

DR. MICHALEK: This is a discussion of EPA and the other studies.

It's worth mentioning that I don't think you'll find another study that has as good follow up, as carefully a collection and sorter system as this study. So it's difficult to compare, in other words. The price you pay is -- that's the good news. The bad news, you can't find anyone else to compare it with. You have nothing but frustration when you attempt to look at other studies because you can't. They don't have good follow up. You can't easily compare rates or dose response.

We're out there all alone, in other words. Federal funding does not evenly apply to the Agent Orange issue, is another way to say it. We wish the NIOSH study had been funded as well as the Ranch Hand study so they, too, would have repeated follow up, medical record review, 100 percent quality control, detailed covariates. They don't have that. We have it, they don't, and I don't know why, but that's the way it is.

In fact, their last physical was conducted in 1987; there was no repeated follow up of that cohort.

This is now the talk that I gave on June 9 to the National Academy.

The idea is that we already know, we've known for ten years that dioxin and diabetes are related statistically in this cohort. Ideas have been suggested to say, for example, that this is an artifact because -- what you're really seeing here is a relation between diabetes and the elimination rate; you know, people that are heavier hang onto their dioxin longer; all you have is that people that are heavier are at higher risk of being diabetic. "So the whole thing is just an artifact. Why don't you just say that and get it over with?"

So that's one idea. Another idea is that well, dioxin binds differentially to the different lipid fractions in the blood. In particular, it binds more tightly to triglycerides. Diabetics have higher triglycerides, therefore they have higher dioxin, and this whole thing is just an artifact; and "Why don't you just say that and get it over with? That there's nothing to this and it's an artifact."

And finally, people have said, "Well, why don't you compute this other metric," which is a favorite in epidemiology and toxicology, and that's the area under the curve measurement. "Why don't we do that instead of doing this dioxin category analysis or the initial dose. Why don't we do that?"

Well, that's what this talk will address, all three of those things.

This talk was designed to be given to people who were fresh to the study, so there's a review and I'm just going to skip through these. you have seen all this before.

[Slides]

You saw that, you saw that. Saw these things, and this is what -- you saw these slides already; this is the check mark pattern that we now believe is an artifact, in effect it went down and then up. We think we can explain that now by tightly matching, and we can get rid of that and get a nice dose response.

So here's the elimination rate hypothesis, that the association between diabetes and dioxin is simply a reflection of a relations between the dioxin elimination rate and diabetes.

So we have the ability to address that question. What you need to know is, this is the only study in the world that has this ability, because we have repeated dioxin measurements for over 300 Ranch Hand veterans taken every five years for twenty years. Plus we have medically-verified diabetes on every one of those individuals to determine whether or not they have diabetes.

So we have the data, and that's what this is; a summary of that data. So there are 343 with repeated dioxin measurements, up to four measurements taken over that period.

The actual cohort has been well studied. The first paper, a recent paper which describes a cohort was published in the Journal of Toxicology and Environmental Health. So it's a well-established cohort and the subject of many papers.

We excluded one individual who had diabetes prior to his service in Vietnam, and of the 342 remaining, 95 were diabetic; that's almost 28 percent. diabetic meaning that they were diagnosed by a physician and we have a medical record to show that, that they have diabetes, or else they had a two hour postprandial glucose of greater than 200 milligrams per deciliter at one or more of our physical examinations.

[Slide]

So here's a little thumbnail picture showing the dataset we have of the 343. 344 have complete data on dioxin in all four repeated measures. 26 have dioxin levels measured only in 1982 and '87. They either died or failed to come after that to our physicals, or else they came and they refused to give blood.

So in other words, about two-thirds of the 343 have complete dioxin measurements in all four years. 34 have dioxin measurements in '82, '87, and '92 but not in '97. So here you see a breakup, showing the missing data.

[Slide]

Here's a picture of the repeated dioxin measurements on this time line, '82, '87, '92 and '97 in raw units on the vertical, up to 700 or 600-some parts per trillion. And you see of course they're coming down. Remember this is on a first order elimination process, which we expect to be linear in log units and certainly after we transform the dependent variable into log units, we see primarily a linearly decreasing trend with some noise in here.

Some of that is due to regression towards the mean that I mentioned earlier, that were selected as being high in '87 and there you see, there you see some of them are high in '87, purely by chance.

Then you see zigzags up and down, and we believe some of that is due to exposures in the United States that occurred many years after Vietnam, just living here in the States.

[Slide]

And here it is on a different time scale, not measuring from Vietnam. Zero here means their tour in Vietnam, and this is up to 40 years later, almost up to the present time, and there you see it in original units and there you see it in log units.

Now in December of this year, I will show you this plot overlaid with Seveso. Just as an aside, we have 30 individuals, 30 adult males who were exposed to many thousands of parts per trillion in the explosion in Seveso. CDC gave us the same repeated measure of dioxin data on them, and you will see a remarkable overlay of the Seveso and Ranch Hand data in a few weeks.

[Slide]

Our point here is to look at elimination rate versus IVs.

DR. GOUGH: May I ask you a question. The Seveso data -- when were the initial measurements made in the Seveso population?

DR. MICHALEK: The very first measurement? A day after the explosion.

DR. GOUGH: And in the next one?

DR. MICHALEK: Some of them were a few months, some of them were a few years.

DR. GOUGH: That's good. So that's going to eliminate the idea that there's a rapid elimination.

DR. MICHALEK: We don't have measurements an instant after the explosion; we have it the day later.

DR. GOUGH: Yes, but that's -- they're still being exposed.

DR. MICHALEK: The hypothesis is that there's a rapid elimination within the first few minutes or hours after the dose, and it drops in a way which violates the first order model. But then very soon after that it became first order.

The evidence from the data I'm going to show you in a few weeks;that but it's pretty flat linear, right up to the initial --

DR. GOUGH: Yes. Okay.

DR. MICHALEK: It's really remarkable.

DR. GOUGH: That's a very important finding.

DR. MICHALEK: You will be amazed.

DR. HARRISON: That also means that you can extrapolate back to the original --

DR. MICHALEK: It also validates our first order model, extrapolation to Vietnam.

DR. HARRISON: Joel, even if you were to extrapolate that back to Time Zero, it would not produce a concentration -- it would not produce an average concentration that was much different than 1000 parts per trillion.

Go back to the previous slide.

DR. MICHALEK: This is log --

DR. HARRISON: Well, but at any rate, if you extract back to zero --

DR. MICHALEK: Yeah, you're going to run a straight line back here.

DR. HARRISON: You're going to go from 4 log units to 6 log units, or 5 log units.

DR. MICHALEK: Right. You might run up to 8.

DR. HARRISON: But the mean is going to be somewhere from 4 to 6.

DR. MICHALEK: Right.

DR. HARRISON: So that's a hundredfold?

DR. MICHALEK: Right.

DR. HARRISON: Okay.

DR. GRUBBS: Joel, is that base 10 or base 2?

DR. MICHALEK: That's natural log.

But we're really digressing here. What we're headed for is an analysis of the elimination rate versus diabetes in the Ranch Hand cohort.

So I have to compute the elimination rate; that's lambda. What we're talking about is a first order, a full body elimination. This is the expression for it. This is the concentration at time T, this is initial dose, and this is lambda, is the elimination rate.

It turns out you can estimate the elimination rate without knowledge of the initial dose. In fact, that's done by means of a statistical model: by log transforming that first order model, you can linearize it and you can identify the elimination rate with a coefficient of time in a repeated measures linear model.

This methodology is published several times now in the Journal of Toxicology and Environmental Health and in Envirometrics. And now in Statistics in Medicine.

The point is we have identified the elimination rate with a coefficient of time in a linear model; actually, the elimination rate is the negative of that coefficient. And the statistical model is to model these; Y is the log

dioxin levels and is multivariate normal. And as soon as you entertain a repeated measure linear model, you need to entertain an auto-covariant structure, because now you need to relate, not just have the measurements relate to themselves, but you need to -- how they relate to each other at a particular point in time; we don't need to know how they relate to each other across time. And that's what's called the autocorrelation model.

There are two favorites in that direction; one is called Autoregressive Order 1 and the other is called Toeplitz. In the AR1 model, you tell yourself that the correlation between models at Time 1 and Time 2, if that's called R, then the correlation between dioxin levels at Time 1 and Time 3 is R-squared. In other words, it goes up as a power of R, and that's the AR1 model which is a favorite because it's simple, and it has a lot of nice mathematical properties.

The other model that people use are called Toeplitz, and that is you don't tell yourself that it's a power. You just say that, you identify separate parameters for each time interval.

[Slide]

The model specifies that every individual, everyone gets his own decay rate in the model. And what the least square estimate can give you is the overall average of these.

It turns out, mathematically, that the individual decay rates are weighted sums of pair-wise rates connecting the various time points. Black I12 is a rate between the first and second measurement, and I13 is the rate between the first and the third and the second and the third, and I'm telling you what this expression looks like if there were three measurements per subject, and this generalizes the four measurements per subject.

If we had four per subject, the formula would involve 1 2, 1 3, 1 4, 2 3, 2 4, 3 4. But I've only told you three measurements, because I didn't want to fill up the slide with too much algebra. I like to keep it simple -- as simple as I can.

(Laughter)

And the weights involve distances that, deltas are differences between the times,

and the D is an expression involving sums of squares of the weights.

[Slide]

And here's all the rest of that algebra. Those are the Ds, those are the Ws

-- omegas are functions of the autocorrelation parameters and so on.

So in other words, I'm able to write this thing in closed form, which means I can estimate which individual the dioxin elimination rate for that subject, which I did.

I can compute them, and I can make a histogram, and there it is. This is a histogram of the elimination rates for 343 subjects using the least square solution.

Some of those are negative. That's because we're using the raw data, we're not making any judgments about people who must have gained dioxin by working in a chemical plant in the United States. They're all in there.

You could go back and cull those out, and if you did, all those elimination rates would be positive, because they would all be coming down. Some people got a dose here in the United States in 1985 or '87, years after Vietnam. They're in there.

[Slide]

So I computed the elimination rate, first using the Toeplitz model and then using the Autoregressive order 1 model; and I plotted one versus the other and I plotted one versus the other, and they're nearly identical. That was a concern of the IOM committee; that it made a difference what autocorrelation structure we used. The answer is that it doesn't. The correlation between these two measures of the elimination rate is .998, is nearly perfect.

What I attempted to do here was visualize the diabetics, so -- a nondiabetic is indicated with an open circle and a diabetic is indicated with a dot. And what you'd expect to see, if the hypothesis were true that the diabetes was related to the elimination rate, you'd expect to see all the diabetics piled up at one end, like down here.

It turns out that that's not true. And what you're seeing in this picture is an unadjusted representation; and I had not adjusted for body fat or age. There is a slight shift to the left, but as you'll see in a minute, that's not significant after adjustment.

DR. STOTO: Joel, a question on that, is lambda the same for every individual?

DR. MICHALEK: No.

DR. STOTO: Or each individual is --

DR. MICHALEK: Lambda is allowed to be different for each individual.

DR. STOTO: Okay. There's no subscript on here, but the fact you have different dots suggests that --

DR. MICHALEK: That's right, and that's why we have this histogram; that everyone has their own lambda.

And that's the spread represented now; we use both the Toeplitz and the AR1 assumption, and you see an almost perfect correlation. And so at this point I give up on AR1 and stay with Toeplitz, I believe. So it doesn't matter which one you use, the results are the same.

By the way, all these results I presented in writing to the IOM committee, and those are posted on our web page, too. So all of the underlying work here is available on our web page.

I've analyzed three different ways. I ask: Is there a relation between time to onset of diabetes and the elimination rate? And for that I use a proportional hazards model. Then I ask, is there a relation between the occurrence of diabetes, simply yes or no, and the elimination rate? For that, a logistic regression.

And finally, I turn the model around and then ask: Do diabetics have a different elimination rate than non-diabetics? So now I put the elimination rate on the left side of the model an diabetes on the right side of the model. We use a linear model for that, analysis of covariants, in other words.

[Slide]

Here are the results. Now I expected to see a negative coefficient when using the proportional hazards, because I would expect to see that individuals who are heavier would have an increased risk, and therefore a lower elimination rate. It is negative, but insignificant; but as soon as I adjust for age and body fat, I find that the coefficient then becomes not significantly different from one. Right there. Coefficient of time -- I'm sorry, lambda, it becomes -.01, P-value .7, after adjustment for all these things.

DR. GOUGH: What's the adjustment for dioxin mean?

DR. MICHALEK: I put dioxin in the model because we already know dioxin is a confounder. It's related to diabetes and it's related to body fat, so I put it in the model.

The point is whether or not I adjust for dioxin. There is no relationship between the elimination rate and diabetes. There is no relation, statistically, between the elimination rate and time to onset of diabetes in the Ranch Hand cohort.

DR. STOTO: But there is a relationship with how much dioxin people were exposed to.

DR. MICHALEK: Yes; there is a demonstrated relation, in all of our reports and articles, between diabetes and dioxin. There is no relation between diabetes and the elimination rate of dioxin.

DR. SELVIN: How correlated is dioxin with the rate of elimination?

DR. MICHALEK: Initial dose is not highly correlated with the elimination rate. In fact, you'd expect no correlation according to the first order model, and we see very little or none; I haven't shown that here, I just know that, that there's very little correlation between dioxin and the elimination rate.

[Slide]

Logistic regression. No significant relation without adjustment; and then after adjustment, we see the same pattern. A decrease -- after adjustment for age, body fat -- and this RELCH is the relative change in body fat from Vietnam to the present. It's the difference of the body fat today, the body fat in Vietnam, divided by the body fat in Vietnam. That turns out to be an important risk factor for diabetes.

DR. CAMACHO: There's no relation of any kind between the body eliminating this dioxin and the onset of diabetes?

DR. MICHALEK: No statistical relationship. No relationship that we can detect.

DR. CAMACHO: But there does seem to be a relationship between the raw amount, some amount?

DR. MICHALEK: There's a relationship between the amount of dioxin in your body, but there's no relationship by how fast you get rid of it and diabetes.

DR. CAMACHO: You would think the longer you kept it --

DR. MICHALEK: That's the hypothesis, that people would think -- if you hold onto it longer, you must be at increased risk. But after adjustment for body fat, it's not true.

DR. STOTO: But before adjustment for body fat, there is a relationship.

DR. MICHALEK: Before adjustment for body fat, there is. Not only on the Cox model, but --

See, you need data. And we're going to send this to a journal; hasn't been sent to a journal yet.

DR. STOTO: And that's because of the body fat. Never mind.

DR. MICHALEK: After adjustment for body fat, there is no relation between the elimination rate and diabetes.

DR. CAMACHO: That's awful odd, though. Doesn't it sound odd on the face of it? If I have so much body fat, then I'm a higher risk. Now I'm getting rid of this dioxin in my body fat, but it doesn't reduce the risk.

DR. HARRISON: But you're not getting rid of it any faster than a skinny guy.

DR. CAMACHO: I just have more of it.

DR. MICHALEK: Uh-huh. But your rate --

DR. STOTO: I don't think it's that, either.

DR. HARRISON: Is that your point, Joel?

DR. MICHALEK: That wasn't my point. What I was trying to say was that some people would say "Well, so what? You've put that dioxin in a very safe place; you stuck it in your fat." It's not metabolically available, or biologically available to the rest of the body, it's hidden in your fat. So some people will say there was really nothing to this anyway, and why are you worried about it?

Other people would say "Well, it's in your body for a longer time if you're happy; therefore you must be at increased risk." These are all speculations. All I'm showing you here is the data.

DR. CAMACHO: That there's no -- there doesn't seem to be any correlation.

DR. MICHALEK: Doesn't seem to be any relationship between the elimination rate and diabetes.

DR. HARRISON: A third person might say that you only get diabetes when you have fat, so that there must be something in fat that is the significant contributor to Type II diabetes.

DR. MICHALEK: It's something else, in other words.

DR. HARRISON: And that since dioxin is in fat, maybe it's where the action is.

DR. CAMACHO: There's an interaction somewhere.

DR. MICHALEK: Someone might say that.

DR. STOTO: I think the issue is that if you just look at diabetes versus TCDD as measured in the study, which was after exposure, you find a relationship. And one possibility is that the fat guys have more TCDD and they also are more likely to get diabetes, so that simple relationship you see might just be due to the metabolism of TCDD.

And what this analysis suggests is no, it's more than that, that even when you control for that using these models, there still is a relationship between dioxin and diabetes. There's no relationship between diabetes and the elimination rate, except the percent body fat in age and so on is in there.

So basically we've explained the relationship between the elimination rate and all these other factors. I think that's the explanation.

So there are basically three things that are related to one another, and this is one way of teasing out that joint relationship.

DR. MICHALEK: In the analysis of covariance we see -- this says that, it's not significant, but because the coefficient is negative, it says that the diabetics have a lower mean elimination rate than the non-diabetics. It supports the idea that the heavier people are holding onto dioxin longer and have a lower elimination rate; and therefore they're more likely to be diabetic.

So this is in the right direction and it's borderline significant, if you want to call it that. But after adjustment, the P-value increases to .43 and the coefficient decreases to .005, after adjustment for body fat, age, and relative change from Vietnam, in body fat.

So in other words, that suggests that the previous slide, the results are misleading because they didn't adjust for body fat, which is an important contributor to the endpoint.

[Slide]

Now I've finished the discussion of the elimination rate v diabetes.

Here is a matched pair analysis of, we were interested in this cohort, 343 that has almost 28 percent diabetic. What can we say about that? What about this 28 percent? Is that high, is that unexpected?

Well, we matched these 340 -- actually 342 because we threw out that one guy with diabetes before Vietnam -- we matched them to controls that had the same body fat, the same family history, the same age and the same military occupation. I can't remember whether we adjusted for, matched on race or not.

What you find is that the percent diabetic in the 342 matched controls is 17.8 percent as compared to the 27 - 28 percent in these men that happened to be in our half life study. And that's significant. Well, relative risk .16, a P-value of 001.

DR. STOTO: Is this the result you said you just got yesterday afternoon?

DR. MICHALEK: No, this is old. I gave you this on June 9. What came yesterday different is a different analysis.

DR. STOTO: It's a different matching.

DR. MICHALEK: Yes.

DR. GOUGH: Would you say again what -- the bottom line?

DR. MICHALEK: We matched on family history, body fat, age, and military occupation. So officer to officer, body fat, so on. Family history.

DR. GOUGH: And then the 17.8 is?

DR. MICHALEK: That's the prevalence of diabetes in the 342 matched comparisons. And the 27.8 is the prevalence of diabetes, and the 342 Ranch Handers in our half life study.

DR. STOTO: The key point is the relative risk at the top, of 1.6.

DR. MICHALEK: Relative risk is 1.6.

DR. GOUGH: And that's the 17.8 that comes out --

DR. MICHALEK: Roughly it's 27.8 over 17.8. Although that calculation was done using a matched pair analysis out of Rothman's textbook. I don't have that formula memorized, but that's where that came from. There's a full display of all the statistics in that textbook.

Then we asked, is there a difference between insulin on the 343 -- we took the 343 and we looked at the non-diabetics in the 343.

DR. GOUGH: Do you remember what--

DR. MICHALEK: 383 were nondiabetic, another 95 were diabetic. Non-diabetics only.

We matched those non-diabetics to nondiabetic controls and then asked, is there a difference in insulin. And the answer is yes.

The Ranch Hand insulin levels are significantly higher than the comparison insulin levels, and that's consistent with other analyses we've done, which has always shown a tendency or significant risk of increased insulin among nondiabetic Ranch Handers. So that's consistent.

[Slide]

Then the there's the idea that, "Well, dioxin binds differentially to triglycerides. Diabetics have higher triglycerides and therefore they have higher dioxin, and the whole thing is an artifact." This was published in 1998 in Epidemiology.

We took the triglycerides that were measured in the same specimen that CDC used to measure dioxin. This is not the triglyceride used by SAIC in their report; this is the same specimen, measured by CDC.

And then we asked whether we could detect a change in the relationship between dioxin and diabetes with triglyceride, using that data. And the answer is no, we can't. We see no evidence in the data to suggest that that hypothesis is true.

The materials for this analysis were those data, those individuals that were represented in our Henrikson, et al, 1997 paper on diabetes and dioxin, published earlier in Epidemiology. And subsequently in 1998.

DR. CAMACHO: I'm sorry, if I might just ask -- because I'm a sociologist, so I don't catch all the medical stuff.

It seems the two slides show a contradiction. Am I right here? I mean, the 78 percent is in a mean, shows something significant with the insulin. Is that correct?

DR. MICHALEK: No. This slide has only to do with diabetes, whether they have diabetes or not.

DR. CAMACHO: Yes, but then the slide after that.

DR. MICHALEK: The slide after that--

DR. MINER: Is in non-diabetics.

DR. MICHALEK: These are all non-diabetics.

DR. CAMACHO: Among them, but the Ranch Handers showed --

DR. MICHALEK: Higher insulin.

DR. CAMACHO: Higher insulin.

Now is that any connection at all to the next slide? I mean, does it contradict in some way the next slide?

DR. MICHALEK: No.

DR. CAMACHO: All right. The noise, and I'm tired, and I don't see --

DR. STOTO: The lipid is a different analysis altogether.

DR. MICHALEK: And we're changing gears. This is the last slide on the elimination rate series. Now changing topics. New topic. Lipid binding.

Forget about half life --

DR. CAMACHO: All right.

DR. MICHALEK: We're not on the 343 anymore. We're talking about the whole cohort.

Dioxin binding differentially to triglycerides --

[Interference from adjacent room.]

It sounds like just kind of --

VOICE:

COL MARDEN: A sports officials meeting.

(Simultaneous conversation)

(Discussion about the noise.)

DR. MICHALEK: So the idea is to revisit diabetes versus dioxin with adjustment for the triglycerides that were measured in the specimen.

[Interference; noise.]

DR. MICHALEK: Anyway, if you do that, you get exactly the same results that we got without adjusting for triglycerides. And not only that -- and by the way, I did put this in because you wanted to know earlier, Dr. Harrison, how to convert whole weight dioxin, how to get lipid dioxin from whole weight, where did that 102.6 come from -- if you remember, you asked me once what that is.

DR. HARRISON: Uh-huh.

DR. MICHALEK: That's the 100 times the specific gravity of serum. If you want, you can study that chart later.

(Laughter)

DR. HARRISON: Thanks, Joel.

DR. MICHALEK: Now what we did was, we drop the lipid-adjusted dioxin and study whole weight dioxin, and ask whether there's a relations between that and diabetes, after adjustment for these triglycerides; and the answer is yes, P-value of 001, relating whole weight dioxin to diabetes, even after adjustment for that triglyceride.

But furthermore, we looked at an interaction model and found no significant interaction between whole weight dioxin and triglycerides.

[Interference; noise]

That means that the relationship between dioxin and diabetes doesn't change with levels of triglycerides in your blood. This does not support the hypothesis that dioxin binds differentially to triglycerides. And that's published in Epidemiology.

[Slide]

DR. SELVIN: A small point, why is it birth year all of a sudden?

DR. MICHALEK: Birth year?

DR. SELVIN: Instead of age.

DR. MICHALEK: Birth year is an important covariate, because risk of diabetes increases with age.

DR. SELVIN: No, I mean why do you put year of birth in rather than just the person's age?

DR. MICHALEK: Because -- let's see. Yes, you could do that.

DR. SELVIN: I mean, they're the same, right?

DR. MICHALEK: You could do that.

Sometimes we like to see a birth year because -- I know why. Because when we do a repeated measures analysis on time, age is strictly linear with time and it messes up the model. So you need to --

DR. SELVIN: I understand.

[Slide]

DR. MICHALEK: And finally, this is another display of the relationship between insulin and dioxin category. What happened in the '97 report was we -- we by mistake used the Scripps normal range, being inconsistent with our previous report where we used percentiles of the comparison group, and therefore we missed the effect.

In the 1997 SAIC report, we used the Scripps normal range, which is a smaller range than the percentiles in the control group. And as you'll see in a second, we failed to see an effect, and this fixes that.

Here's, with the percentiles, using the 97.5 percentile of the control group, we see an adverse, a significant adverse, an elevated risk in the high category of abnormally high insulin among non-diabetics in the Ranch Hand group. Relative risk 2.6, and that's significant. However, if we use the Scripps normal range, we see nothing at all, and that's what's published in our big report.

By mistake we used the Scripps normal range. We should have asked SAIC to use the percentiles.

DR. HARRISON: So how does weight play into that?

DR. MICHALEK: This is adjusted for body fat, age and weigh. These are adjusted.

[Slide]

And to complete the series, this is an analysis of abnormally low insulin, and there's just not enough data to analyze that.

And a series of check mark patterns; now just irrelevant, based on the analyses that I showed you earlier or told you about. So we'll skip all that.

[Slide]

Then there's the issue of area under the curve. Area under the curve is a favorite because it acknowledges a burden on the body over time, which is lost when you simply use an initial, a body burden at a particular point in time.

What you're doing is, you're taking the first order model, first order curve, and you're literally taking interval. You're just computing area under a first order model. And you're using that as the metric of exposure.

Well, to do that, and I can do that and I did do that with the Ranch Hand data, you need to have an elimination rate; you need to be able to compute the curve and take the area. And I did that using the same methodology you saw earlier with the slides on the elimination rate. Every individual gets his own elimination rate from the data using the first order model.

Individuals that are at background levels today and weren't in the half life study are assumed to have been at steady state their whole life. And so their area under the curve is just the area under a really long rectangle. If they're 8 parts per trillion today, never in the half life study, we assume they're 8 parts per trillion forever, and we just say that 8 parts per trillion times the number of years since Vietnam, and that's their area under the curve.

Those are the kinds of assumptions we make. Whenever we do these kinds of analyses, there's a whole list of assumptions and decisions you have to make about what to do; and that's how we dealt with individuals with background levels today.

DR. STOTO: I have to say, I've braved this in the past but there's a lot of new people now; this idea that if the exposure is below 10, it's background, and there's absolutely nothing going on.

DR. MICHALEK: That can be revisited.

DR. STOTO: I think that that needs to be revisited.

DR. MICHALEK: Definitely. Everything we're doing here today, all of this can be revisited, and we will, after we talk some more.

So that's the idea, and then individual Ranch Handers who have high levels but still weren't in the half life study are given the average elimination rate to compute their area of the curve. And then individuals in the control group are, nearly all of them, background levels, and they're given a steady state computation of simply a rectangle, of parts per trillion by years. And units of area under the curve are parts per trillion-years.

So we did that using all available data on those individuals that attended the 1997 physical, and those were the sample sizes, assuming first order models, steady state and below 10 parts per trillion.

If you do that calculation, you'll find that the comparison group, that among the diabetics and non-diabetics, the area under the curve is pretty flat; the mean is 120 parts per trillion-years and the range is just about the same; and so it's pretty flat in the comparison group.

As you have seen in the Ranch Hand group, the diabetics have an area under the curve mean of 821 and the non-diabetics, 450. As you suspect, that's going to be significant, even after adjustment for age and body fat.

[Slide]

[Interference]

There is a histogram of AUC and comparison group, and in the Ranch Hand group, divided by 10^{-5} so I could fit that on the scale, because they run up to 10,000.

DR. STOTO: The fact that all the comparison groups have the same area under the curve is the fact that you basically assigned them all. That having a flat --

DR. MICHALEK: Well, it's a self-fulfilling prophecy, because they're all low, so they all get that steady state computation. But the fact that the diabetics and non-diabetics are similar is interesting.

DR. HARRISON: Diabetics and non-diabetics are similar?

DR. MICHALEK: Okay. Here is the -- in log units here -- here is the area under the curve for the Ranch Handers and there it is for the controls. We see some kind of perturbation here which we have not investigated yet.

So I ask, is there a relation between using the same models I used for the elimination rate? Is there a relationship between time to onset of diabetes and the area under the curve, among Ranch Handers. There are no controls in this model.

And the answer, without adjustment, is yes. And I've log-transformed the AEC.

[Interference]

After adjustment for all these things, age, body fat, personality type -- these are all the covariates that were used in the last report by SAIC; we see a significant and positive relation between area under the curve and diabetes in the Ranch Hand group.

Yes.

DR. GOUGH: Why isn't there an enlisted ground crew there?

[Interference]

DR. MICHALEK: Because they're the reference. There are three strata, and what appears in the model are dummy variables for officer and enlisted.

So in other words, these --

coefficients are saying, officers and enlisted flyers are having less diabetes than enlisted ground, is consistent with the enlisted ground having higher dioxin levels.

[Slide]

Then analyzing it again on the occurrence of diabetes and not simply mean time to onset --

[Interference]

-- the same pattern again; significant relation after adjustment.

[Interference]

And the conclusions are what we just said; no relation (inaudible)

DR. HARRISON: Are you saying, Joel, if you were to plot apply all of these subject's area, each individual area under the curve -- [Pause. Outside noise is deafening.] -- or let's say if you were to maybe have a bar graph, that the patients with diabetes would fall into the category with the higher dioxin; that we'd see a couple hundred or 300 spots at the high end and we wouldn't see any spots down here at the low end.

DR. MICHALEK: Diabetics have higher area under the curve than non-diabetics in the Ranch Hand group, yes.

Please get us another room.

(Discussion off the record.)

DR. HARRISON: Any other questions or comments before we take our break, for a quieter room?

DR. SELVIN: Joel, could you clarify -- I'm kind of confused, because it seems to me there's a contradiction here, that the rate is unrelated but the time-weighted average is.

DR. MICHALEK: The rate is unrelated.

DR. SELVIN: Right, we saw that in the first --

DR. MICHALEK: But the AUC is related.

No, I don't think it is. Because the AUC is basically a function of the initial dose. The initial dose is not related to the elimination rate.

[Interference]

DR. SELVIN: When you say area under the curve, what curve are you -- it's the elimination curve.

DR. MICHALEK: First order elimination. CT is --

DR. GOUGH: C to the minus-T, right?

COL MARDEN: What it's a reflection of is body burden. It's a sigma of body burden.

DR. HARRISON: If you go back to that graph where you had the elimination rate for dioxin -- it's not even in this group, Joel -- where you have the elimination rate for dioxin. Remember, all the solid white going up.

What you're saying is that the diabetics are in the top half of that graph where their initial dose was high, and they're down the scale parallel with everyone else, but they started off at a higher dose, so they've got more area under the curve at the end.

DR. STOTO: When you've adjusted for weight.

DR. HARRISON: Yes.

DR. STOTO: After you adjust for weight.

DR. HARRISON: Yes.

DR. STOTO: Let me ask another thing: The area under the curve also depends on when they served in Vietnam. Some of them started eight years before the others.

DR. MICHALEK: And that takes this into account.

[Interference]

DR. STOTO: So that's why -- (inaudible)

DR. MICHALEK: That's an advantage of the area under the curve, because it takes into account when they were in Vietnam.

DR. STOTO: That's true.

DR. HARRISON: Okay, anything else?

COL MARDEN: Ron, the next meeting that we have in Washington, could you arrange to have them come to it?

(Laughter)

[Whereupon, at 12:26 p.m, the meeting recessed for lunch, to reconvene at 1:30 p.m., this same day.]

A F T E R N O O N S E S S I O N

[1:20 p.m.]

Mechanisms for Additional/New Research

DR. HARRISON: Let's resume.

[Slide]

DR. MICHALEK: These slides are motivated by those freezers you saw on earlier slides. The idea is that, we have collected approximately 55,000 specimens, biological specimens on these men. They're in the freezers, and we're going to have another round of physicals in the year 2002 and we'll collect more specimens.

They were collected for the purpose of answering the Agent Orange question, and there they are. Most of it is serum. They're still there. The point is, at Dr. Harrison's suggestion -- well, more than a suggestion; he wrote a letter to Donna Shalala -- by the way, let's finish the specimens.

In addition to what's in the freezers, we have 331 adipose tissue specimens. A number of specimens still at CDC that have not been shipped back. Adipose tissue; and by the way, we have over a thousand VCR tapes, high resolution video, of each tooth.

(Laughter)

For anybody at NIH. We also measured mercury in every one of these men, along with dioxin. Mercury being measured to study the effect of mercury leeching from dental amalgam on neurological endpoints. So we have a parallel study going on with the same cohort with NIH, and they are shipping us VCR tapes and hard copy from their examination that they give at Scripps from the mouth. We still have not received the hard copy yet, but we think we'll get it.

DR. STOTO: That's an important point; the last time we spoke about this, I remember discussing the fact that the informed consent was focused on the Agent Orange issue.

Is this specifically mentioned in the informed consent?

DR. MICHALEK: What's in the informed consent. Well, there are a number of informed consents. They can spend about an hour filling out informed consent forms on the first morning of the physical. There's an informed consent dealing with specimens, the data from physical exam, there's an informed consent -- there was, for the adipose tissue; all of that is directed at Agent Orange research.

DR. MINER: And there was a separate one.

DR. MICHALEK: There's a separate one for NIH and their study of the teeth and the dental amalgam.

COL MARDEN: If we launch off into a different use, then that will require additional informed consent.

DR. STOTO: So there was a separate informed consent for these data, with a different purpose mentioned.

DR. HARRISON: I apologize for this diversion, but do they receive copies of the informed consents to read before they travel to San Diego?

DR. MICHALEK: No.

MR. COENE: They don't do it each time, though. They did it the first time.

DR. MICHALEK: They do informed consents at every physical; they read those on the morning of the first day.

DR. HARRISON: I suspect that you're in clear violation of consenting procedures.

LTC BURNHAM: No, we are not.

MS. YEAGER: Joel, I believe they got them the night before and signed them the next morning.

DR. MICHALEK: All right, they got them the night before.

MS. YEAGER: And signed them the next morning.

DR. HARRISON: But if they've already traveled out to San Diego --.

DR. MICHALEK: Well, this was approved by the IRB.

This man is on our IRB right there.

COL MARDEN: Yes.

DR. HARRISON: All right.

COL MARDEN: It's been not only through our IRB, it's been approved by the Surgeon General of the Air Force.

DR. MICHALEK: And they've through the Scripps IRB.

DR. STOTO: Well, presumably they --.

DR. HARRISON: It's clearly coercive.

DR. STOTO: Well, presumably before they travel, they have some idea about the purpose of the study. But that may no be enough from your point of view. I wonder whether --

DR. HARRISON: I'm all into this now, and "it just don't work that way."

(Laughter)

MR. COENE: Well, for sure there's been some changes.

COL MARDEN: Yes. We have had people that have said "I'm not going to do it."

DR. HARRISON: I don't want you to get zapped somewhere along the line, you know, for something small stupid like this.

DR. MICHALEK: I understand. We're in constant -- we communicate regularly with the IRB.

DR. STOTO: Do we have any idea about whether they understand that the dental study has a different purpose?

MAJ SPEY: Yes.

DR. STOTO: Do they understand it, or?

MAJ SPEY: That's all explained to us, sir.

That was thoroughly explained to us.

DR. STOTO: Okay. I was just wondering about that.

Because one of the issues that -- it already is coming up here now is, I think that there's a wealth of information from this whole study that's useful beyond the Agent Orange issue. But someone said at the last meeting that if that were explicit -- if other purposes were mentioned, there wouldn't be as much participation. I don't know whether that's true or not. It wouldn't seem to me to be true.

MAJ SPEY: The teeth study -- the study of our teeth and mercury and blah, blah, blah was all explained to us in the introductory literature that was mailed to us prior to our signing up and trying to get a scheduled date and all that.

DR. STOTO: And people didn't say, "Oh, no, I don't want to participate in that because it's not Agent Orange?"

MAJ SPEY: No, sir.

I tell you what, I think you'll find that the Ranch Hand cohort and the comparison group cohort are very honored and pleased to be taking part in the only and finest piece of science dealing with this whole issue.

DR. STOTO: I think that's true, and that's what I would have guessed.

MAJ SPEY: I think the participation rate being slightly under 80 percent, is a sign of that.

DR. HARRISON: I think you're absolutely right. But even so, I would guess that the number of people who participated in the mercury study would still be less than the total number of people who were studied. So there would be some people who felt that either they didn't have time, or they -- you know, for whatever reasons, they didn't want to participate. And that would be what you'd expect, that --

DR. STOTO: Do we know about that? Did some people --

DR. MICHALEK: There were very few who declined.

MS. YEAGER: It's not a significant number.

LTC BURNHAM: If it were a part of the study, since they're there already -- I mean, if it were a separate thing where they had to travel, that might be a different deal.

MAJ SPEY: The examination takes approximately, as I recall, a minute and a half. They go in there with a TV camera and go zip, zip, zip, scrape, scrape. There's no hurting, it's not like having your gums scraped or anything like that. It's just bingo, you're out of there.

DR. HARRISON: And you're saying something else, which is slightly different from the answer to my question. You're saying that there was literature before the travel arrangements were made that discussed what was going to be done this time. It may not have been the consent form itself, but it was -- there was informative literature that said that this is what we're going to do, and this is the schedule, and so on.

MAJ SPEY: We receive a brown manila envelope, that's about 3/8 inch thick.

DR. HARRISON: So even though it's not exactly the consent form, there's no requirement that it is a consent form; so what you've done is obviously prepared an informative brochure or collection of papers that all of these men get before --.

All right.

[Slide]

DR. MICHALEK: So the question is, as always, is there a relation between health and herbicides? That's the reason the specimens were collected. We who have studied the issue would like to see the specimens used for that purpose. There are many unanswered questions. We have, for example, semen collected in 1982, as you saw on the slide; we have serum, we have adipose, we have urine.

During the remaining five years of the study, we're working at maximum rate. We will not answer every question that can be addressed with this data or with these specimens. The idea is to set up the mechanism so that that will happen to the best of our ability. And for that purpose, Dr. Harrison wrote a letter to Donna Shalala on January 16th of this year, recommending NIH funding for an RFP process and subsequent award of an open solicitation of proposals to address the issue with those specimens.

That letter was sent on the 16th. On 17 March, we received a letter from Donna Shalala's office saying that they had directed NIEHS to set up a working group to discuss the issue. That was from Ruth Kiersy of Dr. Shalala's office. On the 10th of April I received a letter from Kenneth Olden at NIEHS, saying that he had been communicated with by the Secretary of HHS' office, and they discussed it but he had not been given any funding.

End of slides.

DR. STOTO: Well, I don't think that's necessarily the end of the story, though. NIEHS has lots of money to do research, for all sorts of purposes, and it strikes me that if many scientists knew about these data and specimen resources, they would think up lots of interesting hypotheses -- >>>NOISE<<<

DR. MICHALEK: Related to Agent Orange?

DR. STOTO: Well, some of them would be related to Agent Orange, but I think others would not be related to Agent Orange.

DR. MICHALEK: Right.

DR. STOTO: That's why --

DR. MICHALEK: That's the rub. You see, these men gave these specimens for a purpose. We are here for a purpose. I don't have to --

DR. STOTO: I understand that.

DR. MICHALEK: The idea is to answer the Agent Orange question.

DR. STOTO: I understand that. I also want to float the possibility that in the last round, they be asked to give consent for uses other than Agent Orange.

DR. MICHALEK: Of new specimens.

DR. STOTO: Either new specimens, or even of the old specimens.

DR. MICHALEK: Well, let me remind you that these are irreplaceable. That they were collected to answer the -- they were collected to answer the Agent Orange question. We have not answered the question yet. They are there for that purpose. I don't believe it's proper to entertain other purposes for those specimens until we could be sure we have answered the question for which they were collected. We have not answered the question.

DR. STOTO: I don't see why that makes any sense at all. I don't think we should stop working on the Agent Orange, but this seems to me to be a very valuable scientific resource that's useful for all sorts of other things, and --

DR. MICHALEK: I knew this would happen, that as soon as we announce the availability of the specimens, that people would want to use them for some other purpose.

DR. STOTO: But that's a good thing.

DR. MICHALEK: I don't think it's a good thing.

DR. HARRISON: I think that life being what it is, if you had an RFP that said that you wanted applications to study the basis of dioxin's effect on -- I mean, even if you made it specific; dioxin's effect on -- Agent Orange's effect on diabetes, the range of applications that you'd receive that purported to be directed towards that fundamental point would be, the range would be enormous. That would be extremely fundamental studies that, you know on the structure of the AH receptor or, you know, some such all the way through.

DR. STOTO: So you're saying that they're really not limited by saying it's --

DR. HARRISON: Well, I'm saying, Joel, that I think that once the -- that unless you put something else in place, you might for instance, you might make it a stipulation that the Air Force would evaluate approved applications for relevancy, for instance.

If the Army does something like that, the Army will take for breast cancer or prostate cancer, will move stuff up and down -- NIH does, too -- based on what they perceive as relevancy.

So you might get around it that way, but what you're going to get is a variety of applications that are all over the range. And who's to say what the mechanisms are? So where's your cutoff going to be?

DR. MICHALEK: Well, for example, we don't understand biologically, completely, the relationship between diabetes and dioxin, do we?

DR. HARRISON: Yes, but I mean -- I'll bet you a jelly donut that I can find some people who will tell you that glucose transport has nothing whatsoever to do with the pathogenesis of diabetes. You know, I'm just using that as an example.

DR. MICHALEK: that's why we have these specimens, and that's why we do the open bid RFPs, to get other ideas. Like you say, some people concentrate on glucose transport, some don't. So we would get a variety of ideas.

DR. HARRISON: I agree. I think the way to get -- first of all, with an RFP you'd get a broad range of applications. The problem that we're discussing is not whether the RFP process is a good one; the problem that we're discussing is that we don't see any -- I think what you're saying is that you don't see any movement since April, and I don't know what the funding issues are. I can tell you that in preparation for this meeting that I placed two phone calls to Ken Olden's office to try and arrange to talk to him, and have not received a return phone call from either one. Now that's no big deal; that happens all the time -- at least to me -- but it sounds to me like NIEHS may have its set of priorities and that this has not been inserted in any way.

DR. CAMACHO: What kind of many dollars are you talking about, anyway? Anyone have a big ballpark figure?

DR. HARRISON: We did something like that in the letter, didn't we?

DR. MICHALEK: Yes, you were suggesting $400,000 research grants, and 20 of them?

LTC BURNHAM: 20, 20. Yes. For a total of $400 million.

DR. STOTO: I guess I want to bring up the question of why does it need any new money at all? If someone knew about this data resource, and specimen resource, and put in an RO1 grant to NIEHS, it seems to me that they would be rewarded for being clever enough to know that there was this resource there, and that they could use it.

DR. MICHALEK: So NIH would fund it, then.

DR. STOTO: Yes, NIH would fund it, but with money that it already has. It has $20 billion.

DR. MICHALEK: That sounds good.

DR. HARRISON: So in essence, then, the Air Force's role in this would simply between whether they agree to be a co-investigator and to provide samples that the research proposal required.

COL MARDEN: The guy in Little Rock that we're collaborating with --

DR. MICHALEK: Phil Kern.

COL MARDEN: What's the mechanism of funding for him?

DR. MICHALEK: We're paying for it.

DR. MINER: We're paying for it all.

DR. MICHALEK: Project funds. And that was relatively -- that was $300,000.

DR. MINER: 450.

DR. STOTO: You know, in the National Institute on Aging at NIH, the agency pays for a number of large scale surveys to be done. You probably know about some of these -- National Longitudinal Survey on Aging, and so on.

And then they make them available to anybody who wants to use them like you guys are doing, and NIA loves to fund these things, because essentially they can get lots of analyses done for relatively inexpensively, because the data are already there. And it's not that there's money set aside for studying the Longitudinal Survey on Aging, it's that they've got an ROI process, and if you're smart enough to come up with an idea about how you can use these existing data to solve a new problem, you get rewarded. That's the way NIH works.

DR. MICHALEK: How do you make that happen with these specimens?

DR. STOTO: I think, just continuing with the NIA, they go around to meetings and they tell everybody about these resources and they put out information about it and so on; and I think that if you got NIEHS to think about it from that perspective, that this is a resource that can enhance what they're already doing; not that you're asking for more money for this purpose. But this is a resource for people who are looking at environmental health issues.

DR. HARRISON: So you'd have the Air Force prepare an exhibit for the American Diabetes Association, for the International Diabetes Congress that would describe the Ranch Hand study, would describe the materials that were available, and would make the point that the Air Force would stand ready to consider collaborating with NIH or let's say NIH-funded investigators.

DR. STOTO: Yes, exactly.

DR. MICHALEK: Consistent with our protocol.

DR. HARRISON: Yes. Yes. So then what would happen -- I hate to say it, I like what Mike's --

(Laughter)

DR. STOTO: Wait a second, maybe I didn't quite mean that.

(Laughter)

DR. HARRISON: For instance, I'm doing a grant now with a guy out in California who's in a very different area from me. I located him, I sent him a little precis of what I was planning to write and asked him if he'd be interested and available to collaborate; and he wrote back and said yes, it sounds interesting, yada yada, so I put

up some more stuff and sent it to him; asked him to send me some information that I can use in the grant application to fill out the necessary parts, and then it goes in with a letter from this person saying that they agree to serve as a consultant on the grant and they agree to provide certain things; and that's the way it goes in to the NIH. If the NIH likes it, then I get the money, they send me the stuff, we're off to the races.

If he didn't like what I wrote, he just -- you know, doesn't answer the letter or just says "I don't like what you're interested in. I'm not interested in doing it."

COL MARDEN: We partner contingent upon the partner obtaining funding.

DR. MICHALEK: Well, those are good words; I want to enforce the protocol, number one --

DR. HARRISON: Yes.

DR. MICHALEK: I want to enforce the IRB rules in a consent form. As long as it can be done under that structure and we don't lose control of this, what can happen is someone can say "I want those specimens, period." And I'll say "No, you can't have them."

DR. HARRISON: Well, I don't think anyone can say that, and that's certainly not what I hear Mike suggesting.

DR. MICHALEK: I know, that's a worst case scenario, and I don't want to get into that fight.

DR. HARRISON: Well, I don't see it as a fight.

DR. MICHALEK: I don't want to get into that kind of confrontational situation. I mean those are great ideas, thank you.

DR. HARRISON: You have an acknowledged responsibility. The Air Force has an acknowledged responsibility to conduct this trial and to manage its samples, et cetera, properly. No one can disagree with that. <<NOISE>>

DR. MICHALEK: All right, then, as an extension of the discussion, realize that in 2002 these men will come back to Scripps and they will be there and available for more specimens. And that's the content of some of the proposals we have today, one of which from Debbie, to study the polymorphism of the AH receptor and other things from fresh specimens containing DNA.

So that's a topic for -- as you see on your agenda, that comes up pretty soon. So the idea of new specimens to collect in 2002, which is still an open issue as to what to collect in 2002, and why, and yet this material in the freezer.

So we advertise the material in the freezers, besides going to international meetings and making announcements, is there an easy mechanism that you all know about?

DR. HARRISON: You know, the way a lot of my colleagues work, I would guess that you must not have the right buzz words in your web page. Because most of us are out here sniffing around, trying to find money. You know, we're doing searches for key words and stuff.

DR. STOTO: Well, you know, the federal government puts out the solicitations in the Commerce Business Daily.

DR. HARRISON: That's different.

DR. STOTO: And then there are groups that search for those things and people subscribe to them, and you can see what's out there.

MR. CAMACHO: Why don't you put just a simple ad in every association annual meeting booklet? If you go to the ASA, there's a whole booklet. Would I go to the meeting, yakety-yak, to open it up and apply for funding.

DR. MICHALEK: That's great, that will help us with a few professional associations. To get the full coverage, maybe what we need is a point of contact. If you could give me an e-mail address of some people who know about these things, then we can start talking.

DR. GOUGH: Well, if you went to the National Institute of Diabetes and blah-blah-blah, and just wrote a letter to them -- those are the people you're trying to reach for diabetes.

DR. MICHALEK: Or Vietnam Veterans of America.

DR. GOUGH: No, I'm talking about going to the funding agency that would inform their potential grantees of the availability of this resource. Then it would be up to them, to either contact you to see if you could work out something, or just forget about it.

MR. CAMACHO: If you did one mailing to all these associations; the American Medical Association, the Diabetes -- down the whole gamut. I don't know, what's that? A hundred, a thousand?

DR. MICHALEK: Where would I get a comprehensive list of such things?

MR. CAMACHO: That's a good idea; I imagine there's one somewhere.

DR. STOTO: I guess I would begin by targeting. Diabetes is clearly a big thing, so think about the diabetes associations and meetings and so on.

DR. MICHALEK: And birth defects, fertility, reproductive outcomes.

DR. STOTO: But from the epidemiology end, what you might do is go to the SER meeting and the ACE meeting and try to get the EPI Monitor to write an article about this.

DR. MICHALEK: Or journal editors; we can send it to all these different journals. >NOISE<

DR. STILLS: I tend to agree with you. I think there have been a number of studies done, and we're in what, Cycle 6 of the studies? And I think based on your presentation today, you have highlighted that there are three or four critical areas that need to be addressed.

I think one of the best ways is just to keep it focused and identify those groups of people like the diabetes association or that group of people. You know, for example if the peripheral neuropathies and the cardiovascular disease is linked to diabetes, then maybe that's the area we really need to focus on, and really get the best researchers.

I think the Ranch Hand study is a critical study. It continues to be highly visible, and I think the best thing that we could do as a committee is really have our studies well thought of and really address specific questions. And it gets back to -- I'm kind of jumping ahead of myself here, but when I reviewed the proposals in this package, I

thought they were good proposals but I think it's important that even if you have the best ideas, you really have the scrutiny and rigorous review of the proposals so that when the study is done that we could really defend -- you know, our studies could stand up and really address the issues.

So I think if we were focused and really go to specific people, I think you could get the kind of research you want to get done.

DR. STOTO: One of the nice things about advertising the availability and then have NIH fund the research is that they've got peer review, and you're not going to get dumb things through that process most of the time.

MS. GARZON: Joel, I think -- you're on the adjunct faculty at UT, at the UT School of Public Health, and their research office has listings of all of the health funding agencies.

DR. MICHALEK: Is that the UT-San Antonio, or Houston?

MS. GARZON: Either -- if UT-San Antonio doesn't have it, they'll funnel you to the right people at UT School of Public Health in Houston, and I'm sure they'll be happy to line you up. I mean, you've given lectures, you've done stuff for us, so it's only fair.

DR. STOTO: Or what you might do is just talk to the people who do diabetes research at the university and say "where do you get information about" --.

MS. GARZON: Yes, but the research people can give you the e-mail contacts and stuff for --

MS. del JUNCO: At least in some of the agencies.

DR. MICHALEK: To me the blanket e-mail mechanism seems to be the quickest and most efficient.

MS. GARZON: And there's like -- just like NIH has project officers and -- so do the other funding agencies have the same sort of thing, and most of them are pretty responsive, especially if you're offering. You know, this isn't the typical "I have a study, are you interested?" This is, "I have a resource."

COL MARDEN: You know, perhaps even something as simple as a letter to the editor in the journals that we've published articles in.

DR. MICHALEK: Yes, Epidemiology, American Journal of EPI. Of course the other point to emphasize here is not only do we have the specimens, we have the entire health history, life history of each individual behind those specimens. And all of their associated lab tests and collaborative data.

MR. CAMACHO: So somebody without touching those samples, if they had the wherewithal, the computer power and the desire, they can go through all that original data and look for something you missed or was there, or didn't have the time to do, et cetera.

DR. MICHALEK: Exactly. We have five years left, and that isn't a lot of time. For example the adipose tissue study that we're doing at UC-Davis, that took over a year to get started, it'll take two years to do it, a year to analyze and maybe two years to publish. We don't have enough time left on the study. We'll be lucky if that's published, and that's when our papers --

MR. CAMACHO: What happens when this study ends? To the data.

DR. MICHALEK: That's another discussion; what to do with this material when the study ends. In the year 2006 we expect, unless we're told otherwise, our funding mandate will end. That happens to be the time in which most of us are going to retire. We want to be able to walk out the door and not have to worry about these specimens and all this private information being available to just anyone. It has to be under custody. There has to be a chain of custody, if it's going to be kept, and it has to be protected. Because those people are still alive and they gave it to us in their full confidence.

MR. CAMACHO: I would say for posterity you'd want to keep that data. I mean, you can scrub names and put numbers there. -- Can't? No way.

DR. MICHALEK: No. We've gone through -- you're talking millions of documents. Doctor's handwriting, names, social security numbers, addresses, phone numbers -- it's all there and it's all private.

MR. CAMACHO: I wouldn't throw that kind of data away; I'd work to find a way to make qualified people get access here.

DR. HARRISON: Let me make a suggestion.

DR. MICHALEK: We're talking millions of documents and all of it is being scanned, by the way, saved in an electronic version of it and you have a hard copy. Yes?

DR. HARRISON: Let me make a suggestion. All the stuff that's scheduled for this afternoon to me is related. How the scientific community is notified, how proposals are screened, and then the proposals that you've got here for us to discuss.

So maybe the thing to do with this is to think that -- well, first of all, I think what we're actually talking about now has gone past the NIEHS interface presentation. We really have touched on but what the available funds are.

Let me try to ask a related question. What do we want to suggest to the Air Force, as a committee, that the Air Force do -- let me back up for a minute.

I am taking the position that the Air Force health study has demonstrated a relationship between Agent Orange exposure and diabetes, peripheral neuropathy --

DR. MICHALEK: Cognitive function.

DR. HARRISON: -- cognitive function, whatever these four or five categories are. I'm willing to accept that those relationships have been demonstrated.

Now if the Air Force were to take its charge, I think that's all that you're supposed to do.

DR. MICHALEK: Whereas the protocol -- we have a protocol. I execute the protocol.

DR. HARRISON: I understand, I understand.

However, logic says that to the extent possible, that what one would like to do scientifically is to, once the phenomenology has been described, is to establish a causal relationship, to establish a mechanistic relationship.

So what does the committee want to suggest as a mechanism for doing that? Because what's being done right now to my view is kind of a catch-as-catch can, very casual sort of approach. And Joel may think that $300,000 is a trivial amount of money, but you can be a hero in a lot of places if you bring in $300,000.

DR. MINER: We've spoiled him.

DR. HARRISON: This is useful dough here.

So it seems to me that we should offer advice on two things, which we're doing, actually; but let's just try to draw some closure here. How should the scientific community be notified of this opportunity? and I'm rephrasing this a little bit: What role should the Air Force play in the selection of research projects?

DR. STOTO: Let's just be clear about what this opportunity is. This opportunity is the data and the specimens.

DR. HARRISON: That's two separate opportunities.

DR. STOTO: Right, and there is also a potential for money, but I think the money that might be available through NIH is far more than the Ranch Hand --

DR. HARRISON: Absolutely. Absolutely.

DR. STOTO: So it's really --.

DR. GOUGH: Well, I think -- what I would suggest is that we focus on these things that are suggested associations. That the chairman of our advisory committee write to the directors of the NIH institutes that are responsible for those areas of research, and any professional societies -- it would be a general letter -- informing them of the availability of the data and the information and the samples that might be appropriate for their use, and not make any commitment at all about any money. Just say this is a resource.

I think the Air Force role, and I guess the advisory panel role, too, is that I think there should be a sign-off saying "this is related." Because we don't want something that's -- I can't imagine; it wouldn't be totally unrelated because people are very clever about writing proposals.

But I think the Air Force should -- and I'm not sure of the legality -- should maintain custody of it.

DR. MICHALEK: Exactly.

DR. GOUGH: But I think the important thing is to go to NIH and let them know, because that's where the money's going to come from.

DR. MICHALEK: Our role will be to be sure we're executing the protocol. And that would be your role, too, as the advisory committee.

DR. HARRISON: Well -- go ahead.

DR. STOTO: I guess I think that that's the right direction to move in. It's going to take more than a letter. Even as much weight as your name carries. I think it's going to take some running around and really talking to people, making sure they understand what the issue is. Not the issue; what the resource is. And you're right, we ought to target the places where --

DR. GOUGH: Yes, we need a target. That's our business.

DR. STOTO: And I think that the way the target is -- to target first of all the disease outcomes that look like there's something going on, and the methodology, the groups of people that have methodology that might have something to do here.

DR. MICHALEK: Doesn't it seem more reasonable that a person who is told "Well, we have 4,000 serum specimens" that's not enough. He needs to know, "Well, what's been done already?" In other words, they would have to hear this overview talk I gave at least, so they would know the full scope of the study and what's available.

DR. HARRISON: You know something that we haven't really thought about, and it's too late, probably, for next year; but this is a gorgeous symposium topic for those scientific meetings that have an interest in these areas. To propose to the American Diabetes Association that there be a symposium on environmental influences on diabetes with, Agent Orange as a major centerpiece in that. I think they would snap that up as a symposium, and I don't suspect you'd need more than one or two like that.

DR. GOUGH: I think you're right.

DR. MICHALEK: And they would network the rest.

DR. HARRISON: You've got to understand, everybody's looking for just a little bit of an edge, just a little something that somebody else hasn't thought of or doesn't have their hands on.

MR. CAMACHO: A shotgun approach covering all these things, you can put it in the Federal Register -- you can get it in there, you can get it into the programs of these pieces. You can try -- it's too late; that's right, they plan these things way in advance, but you could try and get it into a symposium format.

Get a subgroup together and brainbust one day, and somebody who has the data that knows who's who to contact, put the list together.

DR. HARRISON: In fact, this is just off the top of my head, but -- this could be a satellite symposium at the next American Diabetes Association meeting, and I can get you the money for it.

DR. MICHALEK: Great.

You mean the money for my travel out there?

DR. HARRISON: A drug company trying to develop a presence in the area of metabolism? That's what they do, is have satellite symposia that cover these kinds of things.

DR. MICHALEK: What do you mean by satellite symposia?

DR. HARRISON: It means that the meeting is from Wednesday to Saturday. Sometimes they're actually done with the full cooperation of the society, but sometimes you simply have a meeting that's in the same city, in the same locale, during the same period of time, that's not a part of the official agenda -- but because everybody who's there say is interested in diabetes, then you send out a general mailing -- you can use the Society for that -- you send out a general mailing that you're having on this satellite symposium on environmental influences on metabolism, and you have, you're invited -- you have your invited list of speakers and if it's a really terrible

topic, then ten people show up. If It's a really hot topic, then all of a sudden you're trying to renegotiate the ballroom at the hotel for the symposium. And you do it for like a half a day or four hours, and it's done.

DR. STOTO: I guess I feel that this is not something to be done on the cheap, but that it's better to spend a couple hundred thousand dollars being systematic about this then to spend it on the first five proposals that we kind of got over the transom without doing this.

DR. MICHALEK: I want to separate the issues here. The proposals that are on the table today are not part of this discussion. They were contemplated and discussed for many, many months or years prior to this meeting, the materials I've given you already.

DR. STOTO: Okay, well, let me take that back and stop at the first part of it, that this is not something that can be done effectively on the cheap.

DR. MICHALEK: No, it should not be, considering the resources that have been spent so far.

LTC BURNHAM: Another approach to this is if you can think of other tests that can be done on the samples so that we can have the data in the future. Like genetic testing.

DR. STOTO: I think that's a separate issue.

DR. HARRISON: Well, yes, but -- what we're saying is that if you were to take this topic and invite proposals, those proposals would wind up being distributed to 50 or 60 study sections at the NIH, assuming that you got a recent --. 50 or 60 groups of 15 to 20 experts in distinct areas.

Those proposals would then be evaluated and scored, and wind up being further evaluated by the advisory councils of easily, let's say, three different NIH institutes; NIEHS, NIDDK, and NCI. Let's just say, okay? Each advisory council consisting of what, Mike, about 30 to 35 members, I think.

DR. STOTO: Probably.

DR. HARRISON: So what you're asking this motley band of these six or seven people to do is an evaluation that's properly done by this huge tier of people. Even asking me what tests you should do the next time is real risky. I've got my pet tests; I want to make sure that those tests are in. Half the rest of the country feels like they're not really very useful for anything.

DR. STOTO: Were you tests on the existing specimens?

DR. MICHALEK: We're mixing up two discussions here.

COL MARDEN: Or at the upcoming physical.

LTC BURNHAM: Because we have the money in the specimens, it's kind of like having the data. So that when other people want to do research, they have the data and can --

DR. STOTO: Well, that might be one thing you make clear is available; not only are the specimens available, but there are some resources available for analyzing them in ways that haven't been done before.

DR. SELVIN: Something simple that you could do that occurred to me was that Dr. Kang, who just finished the womens' study, in Vietnam, and they are facing or have faced the same issue. They don't have the extensive physical examinations, but they have all the medical records, they have extensive questionnaires.

DR. MICHALEK: No, no. They have reported birth defects -- wasn't that the womens' study? -- not verified by medical records.

DR. SELVIN: No, that's different. That's in the Gulf War.

DR. MICHALEK: I'm talking about the Vietnam women's study.

DR. SELVIN: Anyway, they have the medical records. It's a phone call away and you can ask.

DR. MICHALEK: Han Kang is an important contact, that's true. So was the IOM. David Tallarud.

DR. SELVIN: And I suspect they thought through this a bit, because they have a dataset worth a considerable amount of money, and it shouldn't go to waste just as this one shouldn't.

DR. MICHALEK: I think all your ideas have been captured.

I have a few slides on the six proposals. Do you want to talk some more on this?

DR. GOUGH: Well, when we meet in December, will we hear from the Air Force about the follow up on this discussion?

DR. MICHALEK: Yes. I will attempt to make some progress on this issue before the next meeting, and I'll report to you on that.

DR. STOTO: One thing you might do is try to identify half a dozen people at NIH with the right -- who deal with the right issues, to just come down and join us for a couple hours.

DR. MICHALEK: Okay. Here in San Antonio?

You're talking about coming to --

DR. STOTO: I was thinking if the meeting were going to be in Washington.

DR. GOUGH: Talking about Santa Barbara?

(Laughter)

(Simultaneous discussion.)

MR. CAMACHO: You were talking about something different. Let's identify a number of key people in these associations and fly them to one of these meetings to just break --

DR. STOTO: I was thinking that the meeting would be in Washington, and a lot of these people are already in Washington. So I was thinking, if we were going to be in Washington. I like to travel, too, but --

DR. HARRISON: If we're are going to be in this same room, I would say that we should be in Washington.

DR. STOTO: Well, if we are in Washington for whatever reasons, NIH is of course just in town, too; and identifying a few people and trying to get them involved enough to come to hear for a few hours may have multiplier effects.

DR. HARRISON: It might be interesting. That's not a bad idea, Joel, to -- I know that you all want to focus, I think, on the statement of work for this next meeting.

COL MARDEN: Add a day.

DR. HARRISON: Yes, or half a day.

DR. MICHALEK: I think this is important. Because this is an intermediate step to ending the study. We have to use this material to answer the question before the study ends, so that that can lead to the next question, as to how to close the study. That's important to be on the agenda, I agree.

DR. HARRISON: I think that -- I would also like to suggest that the committee consider whether or not this study should be thought of as closing at the -- there's going to be data collected, and that data is going to be evaluated. And I get the sense from Joel that his thought is that at that point the study ends or closes. And I think that considering the extensive amount of material that's present and the unprecedented amount of data that's already been collected, that some attempt should be made to maintain that material in very accessible forms and to ensure that nothing happens to it.

MR. CAMACHO: If nothing else, the Library of Congress or something. It's not going to end like this, boom! Right? It's not going to fall off a cliff.

DR. MICHALEK: Yes, it will end when the funding ends. It will end like that unless you as a committee do something to prevent that.

COL MARDEN: We've already seen one study that that happened.

DR. MICHALEK: It will happen exactly that way.

COL MARDEN: The West Point study happened that way.

DR. HARRISON: So my question is, doesn't the committee already have a sense that we want to make a recommendation that funding be secured to maintain this in some way past whatever--

DR. MICHALEK: 2006.

DR. HARRISON: 2006.

LTC BURNHAM: Do you mean continue the study, or --

DR. HARRISON: No, no. Not continue the study. I think that you've sucked just about all the juice you can get out of this thing. But to keep what's there --

COL MARDEN: Keep the freezers running.

DR. HARRISON: Keep the freezers running, maybe even by then OCR will be able to interpret physicians' scribblings and you can transfer those to --

DR. STOTO: Or to maintain just copies of them in digital form.

DR. HARRISON: So is it possible that there might be a subcommittee of this committee. For instance, Dr. Camacho looks like he's a good one and Dr. Sills to maybe draft a little letter that we could, or a little statement that we could insert into the Minutes that that's what we would like the Air Force to pursue?

DR. CAMACHO: I so move.

DR. STOTO: Did Dr. Camacho hear what was --

(Laughter)

[Overhead]

DR. CAMACHO: What was that?

DR. HARRISON: Well, we just thought that you two guys should get together and write a little statement for us to insert in the minutes, that we feel that this material and these resources are too valuable to place at risk, and that extended funding, extended past 2006 needs to be --

DR. CAMACHO: Planning for the purposes of --

DR. HARRISON: Of at least maintaining what's here.

DR. CAMACHO: Maintaining the data.

DR. HARRISON: Not extending the study. That's --

DR. CAMACHO: Data acquisition.

DR. HARRISON: Yes, what's been acquired.

COL MARDEN: Preservation. Archiving and caretaking.

DR. HARRISON: And not only preservation, but accessibility is an issue. Accessibility.

COL MARDEN: Yes, caretaking.

DR. STOTO: No, more than caretaking. It's maintaining access to. So --

DR. HARRISON: So it means when someone tries to call the Air Force Health Study, somebody's got to answer the phone.

DR. CAMACHO: The sheer volume, if you have everything on a machine -- you know, you've scanned every document, the whole nine yards is in a huge -- the catalog is there. What are you looking at? Over 100 gigabytes? Has anybody even thought of it that way?

DR. MICHALEK: I would think 12 to 15 gigs. No, that's just the electronic -- that's not counting scanned data.

DR. MINER: 127 gigs are scanned right now and we're going to eat that up pretty quick.

DR. MICHALEK: Figure twice.

MR. CAMACHO: So in the end, about 250 gigs?

DR. MINER: Yes, probably.

DR. CAMACHO: Given the pace of technology, it's not that unreasonable to preserve.

DR. STOTO: But the issue is the physical --

DR. MICHALEK: There's the issue is integrity and security of the material.

DR. HARRISON: And also some administrative structure to handle --

DR. MINER: Exactly. The Air Force, in their budget, does not have any money in here for anything past 2006. I guarantee you.

DR. STOTO: That's what we want to change.

DR. MINER: The Air Force will not change that.

DR. MICHALEK: They have nothing.

DR. GOUGH: Without congressional direction.

VOICES: Right.

[Simultaneous discussion]

DR. MICHALEK: There has to be a directive, there has to be a mandate.

DR. HARRISON: It seems to me that that's a political process that --

DR. MICHALEK: You can do it, I can't.

MR. CAMACHO: I'm happy to do something like that.

DR. HARRISON: The reason I'm asking if you all won't work on a little statement for us is that, I think we have a general consensus on that; let's stop that discussion and go on to this.

DR. CAMACHO: Who am I going to work with on that?

DR. SILLS: The two of us.

DR. CAMACHO: And who on the Air Force side can we just talk to?

DR. HARRISON: We're an advisory committee, we don't need to deal with those guys.

(Laughter)

In fact, you actually would like to be able to say that this is the advisory committee's posture that is uninfluenced by the Air Force Health Study personnel, that this is what we're thinking.

DR. STOTO: There may be factual things that they need to hear from the Air Force, though.

DR. HARRISON: Well, yes. Okay. Agreed.

Okay. On to Review Proposals for Research.

DR. MICHALEK: Before getting into this, I want to just give you some more interesting news, I think.

There are three new collaborative efforts recently underway, recently launched between us and other agencies. Number one, we have contracted with the National Agricultural Library in Beltsville, Maryland to restore a collection of over 300,000 Ranch Hand documents, photographs, index cards, that are in their basement in boxes.

These were collected by Col Alvin Young, who has since retired from the Air Force; he was very active in herbicide testing and the Agent Orange, Stateside, the Agent Orange operation during the Sixties. We want all of that material scanned, catalogued, and restored to a collection, on shelving, available just like any other archive.

So that's underway; that's just beginning.

DR. HARRISON: What is this material, again?

DR. MICHALEK: 300,000 documents pertaining to Ranch Hand. That would include documents that were produced in Vietnam by the Ranch Hand unit in particular, daily reports, rosters, morning reports, incident reports -- any kind of paper that came out of the Ranch Hand operation in Vietnam is in those boxes. Together with notes, index cards, photographs, who knows what? And actually, we're going to have to go up there and take a look at that material to help them decide which pieces to OCR and which one is not, and that will come soon.

So that contract has just now been let and we just -- we're just beginning that. Secondly --

DR. STOTO: Joel, on that one there, I know in the 70s the National Academy of Sciences put together these data tapes of where the spraying --

DR. MICHALEK: That's the Herbst tapes.

DR. STOTO: Right. Are they available and accessible?

DR. MICHALEK: The Herbst tapes are available. I don't know exactly how, but I know they're available. In fact, I think we have a copy in our computer.

DR. STOTO: So you know, anybody who is counting on the Academy to make them available in the future, don't do that anymore. But that may be something you want to think about as--

DR. MICHALEK: The Herbst tapes.

DR. STOTO: The Herbst tapes, making them available either through your group or through --

DR. MICHALEK: Sure. We can put them on our web page.

DR. STOTO: Or the agricultural --

DR. MICHALEK: Right. Through the National Agricultural Library.

By the way, it was at the National Agriculture Library in 1987 where I found the maintenance manuals for the spray equipment on the aircraft that were used in Vietnam. Those were important documents for us because it helped us design the questionnaire that we gave to the enlisted so that we could assess their exposures in Vietnam, which you already saw the data for.

So we've been there, we know that the material exists, and we're trying to take care of it with an arrangement with Natural.

Secondly we have launched a research effort with EPA to study our estimate of the initial dose in Vietnam of the Ranch Hand veterans. The issue, the quality of our initial dose, the accuracy of our initial dose has been raised almost every time I present material from the study. "Well, how do you know how good the initial dose is?" Well, of course we don't have dosimetry in Vietnam. I can't give you that.

What we can do and what we will do, with the EPA through Dr. Mike DeVito is conduct animal experiments where we dose animals with proportionately the same dose that the Ranch Hands got in Vietnam; we measure them periodically in the same regimen that we measure the Ranch Handers every five years, only proportionate to the length of life of the animal, then we apply the same statistical models that you just saw on our half life studies to the animal to estimate the initial dose. We will know the initial dose because we dose the animals; and we can report the predicted and the real initial dose using the same statistical modeling and the same dioxin assays in a controlled experiment.

We're going to do that two different ways. We're going to do that once in rats and once in mice. And by the way, Dr. Harrison, these are genetically engineered mice. If you put them on a certain diet, they will get diabetes. So we're going to have a factorial design, diabetic/nondiabetic, high-fat/low-fat diet, using the same repeated measures, same statistical models, proportionate dose, and repeated dioxin measurements. That has just now been launched, that study with Dr. Devito.

DR. HARRISON: Now of course the fact that rats and mice have different fat from humans --

DR. MICHALEK: Yes.

DR. HARRISON: -- should not deter you from this.

(Laughter)

DR. MICHALEK: It's called doing the best you can. And we put our heads together, and this is the best we could come up with.

VOICE: Might be very hard to find human volunteers.

DR. HARRISON: But this experiment has already been done in humans, though; you just discussed it this morning.

DR. MICHALEK: No; we're talking -- that is the second arm of our initial dose investigation. We're collaborating with CDC and Dr. Makur --

DR. HARRISON: You discussed the Seveso data.

DR. MICHALEK: Yes.

DR. HARRISON: Which was, as I recall, 300 individuals who had samples obtained one day and one week or something like that after their initial dose. And you showed that this was linear.

DR. MICHALEK: Yes. This is the first time, though, that we've been able to merge the Seveso data with the Ranch Hand data on repeated dioxin measurements, in adult males from Seveso who received exposure in the explosion. We have repeated dioxin measurements on those men, just like we do on the Ranch Handers; the difference is at Seveso we have the first measurement the day after the explosion.

DR. HARRISON: So what additional are you going to show with the rodent study?

DR. MICHALEK: Well, I'm getting into the talk we'll show you in December.

The point is that the elimination rate among those men is almost identical to what it is in the Ranch Hand group; it is linear in log units. The overlay is impressive, the straight lines you saw in those plots are extended to Day Zero, to Time Zero.

COL MARDEN: So what's the rodents going to show you?

DR. MICHALEK: The point is, what's compelling about this is that that's real data, that is not speculation.

DR. HARRISON: I know. So what's the rat going to tell you?

DR. MICHALEK: You're not impressed. Okay.

DR. MINER: No, no. His question is, why are we doing the mouse and the rats?

DR. MICHALEK: Why are we doing the mouse and the rats? Because we want to be able to control -- we want to be able to control for diabetes, want to be able to control for --

DR. MINER: It's the diabetes piece.

DR. MICHALEK: -- body fat, we want to be able to address all of the issues that are raised whenever we present data to -- "Well, we're not sure about this initial dose, what about changing body fat and diabetes, how does that affect your initial dose?" Well, we can't control that with Seveso, but we can with the animals.

DR. STOTO: I think that's important. The Italians weren't genetically modified. Seriously.

(Laughter)

DR. HARRISON: Well, just intuitively, just right off the bat, just think of how much brown adipose tissue rats have, and I believe mice, too, compared to --

DR. STOTO: Is there a different animal model that might work?

DR. MICHALEK: We talked about that.

DR. HARRISON: Rodents have two different types of adipose tissue.

DR. MICHALEK: We talked about other possible animal models.

DR. GOUGH: I'm completely in agreement with Dr. Harrison, but I think that -- the mere fact that you're doing it in both rats and mice, why is it necessary to do that? Because you don't know which is a better predictor for human beings.

DR. MICHALEK: I think the more species the better. I'm trying to --

DR. GOUGH: Well, I disagree. Species are different, as Bob says. But I know you're going to go ahead and do this.

DR. MICHALEK: But the pharmacokinetics may not.

DR. HARRISON: If you've got it in man, whatever you get in the rat -- if you get something in the rat that's different -- let's suppose you get something different. What are you going to do with the Seveso data?

DR. MICHALEK: Sit back for a second. The purpose is not to investigate how rats are different from mice; the idea is to understand how well our statistical modeling is working. The statistical model that we use will be fit to the animal data, separately on the rats and separately on the mice.

I want to know how good are these least square estimates of the initial dose in this first order model. I believe that the rats will have a different half life from the mice. Fine. The statistical modeling will accommodate that.

DR. HARRISON: You know, the -- go ahead.

DR. STILLS: But I agree with Dr. Harrison and Dr. Gough, that I think you have to be careful, though. The question that you're trying to address is in terms of the toxicokinetics, in terms of -- the issue is, you're really trying to understand dioxin and the health effects of diabetes.

So it seems as though rather than using rats and mice, you have this model that -- you know, you have these animal models where you can really look at diabetes. It seems as though you would pick one -- I mean, whether it's rat or mouse I don't know about the models, it's most similar to the human situation. And we need to focus on that and address your questions in one model, because as you said, Dr. Harrison, once you start using two models, you are going to get all types of data. And then you're going to have more issues to deal with.

So it seems as though you would want to use the model that mimics the human situation and really address your questions in one model.

MR. CAMACHO: Wait a minute, now I'm confused. I thought what you were trying to do was to get a proof that the model is working.

DR. MICHALEK: The statistical model.

DR. MINER: It's the model that we're testing.

DR. CAMACHO: Not what the predictors are --

DR. MICHALEK: I don't particularly care what the half life --

DR. CAMACHO: -- not the material, but rather the methodology.

DR. MICHALEK: Right. I don't care what that half life is in the rat; all I want to know is, is the model working.

DR. HARRISON: I thought --

DR. SELVIN: If the model fails to work, are you going to abandon the models in humans?

DR. HARRISON: When you started off, you said that the question that you're always asked is what the original level of dioxin was, what the level was at ground zero.

DR. MICHALEK: Right.

DR. HARRISON: Now you've got a rock-solid half life. So the real question is, are there two different half lifes? Is there an acute half life and a chronic half life? And the Seveso data says there's no acute half life; that the slope stays the same from Day Zero out.

DR. STOTO: I think there's much more at stake than this. I think that the relationship between diabetes, obesity and dioxin metabolism is a very complicated one, and it's complicated things. We have some data from Seveso; but the way we do science is, we try to look at it from every angle we can. And if things are consistent across species between animals and man, then we learn something. If they're different, then we have to puzzle out what that means. We learn something again.

This is exactly the way we ought to be doing science, by doing replication in slightly different variance.

DR. MICHALEK: Yes. I'm not doing such a great job of defending that proposal, so why don't I -- we'll take it up in detail at the next meeting, because I don't have it with me.

LTC BURNHAM: Then the other piece is that we've already spent the money from last year's funding; it's out the door and spent. So there's no turning back now.

(Laughter)

DR. HARRISON: That gets to the problem that I have with this whole process. And that is that you're asking us to accept some level of responsibility for things that I'm not real comfortable with. And yet, if push comes to shove you're going to say "Oh, well, this was discussed with the Advisory Committee," and I don't particularly care for that.

DR. MICHALEK: No, that particular piece was not discussed with you.

COL MARDEN: That came about quickly --

DR. HARRISON: And it gets to the other problem that I have; and that is that this is the best way to do bad science that I know of. And that is -- "You know, we've got a couple of hundred thousand bucks, what are we going to do? Well, so-and-so has an idea, let's do that so we can get rid of this money." That's terrible.

DR. STOTO: We are an advisory committee, we're not like a council to NIH where we don't have to approve what they do. So I don't think they were represented in that way.

DR. HARRISON: I'm not saying that they -- but we clearly provide cover. And I'd personally --

DR. STOTO: Well, we can't provide cover on this thing that we didn't discuss with them.

DR. HARRISON: I personally don't feel comfortable providing cover for this type of a process.

LTC BURNHAM: Well, we need to start meeting at least quarterly, then.

MR. CAMACHO: I think we can do a better job helping you. I think I can do a better job as an advisory committee member helping you, if we're meeting -- the advisory committee or all of us are meeting on at least a quarterly basis -- at least three times a year, and I get the stuff in advance. Then I have a couple of clues; I'm not coming from so far behind the curve all the time.

DR. STILLS: But I am like the committee in terms of, I think it's really critical. I think -- I was impressed with the list of publications that I saw -- this has been done here. I think as you look towards the future, any project that is taught about now, the hope is that it will be published. And if it's going to be published, it will be scrutinized, it will be -- appears in the field of diabetes or in the field of toxicokinetics, are going to be looking at this data.

And I think the study will be in a better way in terms of the future if we were to design good studies.

As I listen to the comments here, I think if we really have a list of priorities in terms of water or research issues and get the best people to come in and help us to really get the best group of people doing the studies, this study will even be better than it is. It's already an outstanding study, and I think we've got to make sure that we -- with my being a part of the advisory committee, I would like to see that we have -- that the science that comes out of here really reflects excellence in terms of science today.

My research, when I design studies or anything that I do, it really goes through a number of my peers who are experts in the field, review it, and they give me good and bad criticism, and it makes my study a better study. And I think we really need to -- I would suggest that we have something that we should really strive for, having people who really know the science be a part of this process so that we get the best studies done.

With the bottom line being that whatever we get out of these studies, that it's going to help in terms of understanding the health effects of dioxins in terms of people exposed to Agent Orange; and that's all I'm trying to say as I make these points, even though I may be going around in circles, is the bottom line, we need to, at the end of the day we need to be able to defend that the health effects are true, we have the science to back it up, we don't have anything to worry about. And again, if we have designed good studies, we have the science to say yes, and we can defend this at all levels.

MR. CAMACHO: Well, you always try to shoot for this ideal type, but in reality money, time, budgets and everybody getting involved, we're not going to make this. So you're going to fall short. That doesn't mean you don't do anything at all. So I think we've got to keep our heads on.

COL MARDEN: One of the immutables is the sample size.

DR. MICHALEK: Right.

COL MARDEN: And that's going to give us a certain amount of problems.

DR. MICHALEK: Just two things to add. First of all, I have not defended that protocol adequately; I will do so at the next meeting. Secondly, the protocol of DeVito received peer review within CDC and EPA, and he had to go to Washington separately to defend it. So didn't have a peer review process, just like you have at NIEHS, within the agency. Not only had to get our approval, but he had to go through several hoops in his agency to receive approval to take our money.

Secondly, there is a timeline. In fact, if we had attempted to do this particular study on open bid solicitation, it would be years before we see a result, because it would take a long time, wouldn't it, to do an open bid solicitation on an issue like this. We wouldn't get results in a timely fashion.

So we brought together the best people we know in the field, which are Professor Macharelli, Larry Needham at CDC, Linda Birnbaum at EPA, Mike DeVito at EPA, Bill Farland at EPA, and we discussed the issue about how to understand better how the statistical modeling is predicting the initial dose in the Ranch Hand veterans. How could we do that with people and how could we do it with animals?

We discussed both arms of the study. One was to collaborate with the Seveso investigator, Professor Macharelli, Dr. Macharelli. We attempted to work with CDC but realized we needed to work with EPA, because EPA works with animals. They are federal experts, anyway, the in animal experimentation. And this protocol, by the way, was seen by other people we were doing work with. I don't remember if we gave it to Matt Longnecker or not.

In other words, not just to throw it out and get it funded. There was a lot of thought put into this. And I'm sorry we didn't get this to you in time.

DR. HARRISON: When you come to the next meeting, could you bring the reviews that that project got?

DR. MICHALEK: Sure, I can get that from Devito.

DR. HARRISON: I'd be real curious to see what they said.

DR. MICHALEK: I've got -- I'm sorry, I did not defend that adequately.

DR. STOTO: Let me -- can I just say on that one that I think that we should be clear that we're not criticizing the study because we haven't seen any of the details of it.

DR. MICHALEK: You haven't seen it. You haven't seen the rationale, you haven't seen anything yet.

DR. STOTO: The committee is not criticizing it.

DR. GOUGH: Individuals are, have reservations about it. That's why it's a topic of discussion.

DR. HARRISON: But also, the criticism is of the process.

DR. GOUGH: Yes, and the process is --.

DR. HARRISON: And it's the process that concerns me more than any particular study. I don't expect to agree with every study that everybody proposes that's good, but the process, driven by time constraints and so on, just makes me uncomfortable and has always made me uncomfortable. The lack of a medical scientist of comparable experience to yourself, Joel, is a real problem, because it means that you don't have someone --

DR. MICHALEK: Well, I have a lot of respect for DeVito. Once you meet him, you'll understand. In fact, I can get him to come. But let me finish, please.

We also have a contractual relationship now, almost, with Professor Arnold Shecter at University of Texas at Dallas. He's funded for 10 percent -- is that the figure -- 10 percent plus administrative support to coauthor a paper on thyroid function with us. For two years.

DR. HARRISON: Just in case you didn't really get my point, though -- it's that from my perspective, the biological relationship -- the relationships in a biological organism are important in driving research decisions. I've known you for a long time and I know that you know a lot of biology, but you don't know as much biology as a biomedical person knows, and so you're simply not aware of some things that people who function with you, the physicians who function with you come and go; so their involvement in the project is somewhat less, and while you may have consultants, people that you talk to that are real experts in their area, I don't think you have someone with an overview from a biological perspective. And I don't think you're going to get it -- I mean, that would require the Air Force to fund a co-principal investigator, and that just doesn't seem to be happening.

DR. MICHALEK: You really put your finger on it there. You saw the list of all these papers we write. What we have here is a networking. For example, and all these experts work with us. The purpose of answering the Agent Orange question, number one; and secondly because we have great data, and because we work well together.

For example, James Albers, University of Michigan is the expert in neurology. James Dwyer, University of California-Los Angeles, on the carotid artery -- U.S.C., sorry. Robin Morris, Emory University on cognitive function with Drew Barrett, CDC. We have a network of experts around the United States who collaborate on this study. They're coauthors on all of our papers. Matt Longnecker is a key person for us. He is the kind of person you're talking about. He's around, he's been in the area for a long time, he's not going away, he's there, he's available, he's interested, and we coauthor papers together.

So yes, it's an important networking, and it works.

DR. STOTO: Are they not on this advisory committee because of a conflict of interest?

DR. MICHALEK: Well, yes. Matt Longnecker is a federal employee, so he can't be on the committee.

DR. STOTO: How about the others?

DR. MICHALEK: Albers could be on the committee. By the way, Albers is on the NIH committee to oversee the NIEHS study of mercury in amalgam; that's how I got collaborative with Albers, because Al Kingman at NIDR, through the link between amalgam, neurology, and mercury in our Ranch Hand veterans.

DR. MINER: But we still have no one in house, that is correct.

DR. MICHALEK: True, and we won't.

LTC BURNHAM: Which is exactly your point.

DR. MICHALEK: The staff will not change between now and the end in year 2006.

DR. STOTO: Well, given that, though, might it not make sense to try to get more of these people involved in this committee?

LTC BURNHAM: I don't know that you can get enough people. I mean, just the people he's described -- the people we work with are more than nine.

DR. STOTO: Maybe not all. Maybe some of them rather than us would be better.

DR. MICHALEK: All we can do is invite them, one or two at a time, to come and make presentations and answer questions.

DR. HARRISON: Just a minute.

MAJ SPEY: I'd like to make just one comment. I know I'm a lay person, I'm a high school graduate, but I've been involved in this study since 1978. Our association assisted with the operational element of Operation Ranch Hand as it evolved into the protocol. The protocol took over two years of peer review by the finest organization in this nation, in the scientific community.

In every case where a small health variable was discovered; for example, the conductive studies, the wall thickness studies of the heart, et cetera, a separate contract has gone out to biologists and doctors to examine those particular findings where state of health or current health seemed to be changed in some way or another.

And I think that a time like this where we were to throw in, you might say in the 11th hour, and affect the overall protocol of this study, is going to place this study or allow this study to receive criticism that it's received before for political reasons, and I would hate to see that happen in the 11th hour. I think it's extremely important that the protocol be followed as it was written; when deviations are noted they are being handled by subcontractors and being evaluated separately.

DR. STOTO: I don't think we're talking about changing the protocol here.

DR. HARRISON: Not at all.

DR. STOTO: What we're talking about is getting more help in interpreting the results; and if there are people with the appropriate expertise who are already involved in the research, and they somehow get -- help us.

DR. MICHALEK: I think it would be helpful at this point to go through these particular slides because they will address some of the issues you're talking about.

DR. HARRISON: Okay. I appreciate your comments though. And I can always speak for myself, but I don't feel that I'm suggesting a change in the protocol. The overall protocol has got to go the way it has to make the study remain as valuable as it is, and I agree with you about that. What we're talking about, really, are some of the nuances -- we're talking about how to select a subcontractor, and should American Airlines be allowed to select its own FAA investigators, or inspectors, or should inspectors somehow be selected by some other mechanism so that they're not in some way directly connected with what they're inspecting, might be one way of looking at it.

Review Proposals for Research

DR. MICHALEK: Well, we have included in your loose-leaf six proposals that are important, at least to me, because they address very directly issues that we are seeing in the data. The first two have to do with the possibility that certain people --

DR. STOTO: Not to be rude, but I just wonder whether some of the people whose names are up there ought to be here in the room for this discussion.

DR. MICHALEK: Well, we invited her specifically to answer questions in case you have any. Actually, I invited all of them, but only one came.

DR. STOTO: That's what I want to hear; did everybody have the same opportunity, or --

DR. MICHALEK: Yes, everyone was invited.

DR. STOTO: -- did other people feel comfortable.

MS. del JUNCO: I'd be happy to leave if --

DR. STOTO: I'm not saying one way or the other, but I think it's just something, a procedural issue we ought to discuss.

DR. HARRISON: It all depends on what we're being asked. If we're being asked to provide critical comments, traditionally that's not done as -- traditionally that's not done quite so openly. I don't particularly care; I'm going to make my comments no matter what, but --

(Laughter)

-- but I think that's something for the committee to at least decide whether they want to or not.

But basically what you're reporting to us are projects that you're moving forward on, right? So we're not being asked to approve or disapprove funding for these projects.

DR. MICHALEK: This is only an introduction.

DR. HARRISON: We're simply being told what projects are being done.

DR. MICHALEK: We're handing to you the projects that we think are reasonable and important.

COL MARDEN: What do you want from the committee?

DR. MICHALEK: We're asking for your opinion. You agree, you disagree. What better way to do this, or should we do something else?

LTC BURNHAM: For the next exam in '02.

DR. MICHALEK: The next exam.

LTC BURNHAM: These would affect the statement of work for '02.

MR. CAMACHO: This has to be decided on when?

DR. MICHALEK: April next year.

COL MARDEN: Before April.

COL MARDEN: So that it can be incorporated --

DR. STOTO: So this is just a discussion of the ideas at the moment, not a recommendation on whether or not to fund these proposals --.

COL MARDEN: That's correct.

DR. BLANCAS: We're not walking out of here with a stamp of approval --

DR. CAMACHO: But we're going to have to come to this in December?

DR. MINER: Next time, yes, sir.

DR. MICHALEK: We'd like to discuss it again in December.

DR. STOTO: Okay. So I guess I'm comfortable with them being here.

MS. del JUNCO: If anyone is not, it's fine with me. The only thing I would ask is that Joel had asked me to make a budget and be a little more precise about the study objectives and the design and -- and I had a handout; and if you want to me, I will just leave that with you.

DR. HARRISON: Well, in actuality, you know, other researchers have presented what they were planning to do during these meetings; and I think since we don't have a decision to make as such, but are more or less offering advice, I don't see where there's a --

DR. STOTO: I think it's okay, too; I just wasn't sure what the question was, and I thought we needed to discuss that. I'm happy with the outcome of discussions.

DR. HARRISON: There's a sense of the committee that we'll proceed as presently configured?

DR. STOTO: Okay.

DR. MICHALEK: Debbie, did you already circulate your handout?

MS. del JUNCO: No.

DR. HARRISON: Do you want to do it now, or do you want to do it after Joel's --

DR. MICHALEK: Afterwards.

MS. del JUNCO: After you go through -- oh, sure.

DR. MICHALEK: We appreciate the possibility that variation and response of an individual to dioxin could be related to -- some people have different kinds of AH receptors than others. In other words, the AH receptor could be polymorphic.

To address that issue, Matt Longnecker -- actually he has independently suggested doing the same thing; but Debbie added more detail. Matt Longnecker sent me materials suggesting a collection of whole blood at the next physical of the purpose of simply "put it away, store it, and wait for the technology to evolve that would allow a careful study of AH receptor polymorphism.

So really that's, all that Matt Longnecker's proposal comes down to is to collect the blood and store it and wait.

DR. STOTO: Isn't that already going to be done?

DR. MICHALEK: No. What we have done in the past when we collect whole blood is, we extract the serum and dump the red cells. So instead of flushing it, we would just keep it. We have no whole blood stored in our freezer. We have serum, but no whole blood.

Secondly, Debbie del Junco proposed a similar idea; only she went further to look at chromosomal fertility and other things; DNA adducts. I cannot defend the biology, and that's why she's here. If you would like to hear a more elaborate elation on her ideas, she can do that.

Let me run through these slides, and then you can have an opportunity.

[Slide]

Now this is a clinical proposal -- it's more than a proposal; this is a clinical device by James Albers, University of Michigan, who coauthored our paper on peripheral neuropathy, and who has concluded that there is an adverse relation between dioxin and peripheral neuropathy in Ranch Hand veterans. This, to him as a medical doctor, is the next logical step; would be to apply the electrophysiological confirmation of what we see with the methodology we'd used so far, which is described in another talk I brought with me; we probably don't have time.

There we define peripheral neuropathy as present if we had bilateral abnormal ankle vibration, bilateral and feet, bilateral abnormal pinprick, and bilateral abnormal something else. And a bilaterally abnormal vibra tactile measurement in the feet.

With that definition, we'd find a significant and adverse relation between that and dioxin body burden in Ranch Hand veterans.

He wants to know, and the other medical doctor working with him, David Erbrandt, University of Michigan School of Public Health, wants to know whether this is real, and that's why we have -- I asked him to tell us what measurements we should do in neurology next time; and that's the material that you have with you.

DR. MINER: Did we ever look at what was done at Cycle 1? We did nerve conduction in Cycle 1.

DR. MICHALEK: At baseline. but this is a newer -- that's old technology. Apparently, there's some newer technology in that direction and that's why I asked him to give us the latest methodology.

DR. MINER: Did we ever bounce that off of the assumed dioxin level?

DR. MICHALEK: Yes, we did. There's no relationship between nerve conduction velocities at baseline, but it wasn't done properly, according to Jim Albers. The nerve conductions that were done in 1982 were not done properly, and he can defend that.

We have an ongoing relationship with Dr. James Albers, University of Southern California. Last time he measured the carotid wall thickness in about half of our study subjects, until he had to quit when his funding ran out. He was not part of our main contract; he was an add-on at the very end of the process prior to physical. He had his own funding, his own operation, and he ran out of money so he quit.

Meanwhile, we are analyzing that data, and we are seeing a significant and adverse relation between intimal thickness and -- dioxin body burden. It is a complicated pattern to say the least; but it's there, and the idea is to measure everyone next time.

This is a noninvasive measurement of the thickness using an instrument that looks very similar to what a woman would get at an ultrasound for a baby; they run it across the neck.

DR. STOTO: And that essentially is a measure of cardiovascular disease?

DR. MICHALEK: It's an indicator, I believe, of cardiovascular --

DR. HARRISON: It's actually a popular measurement. The NIH has just began a long term study of the health effects of obesity, and the only endpoint specified in the original RFP was carotid ultrasonography and determination of wall thickness, which is related to atherosclerotic changes.

So that's not -- number one, that's a measurement that's being used, and number two, it's a measurement that you would expect is going to yield correlation because of its relationship to obesity and presumed relationship to diabetes.

DR. STOTO: But it measures cardiovascular disease before waiting for people to have heart attacks?

DR. HARRISON: Yes. Or strokes.

DR. MINER: Plus its predictive value.

COL MARDEN: Final common pathway.

DR. HARRISON: Yes. And we don't know --

DR. GOUGH: Do we know that?

DR. HARRISON: I don't know what the predictive value is. I don't know if there is a predictive value. My recollection is, from having looked at that RFP was, that it just -- there's a relation between -- this is an easy, indirect way of assessing vascular intimal changes.

DR. STOTO: And may be a better measure of disease in the sense that you don't have to wait for someone to have a stroke.

DR. HARRISON: Although stroke is the definitive evident endpoint for --

DR. STOTO: Right, but --

DR. HARRISON: Joel would like the stroke.

DR. STOTO: But there are some people with disease who are lucky enough not to have had the stroke yet.

DR. HARRISON: I agree.

DR. MICHALEK: Then we are told by Dr. George Lambert, University of North Carolina, that this caffeine breath test is an extremely sensitive measure of dioxin activity in the liver, through enzyme induction and p450

by dioxin, and that we should be doing this test at the next physical, and ut has been done in other epidemiologic studies related to dioxin.

It's interesting to me, and I'd really like to know your opinion on this; the attributes of the test are that it's very easy to administer, and it's not expensive; it's relatively cheap, it's about $190 per subject. Maybe that is expensive.

(Laughter)

DR. MICHALEK: I think that's about a half a million dollars.

COL MARDEN: Mounts up, $600,000.

DR. MINER: Joel, that's expensive.

(Laughter)

DR. MICHALEK: One of the most sensitive indicators of dioxin effects. And then we have seen through many physically examinations in the study relationships between peripheral pulses in dioxin levels in Ranch Hand veterans. The discussions with Dr. Jeff Calvert at NIOSH led to the idea of applying the same measurements in this study that they used in the NIOSH study, which are measurements of peripheral blood pressures in addition to peripheral dopplers on pulse abnormalities; and provided a protocol which is exactly the same protocol that was used in the NIOSH study.

DR. HARRISON: What's the hypothesis and what's the objective here?

DR. MICHALEK: Well, there's a line of thought that dioxin destroys vascular tissue, and therefore should be looking in the vascular system, like you mentioned earlier, and that the peripheral vascular system is the most sensitive. And we did see significant and adverse relation between pulse abnormalities in the legs and dioxin in earlier physical examinations.

In other words, it's a line of research in the area of cardiovascular that is sitting there and in my mind, needs to be pursued, because we have a series of findings in that direction that have not been pursued. And this measurement has already been made in another study where they have measured dioxin; this is the same NIOSH study where they measured dioxin in the herbicide factory workers.

DR. HARRISON: In that study, after they did these measurements, they said that it showed what?

DR. MICHALEK: I'm telling you what we saw -- what we've seen as the -- I can't remember what they saw. But what I'm saying is what we saw where adverse -- an increase in the risk of pulse abnormalities in the feet and legs in Ranch Hand veterans.

DR. STOTO: Just to see if I understand it, it sounds to me like this one is like the carotid artery measure, in that it's a precursor of disease if not an early stage of disease.

DR. MICHALEK: This one would be cheaper to do, I believe.

COL MARDEN: It's peripheral rather than semi-central.

DR. STOTO: But its purpose is the same.

Is that true of caffeine breath test?

DR. MICHALEK: The caffeine breath test is measuring liver function, changes in liver function with dioxin.

DR. STOTO: And do we know that those changes are --

DR. HARRISON: We already know there's a strong and consistent relation between GTT and dioxin levels from serial measurements on the Ranch Handers.

So this is a pursuit of the liver enzyme issue, liver function issue versus dioxin. That would be the George Lambert approach.

DR. STOTO: I'm not sure in what sense it's pursuing it.

DR. MICHALEK: Because it's another measure of liver function.

DR. GOUGH: There are so many inducements of p450. There are so many inducers of p450 activity.

DR. MICHALEK: Right.

DR. STOTO: I could understand the two cardiovascular ones in the sense that when you have rare events as the outcomes, it sometimes helps to look at the precursors, because they're more common and you may have more statistical power for some issues.

I just don't know enough about the caffeine breath test to understand whether it's the same kind of thing or something different, or --.

DR. MICHALEK: That's why I've given it to you.

DR. SILLS: I didn't have that in my package.

DR. GOUGH: We don't even have these write-ups, for some of these things.

MR. COENE: The caffeine one we didn't get, Joel.

DR. STILLS: The caffeine I don't have.

DR. MICHALEK: Oh, that's new; and I gave to Ron. I can distribute that tomorrow.

MR. COENE: Okay, tomorrow. I added the one, but I guess I didn't get the other one.

DR. MICHALEK: I'm sorry. I'll go back to the office and hand that to you tomorrow, the caffeine breath test.

DR. HARRISON: You know, Joel -- and I know that I'm looking at this from a fairly narrow perspective, but if you know that you have a higher incidence of diabetes in one group versus another, there's very solid evidence to say then that you will have an increased occurrence of small and mid-vessel changes, that you will have accelerated atherosclerosis.

And so as you were presenting these, I was thinking of them in terms of how they would support or enhance the finding of an increased occurrence of diabetes. And I find them to be so tangential to the question that I'm not sure that they help a lot.

If the question is to do a general study of, say of the vascular changes, again, since you already established -- well, maybe 'established' is too heavy a word but I'll say it -- established diabetes is a confounding factor here, then I wonder what the vessel studies are going to get you.

DR. MICHALEK: Okay, that's an opinion; we're asking for your feedback and you're giving it to us, and that's great.

DR. STILLS: I want to second that because I think when we look at these studies in terms of dioxin and the health effects in terms of the Ranch Hand population, the bottom line is, in my eyes, and I think you were saying the same thing, Dr. Harrison, and correct me if I'm wrong, but I think we need to look at -- there's diabetes which seems to be the major issue here, and then there are secondary effects; the cardiovascular disease, probably the peripheral neuropathy. Is the feeling that the peripheral neuropathy is secondary to diabetes?

DR. MICHALEK: That's a hypothesis.

DR. STILLS: That's one hypothesis. But I think we'll be better off, the study will be better off if the data was presented as all of it being related and really trying to address -- the question is understanding the adverse effects from the TCDD or from the dioxins. And I think you need to look at it globally, as a comprehensive package, diabetes as it relates to the vessels and maybe the peripheral neuropathy so it's presented in the best form. If you just measure the thickness of vessels, without coming back to what does it means in terms of understanding the health effects in terms of diabetes, then you're really doing things in a vacuum and it really needs to be a coordinated effort, really look into the biological mechanism of TCDD's role in terms of health effects.

I think that we have to be careful that that comes across as we do additional studies.

DR. STOTO: I don't know the biology well enough to judge this, but let me see if I -- I'm trying to look at this group of studies that are on the six slides here and try to understand what's the purpose of doing this kind of study. And it strikes me that three of the proposals have to do with better measurements of things. The carotid artery and the peripheral vascular examination have to do with their measurements of early stages of cardiovascular disease.

And that the nerve conduction studies are kind of a gold standard for what has been measured improperly or less accurately in the past. The genetic studies I guess are something quite different from that; they're helping to understand the mechanism of something that might be happening. So that seemed to me to be a very different kind of purpose than the other three, and I just don't know where the caffeine test fits in. It may make a lot of sense, but I just don't understand it enough to understand what's the purpose.

DR. MICHALEK: Well, I'll have you that tomorrow. I asked Lambert exactly that question; why would we want to do this test?

DR. HARRISON: Was the idea that dioxin is a cytochrome-p450-inducer and so he's trying to determine if there's a persistent dioxin effect?

MS. del JUNCO: I don't know if this dovetails, but actually it's in my proposal as well, but not that particular form of the test. My collaborator is Fred Kadlibur and Nicholas Lange at the National Center for Toxicological Research, and they have experience in the phenotyping, the SIT-1A2, and it's uniquely expressed in hepatic tissue, whereas some of the other dioxin-inducible genes are expressed more broadly in multiple tissue sites.

But 1A2 is, as Dr. Gough mentioned -- I'm sorry, did I pronounce it right?

DR. GOUGH: There's seven ways to pronounce it in English; I've heard all eight. Go ahead.

(Laughter)

MS. del JUNCO: But in any case, it's one of the dioxin-inducible genes, and it is polymorphic. But in this case what he's looking at is expression, so it could be an indicator of TCDD exposure in a case where the TCDD level may have fallen before it was even detected. It might be a more sensitive test, it might not, for actual TCDD exposure. It's induced by dioxin and it measures expression.

DR. STOTO: So that's really a third category of measures. That may be an improvement on the exposure measure, is the --

DR. GOUGH: I can't believe that. Inducing an enzyme 35 years after exposure is a good measure?

DR. STOTO: I'm not saying whether it works or not, I'm just trying to understand what's the purpose of it.

DR. GOUGH: We need the write-up.

DR. MINER: Again if I might add; I think our purpose here today was just to toss these out, introduce them to you, and let you mull over them; and then when I come back in December, we can rip, tear, snort and stuff.

DR. HARRISON: Anything else?

DR. GOUGH: I have a request.

DR. MICHALEK: We have Debbie's --

DR. HARRISON: Because Dr. del Junco -- has got the handouts and probably something to say, too.

DR. GOUGH: As part of the December package, could we get some synopsis of the results of this IMT exam before it causes you some confusion? Particularly, did you look at people with diabetes separately from people without diabetes?

I mean, without that, there's no point in considering this test, I think, because if it's confusing and can't be sorted out, then we have to think of what else might be done.

DR. MICHALEK: We will give you a summary of what we've done at IMT.

LTC BURNHAM: We did half the people last time, right? So there should be a significant --

DR. GOUGH: If you did it and it didn't work, it won't work if you do twice as many. You get two end mistakes instead of one.

DR. STILLS: A quick comment. I think what would be helpful for the committee is --

DR. HARRISON: One conversation at a time.

DR. SILLS: -- I'll try to capture this very quickly. I thought you did a really nice job of trying to figure out where each study fit in terms of the study. But will it help us as a committee in looking at these proposals, are simply things like what is the justification for the research, what are the aims, what are the goals, what is the hypothesis? Is one goal to measure, to better define our measures so we could be more consistent or more precise? Then when we review these, we really know exactly what we review.

When I looked at the proposal, there were so many differences and so many variables that I couldn't tell if one was research, one was testing, one was -- and so I think we can help you better if we knew exactly why these studies were being proposed.

DR. STOTO: It just occurs to me, part of the problem is that the title here is "Review Proposals for Research" but I think what I've learned is that this is proposals for new measurements that would be done in the next round, so that's a very different thing to do.

LTC BURNHAM: Maybe we could get a list of those criteria that you want for next time, and you could organize it that way.

DR. SILLS: That would help us a lot.

DR. HARRISON: By the way, I want to bringing up a proposal. What cutoff -- are you going to do two hour postprandial glucoses this next cycle? Where's your cutoff going to be?

[Simultaneous discussion]

DR. MICHALEK: First of all, there's a legacy here. We'd like to be able to compare results with the last study cycle; and if we don't use the 200 milligram per deciliter cut point then we can't compare results with our previous report.

So if we introduce a new cut point --

DR. HARRISON: You've already suggested that you're going to replace bad tests with better tests.

DR. MICHALEK: In what way?

DR. HARRISON: You just finished proposing --

DR. STOTO: No, they don't replace; they add but they don't replace.

DR. HARRISON: All right.

DR. MICHALEK: In addition, we would do fasting insulins. We didn't do fasting insulin last time.

DR. HARRISON: Well, I can't tell you how concerned I am about that level for the two hour postprandial, and I can't tell you how much I would like to see the previous data reanalyzed.

DR. MICHALEK: With a different cut point?

DR. HARRISON: With a value that, it either meets with the American Diabetes Association or with the World Health Organization criteria.

recognized by American diabetes association.

DR. MICHALEK: We have reanalyzed that, using the ADA criteria. And I have a document -- we did that for the IOM. The document ready, we can put it on the web page and you can get to it.

DR. HARRISON: What are you going to do now -- if you already have that data reanalyzed, then there's no excuse not to change it of the next cycle. I mean, if you've already reanalyzed the data, then why not --?

DR. MICHALEK: Well, we analyzed it in a separate analysis, separate from the SAIC report.

DR. HARRISON: I'm just saying, why not use it in the correct --

DR. MICHALEK: In the main report? It could be put in the main report, yes.

LTC BURNHAM: You could analyze it both ways.

DR. MICHALEK: Or do it both ways in the main report.

DR. HARRISON: That 200 cut point is --

DR. MICHALEK: You're exactly right.

DR. HARRISON: -- is disturbing.

LTC BURNHAM: What should it be, 140?

DR. HARRISON: I think it's 140, but I wouldn't bet on it. And I'm glad that you did reanalyze it. I'm comforted that it didn't turn out to be some funny, skewed --

DR. MICHALEK: We responded to a series of questions from the IOM, specifically in that direction.

DR. HARRISON: I'm glad to hear that you at least respond to the IOM.

(Laughter)

DR. GOUGH: Were the results the same?

DR. MICHALEK: Yes; nothing changed.

DR. HARRISON: Now that we're all primed.

[Documents handed out.]

MS. del JUNCO: Well, actually there is a bit of overlap in my proposal with some of the tests that were mentioned in Dr. Longnecker's, but I think his intention was to bank the blood. And I didn't know about Dr. Lambert with the breath test; but in fact Zip 1A2 polymorphisms and Zip 1A2 expression is one of the things that's included in our proposal.

Perhaps this is a beginning to address some of the issues that you have all raised, about you would like to see what are the specific aims, what are the hypotheses, what is the design, what exactly are we talking about; and there's in addition a detailed budget in the back section.

But this is basically, for those of you who are epidemiologists or statisticians in the group; you may have heard of the term "nested" case control study. That means it's an efficient design in that rather than study the entire cohort of Ranch Hands, we identified disease outcomes of interest, and I've named several; diabetes is one. There is some interest on my part and there's still some question about cancers. Other studies have found all cancers combined are increased; the Ranch Hand study has found that in the low exposure group, all cancers combined are increased but not in the high exposure group; so there's some possible unanswered questions that may have to do with misclassification and cancer. Cardiovascular disease is still a bit of a puzzle, and its dose response pattern, et cetera.

So my proposal, along with my colleagues Fred Kadlibur and Nicholas Lange at the VA in Little Rock, Arkansas, is to begin to look at some of the possible genetic susceptibility or susceptibility genes that are induced by dioxin exposure, and also look at the downstream, if you will, phenotypic expression of these genes.

And there actually is some new data that came out at the Dioxin 2000 meeting, not on Zip 1A2 expression relative to dioxin exposure, but on Zip/SIF 1B1 expression in cadaveric livers. It was Gene Grassman, actually, from the intramural program at NIEHS presented a very interesting study about Zip 1B1 expression actually being a more sensitive indicator of background levels of TCDD and TCDD exposure, even that many years after the exposure; that the expression of Zip 1B1 turned out to be a more sensitive indicator than the actual TCDD levels measured in the cadaveric liver tissue.

DR. GOUGH: How can you say that? Because you have two variables, neither of them is pinned down. How can you say one's a better measure than the other? How can that be said.

DR. HARRISON: Why don't we let her finish, and then we'll start --

DR. GOUGH: Okay. All right. All right.

MS. del JUNCO: Well, Dr. Grassman would be the better one to answer that.

DR. HARRISON: I hate to interrupt like that, but --

DR. GOUGH: No, no. You're quite right. Sorry.

MS. del JUNCO: In any case, there is actually an AH receptor in polymorphism that has been identified in humans. There was only one identified in a mouse model previously, but there is now polymorphism in humans.

So my proposal plans to do the AHR receptor, 21, Zip 1B1 and Zip 1A2 genotyping, and then Zip 1A1, Zip 1B1 and Zip 1A2 phenotype, so at the end you get not just what's going on at the level of an allele; is it a variant and might there be susceptibility with a impatient compared with a wild-type gene. But also, might there be a predisposition because of the different metabolic pathways and the way in which TCDD induces these genes, induces the expression of these genes.

So the case control nature of it is, again, to be efficient is to simply identify those with disease and work only within the Ranch Hand cohort. There would be no need to draw a sample from the unexposed cohort, because

we're again looking for TCDD level compared with these other measures of genetic susceptibility and possible exposure levels, exposure measures.

So we'd be looking strictly within that cohort and identifying cases as those who have a diagnosis; and the diagnosis doesn't have to be at this next physical exam; it could be anywhere in the time interval since follow up began.

And in addition, if you look through the proposal, he mentioned the use of -- one of the concerns that the three of us, Dr. Kadlibur and Lange discussed, was that some of the veterans are now, this many years out, some have died, some are ill as you discussed, Joel, and some are unwilling or unable to show up.

There are semen specimens available; I think you mentioned 4300, and semen is actually a biological sample from which DNA can be extracted, for PCR analysis. So we had the thought that, depending on the human subject's requirements and the allowances for that, the options being going to next of kin to request permission or making some other arrangements, given that they're deceased. I'm not exactly sure how your human subject's requirements work; they work differently in different places.

But in any case, this would be a way to actually do, get the genotyping; we couldn't do the phenotyping because you need whole blood lymphocytes and urine to do that. The genotyping could be done on the semen analysis; and in turn a validation study, a small validation could be done on a 10 percent sample of veterans who have stored semen and are able to show up and provide fresh blood lymphocytes. So that would be a way to extrapolate anything that we might find in terms of the Sacability? gene to the veterans who've now passed away or are ill or unable to come for any other reason.

So that's sort of the plan. The difficulty, as Joel mentioned, is that the net is cast so wide and the power -- its statistical power is relatively small for any one distinct disease entity. So we're forced with doing some kind of grouping in order to maximize power. And the studies that have been done report all cancers combined, and they've been pretty consistent in showing relatively small but nevertheless significant increased risks in all cancers combined.

The diabetes question has been raised, the cardiovascular disease question has been raised. These are rubrics that could be examined and however many patients, however many cases have been identified since follow up period began, if those could be grouped and the polymorphisms as well as the venotyping could be examined in each one of those groupings to look for patterns, possible susceptibility genes.

And it is also possible, even though I'm an epidemiologist and I was trained with Bradford Hills criteria, that we should expect specificity when we look for causality. It is the case, and I think we're all becoming more mature scientifically; we realize that a lot of diseases are interrelated and interdependent.

So it is possible that reproductive outcomes say, for example, a veteran who has had a spina bifida child, for example; might also for some reason be more susceptible to a particular type of cancer; say for example prostate cancer.

So that's basically the study design, and the hypotheses are to correlate the expression of the genes with TCDD levels; again to see whether there might be an association, to see whether it's possible that the expression of the gene might be more highly correlated with some of these disease entities than the TCDD levels are, that's a possibility. And the same is true for the polymorphisms.

COL MARDEN: You mean sensitivity based on the phenotype or genotype?

MS. del JUNCO: Well, okay, right. It's like with the phenotype it would be more sensitive; the hope would be that it might be a more sensitive measure, or it might demonstrate predisposition in a certain group that may be metabolizing it along one pathway compared with those who metabolize it along a different pathway; but the genes, the code for those pathways, aren't among those that we yet have the capability to measure. And that's why it's important -- I agree with Matt wholeheartedly that these can be, the blood samples can be banked long-term. Because more and more genes and their function will become available, thanks to the Human Genome Project.

But right now, while we have the genes that we know are induced by dioxin, it seems reasonable to look at some of those genes in relation to this cohort, this unique cohort.

DR. HARRISON: Other questions?

Mike, now.

DR. GOUGH: I just don't understand what you're claiming to do. First of all, I think if you're going to go look at anything where there are effects, the only effect that we have seen with any consistency is diabetes. And the idea that we're going to, you're going to learn anything from the study -- I guess those five children with spina bifida were fathered by five different people. There's just no power there.

What do you mean expression, gene expression? What gene expression were you going to measure.

MS. del JUNCO: Well, it's the phenotypes. Like for example the Zip 1A2 phenotype.

DR. GOUGH: Okay. Is Zip 1A2, is that specific to dioxin?

MS. del JUNCO: Zip 1A2. All of them are PAH-induced genes.

DR. GOUGH: Yes.

MS. del JUNCO: None of them are specific; that is that they only are induced by dioxin. However Zip 1A1 is more highly induced by dioxin than anything else.

DR. GOUGH: But those measurements have been made in animals following exposure, acute exposure. And these exposures were a long, long time ago. Every time I eat a serving of broccoli or something, those enzymes go popping up in me, as they do in you, because they're induced.

I just don't understand what those measurements of induction now -- I mean, these are people who are going to have been fasted, right?

DR. HARRISON: You're making the point of sensitivity, you're raising the question of specificity.

DR. GOUGH: I'm just -- what does this mean? Because they're not being exposed now, and those enzymes are -- those genes are always expressed to some level, and you are going to fast people. I guess you do this when people have been fasted, and you are going to look at the levels of these receptors, right? No, these are enzymes.

So you're going to look at the levels of these enzymes and say from that how much dioxin that person has in his body?

MS. del JUNCO: Well, it's not enzyme measures. It's immunoblotting, it's immuno- chemistry done on --

DR. GOUGH: Well, it's an expressed protein, then; let's say that.

MS. del JUNCO: Yes, an expressed protein.

DR. GOUGH: I just find that bizarre.

DR. HARRISON: Well, it comes back to something that I think Mike said earlier, and that is Mike would argue that 10 parts per trillion, a 10 parts per trillion cutoff may not be correct; that there may still be activity at levels less than 10 parts per trillion. Now that's the place where I disagree with Mike. But that's --

COL MARDEN: Especially if you have an induced enzyme that's abnormal in some way.

DR. HARRISON: Well, 10 parts per trillion goes way below -- the AH receptor's binding affinity for TCDD is something like 10^{-9} to 10^{-10} molar. And parts per trillion is 10^{-14} or 10^{-15th} molar.

DR. STOTO: Let me try to ask -- I've got two questions.

It seems to me that part of this is you think that you might have better measures of exposure than just measuring serum TCDD, and I presume that means that if these enzymes were induced 25 years ago, there will still be some record of them now; and that things that people have since they have been in Vietnam won't show up in that way. Is that?

MS. del JUNCO: Okay, let me try to explain it this way. It isn't necessarily that they're going to be a better measure of TCD exposure; they may be better predictors of those who go on to develop specific diseases that might in turn be related to the TCDD exposure. It isn't that they're going to be an alternative for a quantitative TCDD estimate.

So they may be better --

DR. HARRISON: So if you have an enzyme that's easily induced, it may protect you against dioxin --

MS. del JUNCO: Exactly.

DR. HARRISON: And so it's not a bioassay of dioxin as much as it an analysis of --

MS. del JUNCO: Of induction of that gene.

DR. STOTO: I see.

DR. HARRISON: And an example of where that has biological relevance is -- that's already been demonstrated?

MS. del JUNCO: Oh, I'm sorry; Dr. Grassman's data at the Dioxin 2000 meeting.

DR. HARRISON: No, not on dioxin, but on some other system.

MS. del JUNCO: In the specific --

DR. HARRISON: That the Cytochrome p450s protect against a poison or against a hormone or anything that uses the nuclear receptor family.

DR. GOUGH: Well, in fact there are some samples of that using dioxin as a protector for subsequent exposure to PAHs, for example.

COL MARDEN: Or that we know some people metabolize theophylline faster than others, and that affects theophylline levels, if you're going to treat asthma.

DR. HARRISON: Okay, so that's the rationale, then.

DR. STOTO: So then I guess the whole thing then boils down to better understanding of what's going on.

DR. HARRISON: So you'd expect the non-diabetics then to have higher insulins.

DR. STOTO: But the whole proposal really is focused at that.

MS. GARZON: Right. In fact, the dioxin index that you have done with the dioxin analysis will be used for something indifferent on levels of exposure, high and low. Instead of the dioxin index. The dioxin index would be integrated into the sample in order to look for beset position.

DR. STOTO: Okay. That helps me a lot.

DR. HARRISON: Actually two comments that I have -- are we running behind? is it time for our break?

MR. COENE: No.

DR. HARRISON: I thought, when I first heard about this, there really -- for instance in prostate cancer, there's a repeat element in the first exon of the androgen receptor gene that, if it's very long, results in a neurological disorder called Kennedy's syndrome. Which maybe the best way of thinking about it is that as this repeat extends, the androgen receptor becomes weaker, becomes less likely to translocate in the nucleus in cause and effect.

And this turns out to be race-based, so that the shortest repeat is in African-Americans, the longest repeat is in Asians, in normals, and Caucasians are intermediate, which reflects the incidence of androgen-associated conditions like prostate cancer.

So that makes for a very nice story that you can have different levels of susceptibility. Now that raises to me an interesting -- not interesting; you'll have to decide whether it's interesting -- that raises to me a thought, though, that there are not many more chances to capture genetic information from this well-studied cohort.

Right now we're being asked to pass on someone's expert guess about which genomic studies will be useful. And you made the point that with the Human Genome Project and yada-yada there are going to be all these genes and everything. What would make more sense to me, and you have not proposed, is something that is frequently done now, and that is to perform what's called an Epstein-Barr transformation of the peripheral white blood cells of samples, which then immortalizes the white blood cell and allows you to culture them and then preserve the living cells, from which additional cultures can be performed when it turns out that there's something else that you need.

So, it seems to me, even though as powerful as PCR is in terms of genomic analysis and everything, this gives you the chance to actually go back -- even though these are peripheral white blood cells, who knows what we'll be able to do in another year or two; this gives you a chance to actually go back and look at the machinery itself, at some other time, and at the same time if you did preserve white blood cells using the Epstein-Barr transformation, you could provide genomic DNA for everybody, anybody, whoever needed it.

DR. MICHALEK: Now this transformation is something that would be done at Scripps Clinic, or would the blood be then frozen and worked later? How is this done?

DR. HARRISON: Probably what you do, and this is something -- actually that's something I have some familiarity with, is you'd probably take the samples, non-coagulated samples, you'd probably ice them and FedEx them to a tissue culture lab.

DR. MICHALEK: In other words, flash-freeze, as they say?

DR. HARRISON: No, no, just on ice. Just cool, not frozen. When you freeze cells, you break them. And they don't like that. So you just put them on ice, ship them, have the transformation done.

MS. del JUNCO: Yes, that's something NCTR can do, the molecular group that Kadlibur heads up.

DR. HARRISON: Well, that's something that a lot of us can do.

DR. MICHALEK: Well, a federal lab is convenient for us. It's a lot easier to work with a federal facility than it is --. Contractually, it's a lot easier to work with a federal agency than it is with a private laboratory.

DR. HARRISON: But at any rate, that's something that you might want to think about.

DR. MICHALEK: In terms of overhead.

COL MARDEN: We might even be able to do it at SDE.

DR. MICHALEK: Lower overhead, right.

What's SDE?

COL MARDEN: The clinical reference lab.

DR. MICHALEK: At Brooks?

COL MARDEN: We may be able to do it.

DR. MICHALEK: We have labs at Brooks, too, that might be able to do it.

MS. del JUNCO: Actually, Dr. Pearson described the AR, polymorphism in the AR and prostate cancer. Dr. Kadlibur just published an article in Pharmacogenetics on this very similar phenomenon that was race-dependent, on Zip 1B1 and prostate cancer. And the association between that polymorphism was stronger in blacks than in whites. So again it's supportive of the pattern in the distribution of prostrate cancer.

DR. HARRISON: One of the things I was asking Ron about is, if we're going to be asked to provide opinions on these things, that maybe what we could do -- I was asking Ron if he had any funds for it is that we could

send some of these proposals out for mail review, get a couple of mail reviews on them that then we could then really act in our advisory capacity.

DR. MICHALEK: Your current document you just handed out, you need to e-mail that to me. That is your cleaned-up proposal, because all I sent to them was our e-mail.

MR. CAMACHO: When you send these proposals out, we're giving the backdrop as well with the money, the research, the timelines, and the realities. That's my concern, that some of the stuff has got to be anchored in the environment that it's sitting in.

DR. HARRISON: When you write a proposal, that's what you write. I mean, that's a part of what the background is, is the relationship of what you're going to do to --

DR. CAMACHO: To this whole study. That's going to be clear.

DR. HARRISON: -- to what's already known.

DR. STOTO: I think we need to communicate with our mail reviewers about, what are the criteria that we're interested in.

DR. HARRISON: Well, that's something we might discuss either today or tomorrow, is just what kind of criteria you might give to a mail reviewer, because they're not going to be reviewing a stack of studies; they'd be getting a single study and being asked not to rank it, but to --

DR. STOTO: Will this meet some purpose? And they need to know what the purpose is or something like that.

DR. HARRISON: I agree. It's just a thought, and I didn't even know to mention it unless -- because you're not going to get people to do this for free. You're going to have to throw a couple of hundred bucks at them to at least get it back before next year.

DR. GOUGH: Let me ask, tell me ask, it seems to me you're proposing a number of things, some of which you didn't talk about, like chromosome fragility. That's mentioned in this here.

MS. del JUNCO: Yes. Well, the collaborator that I work with who does the chromosomal fragility and the DNA adducts, has had a baby. And so I figured I'd put together the proposal that I knew we could get off the ground more quickly. But the ability to do those, one of the methods is using metaphase lymphocytes --

DR. GOUGH: Okay. But is there any reason to think this would shed any light on the mechanism of dioxin?

MS. del JUNCO: Well, all of these methods that I've described have been used in a very general sense to look at environmental hazards, and their carcinogenicity.

DR. GOUGH: yes, but we're not in the business of funding the development of tests for exposure verification or exposure measurements. We're interested in, does this relate, is this going to advance our knowledge of possible connection, about dioxin and disease? So that's a different question from what you're asking.

DR. HARRISON: I'd say it's even more narrow than that. Because what this study has come up with is a relationship between Agent Orange and diabetes, and if -- it seems to me that a study that can shed some light on how that can happen is a study that's consistent with the protocol, a study that is -- well, okay.

DR. GOUGH: And if it's case control, I think the only case control study you can do right now is diabetes.

DR. MICHALEK: Well, 16 percent or so have one form of cancer or another.

DR. GOUGH: Yes, but that's about the same, in the comparisons and the Ranch Hands.

DR. MICHALEK: Well, it's 1.5 relative risk.

DR. HARRISON: 1.5 --

DR. GOUGH: "Oh, I'm sorry, I didn't realize that."

DR. HARRISON: Joel make a joke.

(Laughter)

MS. del JUNCO: But it is higher in the low group.

DR. MICHALEK: Yes, it's a backwards dose response on dioxin, which is puzzling.

DR. GOUGH: When you have biology that doesn't make sense, I don't think it's a good idea then to invest a lot of effort and time and sophisticated measurements about biology that doesn't make sense. And if --

DR. HARRISON: That's actually your comment to the committee, then, right? As we discuss this proposal, that would be your comment to the committee.

DR. GOUGH: You mean I can now say, "please ignore that remark"?

(Laughter)

DR. HARRISON: I'm just saying that that --.

DR. GOUGH: Yeah.

LTC BURNHAM: Great.

DR. HARRISON: Yes, almost. Almost.

When we discussed how we were going to do this, we didn't discuss that we were going to make this into a real --

DR. GOUGH: No, but I'm just -- if you're talking about case control, and I think -- and there's a list of case controls here, or possible groups, and I don't think they exist. That's all.

DR. HARRISON: Any other comments?

DR. STILLS: I think one positive thing that our discussion could have in terms of future studies is for example in terms of the drug metabolizing enzymes, you know if there are polymorphisms that really tell us that these people are more at risk for developing diabetes, then that's something that we could use in terms of not only dioxins but in terms of understanding toxic responses, diabetes in terms of humane exposure.

As you were saying, and I think we are all trying to say, if it's in that context and we really -- if the research is going to help us really understand the mechanisms of how we can really determine who is more at risk for developing these type of diseases, that would be extremely helpful.

And I was going to say something else, but I forgot. Go ahead.

DR. STOTO: I was going to say that if what's proposed is a nested case control study, the relative prevalence of cancer in the Ranch Hands versus the controls is absolutely relevant to this issue. Because it only would be done within the Ranch Hands; and the issue is do the Ranch Hands who have cancer have more of something than the Ranch Hands who don't?

DR. HARRISON: I'll tell you something that would I think make sense; and of course you're not supposed to write people's proposals for them or anything, but if you said that you were going to take, if you were going to do one of Joel's supermatch kind of studies --

MS. del JUNCO: That's exactly what it says.

DR. HARRISON: With the diabetic cohort and with a nondiabetic and a real nondiabetic; not this b.s. about 200 -- and you wanted to ask if there was a difference in the ability to induce this enzyme within those two groups, then --

MS. del JUNCO: That's exactly what --

DR. HARRISON: -- and your hypothesis was that you were going to protect against database in the nondiabetic group by being super-inducers, that's a pretty decent study.

MS. del JUNCO: That's exactly the proposal.

MS. GOVAN: I'm sorry it didn't get --

MS. del JUNCO: That's what it says.

DR. HARRISON: But that's -- you know, there's been all this other stuff discussed. If that's what you're narrowing down on --

MS. del JUNCO: That's it.

DR. HARRISON: -- I think there's a logic to that.

MS. del JUNCO: The analogy would be, if what you're saying is true, Dr. Gough, then there would have been no point in pursuing HLAB27 in ankylosing spondylitis because there was an unknown point at which we didn't know that association, and it's true that some --

DR. GOUGH: We can't do basic research, I think.

MS. del JUNCO: -- you know, you take risks.

DR. HARRISON: Yes.

DR. GOUGH: I think what we're interested in -- well, I don't want to get into this but -- okay, that's all right. Fine.

DR. HARRISON: Any other --

DR. STOTO: I just want to say that I disagree with Mike on this issue. It seems to me that when we don't understand something, that's when we need to --

DR. GOUGH: But she's -- she is not proposing -- I don't think she's proposing the tests to do that. I'm not quite sure what --

DR. STOTO: Well, I'm not quite sure about that; but just as a general principle if we find something in an epidemiological study that we don't understand biologically, then we need to pay attention to it and do more research there, and I heard you say just the opposite.

DR. GOUGH: You mean about the cancer?

DR. HARRISON: No, this is not a cancer study. She's already said that.

MR. CAMACHO: Will we have our chance to sum up at the end? Because I was going to -- this ricochets back to what you said, and you argued against, about doing some kinds of research that go beyond this, and I was coming to the -- well, what kind of studies can we get that are going to capture data so that years down the road some new technique comes up that can analyze that data? And at that point we may not even have to worry about confidentiality, because we might be dead, as far as that goes.

[Simultaneous discussion]

DR. HARRISON: Let me propose that we just stretch our legs for ten minutes.

[Recess]

DR. HARRISON: Joel, I take it that you're spent. I can see that they're allowing you coffee again.

(Laughter)

DR. HARRISON: All right, committee? What is your wish? Anything other than an immediate adjournment. The topic are the Research Projects, and there obviously isn't enough -- there obviously isn't enough presented for us to discuss each project in its entirety, so may I suggest that what we might want to discuss now is how we would like to proceed with what I think we're being asked to do; and that is offer some comments and advice on the proposed projects.

MR. CAMACHO: Are we restricted to just these proposed projects? I mean, this is just what we're talking, looking at these here, or are we talking about the December for what --

DR. HARRISON: Well, I think that's a reasonable question. Can we sort of come up with a mechanism that, because we're going to be a committee for longer than December and the Air Force is going to come to us with other proposals, I suspect. So rather than just kind of ad hoc each time, can we take a few minutes to think about what we want to see and how we want to go about doing this.

I mean, we've talked about RFPs and NIH and all that, but the reality is that we've got these projects, and we're going to have some more projects. So how are we going to do this?

And yes, everybody can participate in this discussion; this is not a restricted thing. So you and then you.

DR. STOTO: I've got a question; are we talking about proposals for measurements to be included in the next round? Are we talking about new measurements that can be done on existing samples, are we talking about new analyses that could be done with existing data or that might be done with some of these new measures? I guess I'm not even sure what the --

COL MARDEN: In the short term we're talking about stuff to add to the evaluation on the coming exam cycle so it can get into the Statement of Work, et cetera, et cetera. But in the global sense, I think the answer to your question, to your series of questions, is Yes.

DR. STOTO: What about these five? How do these five flow out?

DR. HARRISON: Okay, hold on.

Paul and then Joel.

MR. CAMACHO: I have no knowledge of medicine; I'm a sociologist. Stats I understand. The big picture of war and social consequences, I have a very good grip on.

I would like to see us do categories for the future, if not immediate categories, along the lines that you indicated. And as far as these tests, I would think that you would want -- somebody said whole blood. I agree with that idea because down the road, long after the study is shut down, if those samples are still there and if the requirements of privacy and et cetera, et cetera are all met, they may be very valuable to the future of our soldiers. Limited wars, new technologies, new injuries, whole new ballgame coming out there. But the Infrasound, the Project Flicker and all of that stuff, who knows what this might show? We don't know.

And the other piece is the preservation. I'd like to see a study on, how are we going to preserve these data? How are we going to preserve this data of the long run? That's a study in itself, at least a small one, about how would we do this, and what would be the best way to do this.

DR. SILLS: Joel had something to say, and then Mike.

DR. MICHALEK: Very specifically to Mike Stoto: The answer to two of your questions are yes; two or three of those proposals have directly to do with the next physical. Number one is peripheral neuropathy. And when you see that data, I think the issue will become more compelling to you. That we have a physician who has seen that data and has coauthored this paper, and is telling us to do these additional measurements next time to further understand what we're seeing in peripheral neuropathy, and that's the James Albers electrophysiological measurements.

Secondly there is the James Dwyer and the IMT measurements of the carotid wall. We are seeing a significant clear trend in the adverse direction, of dioxin versus carotid artery thickness. The proposal is to do that same measurement on everyone next time, not just a few.

DR. GOUGH: Why did you say it was confusing before?

DR. MICHALEK: What?

DR. GOUGH: When you were discussing those results before, you said they were confusing or hard to understand.

DR. MICHALEK: Well, they're confusing in that we see a trend in the Ranch Hand group; we also see a trend in the control group. However, the trends are parallel, meaning that Ranch Handers with high levels have thicknesses that are about the same as comparisons with high levels; whereas comparisons with high levels are up near 10 parts per trillion, Ranch Handers with high levels are way over 100 parts per trillion, and we don't understand that.

But simply because we don't understand it doesn't mean we shouldn't look at it anymore. We should look carefully, we should look harder, not just decide not to measure it anymore because of the findings.

So I'm suggesting that -- the suggestion is, and it's on your plate now, is, I'm asking you to render an opinion: Do you agree with me, my own personal opinion "Yeah, we should do that, we should do the IMT measurement again." But I'm asking you to render an opinion.

I'm asking you to examine Dr. Albers' procedure and render an opinion. Do you agree with James Albers? Yes, this is a reasonable thing to do given that this peripheral neuropathy finding is there? And I can give you that talk tomorrow.

Then there's the peripheral vascular measurement of Jeff Calvert: Should we do that measurement at the next physical?

So there are three specific questions about the next physical exam. In other words, we're asking you how to spend our money. In particular -- and finally, there's George Lambert and the caffeine breath test. The caffeine breath test may or may not be a good idea, and you may find reasons to believe it's not a good idea. And therefore, we would listen to you and decide how to spend our money based on what you tell us.

DR. STOTO: But that's a test that might or might not be done at the next exam?

DR. MICHALEK: May or may not be used. The George Lambert test. That's on the table, it's for you to think about.

Then for us that's really important to hear your opinion, because that's an expensive test. Now some of these tests are not expensive, and they're easy to do, such as perhaps the peripheral vascular blood pressures are easy. Already on the table they're already getting the Doppler testing on their peripheral pulses. It could be relatively cheap to go ahead and do the peripheral blood pressures?

So those are particular ones that have to do with the next exam and how should we spend our money, and we're asking for your opinion.

Finally there's the Debbie del Junco and Matt Longnecker. Now those to me are really state of the art biology. They're asking now at the molecular and biological and cellular level what's going on with dioxin and the AH receptor. And those, from our point of view from the program -- first of all, there's a technical question of should we do these; is there any way to do them better; should we modify Debbie's proposal? Is there something else that should be done?

But from a program point of view, they're easy. All you've got to do is don't flush the red cells. That's all, instead of flushing them down the toilet, save them. Piece of cake in terms of the $16 million we're going to

spend to send these men to La Jolla, California. Doing the $80,000 proposal of Debbie del Junco is a piece of cake.

So we're talking about basic biology; that's Matt Longnecker and Debbie del Junco. Matt Longnecker is free. Matt Longnecker says, "Just don't flush it. Save it." It's free.

So I'm happy about Matt Longnecker -- and I was equally happy about Debbie del Junco; that's almost free.

DR. MINER: No, it's not.

(Laughter)

DR. MICHALEK: The denominator here or something -- it's about $16 million.

So those are the issues.

DR. HARRISON: Mike and then Jay -- either was having a seizure or --

(Laughter)

DR. MICHALEK: Whenever I talk dollars, Jay gets very--

DR. STOTO: It seems to me that for the four studies here that are not the genetic ones, they're all proposals for things that might be included in the next exam.

DR. MICHALEK: Yes.

DR. STOTO: And if that's true, I think what we need to hear from about each of them is, what would we know if we did them that we don't know now and sort of a justification for that based as much on what's been done so far and so on, and secondly, what is it going to cost?

DR. MICHALEK: Right.

DR. STOTO: In a parallel fashion, so that we're comparing.

MR. CAMACHO: You also still missed what else could be out there? I mean, are we going to end up saying "We could've had a V8"?

DR. STOTO: Well, that's right, we missed that, but we have four things on the table, and we're going to compare them. I'd want to compare them in a parallel fashion.

DR. MICHALEK: On the Calvert one, he readily admits that he's now --

DR. HARRISON: Hold on. I suggested this mail review business. What if we divide these into tests and investigator-initiated studies, okay? So for a test, what if we were to be able to say what the test objective was? What we were trying to measure. What the test is.

And then why don't we ask our reviewer, is there a more sensitive test? Is there a more selective test?

DR. STOTO: Yes, or I would ask them more generally, "Will this test in fact give us what's proposed?"

DR. HARRISON: Let's in fact compare it to whatever test it's either being proposed to replace or to extend. We could add that as a piece of information as well. That's a very straightforward set of questions that we could then use to -- in our discussions. And the advantage would be of us doing it is it gets the project personnel out of the evaluation loop and puts the review where it should be; and that is in a separate box.

How does that strike you?

We could probably come up with a couple better questions.

DR. STOTO: I wouldn't limit it to sensitive and specific, but I think that's the kind of thing.

DR. HARRISON: Yes, and whatever you'd like to add.

DR. GOUGH: And how do we buy, as compared to what we know already?

DR. MICHALEK: What are we getting for this?

DR. GOUGH: Yes.

DR. HARRISON: Maybe what we need is, and we can do this fairly quickly is to get that kind of an evaluation and then we can -- and we can make judgments.

DR. STOTO: I would also add, is it really feasible and are these cost estimates --?

DR. HARRISON: So you'd include the cost evaluation. See, I wasn't going to include the cost evaluation.

DR. STOTO: I just want to say --

DR. HARRISON: I don't think Joel includes the cost evaluation.

DR. STOTO: No, no. I'm not is it worth it? I'm not going to ask is it worth it; but if they say we can do this for $5 a person, is that really true.

DR. HARRISON: Either way. In other words is it really a 50 cent test or is it really a $50 test, and either way it's--

DR. STOTO: Okay.

DR. HARRISON: Okay, Jay?

DR. MINER: Yes. I have similar thoughts here, that the Air Force also needs to give y'all -- and I think this is where you were coming from -- how does this research fit into the study? Does it increase measurement accuracy? You just said about four or five things on each one of these that was not given to our advisory committee members that might help them to say "Yes, this is important because" dat dat dat.

But that not ought just come from you; it ought to come from the people proposing, how they see it fitting into the study, and how does it help answer the question?

DR. HARRISON: Well, I hadn't addressed the investigator-initiated. What I'm accepting is that this study has been going on for a long time, and so if you say there's a better way to mention neuropathy, we've measured

neuropathy before but that wasn't a good way; we're told that there's a better way to do it. I say "Okay, that sounds reasonable. Let's send this off to a couple of people and see if they agree."

DR. MICHALEK: Yes.

DR. HARRISON: And if they do, then I'm not really going to worry too much about its -- whether it's going to give us an answer, because it's already -- the evaluation for neuropathy, it's already a part of the study and you're just saying that you found something, a better way to do that and asking us to sort of evaluate that with me.

Now for the investigator-initiated stuff, I would say that we as a committee might do what Mike intimated earlier, and said that the connection has been shown between diabetes. The investigator-initiated stuff has to serve the purpose or at least has to show promise of a better understanding of how that happened.

DR. STOTO: I think that's a good general principle.

MR. CAMACHO: Are we mailing these out? It's as if we're taking this --

DR. HARRISON: I'm saying we're going to do a mail review -- I'm proposing that we do a mail review hat somehow or other I'm going to come up with -- I think I can do this -- I'm going to come up with people to do the reviews. Or you all can come up with the people -- whatever, but we're going to do it.

DR. CAMACHO: Okay.

DR. HARRISON: And what we've got to tell the reviewer is what the review criteria are. that's what we've got to tell the reviewer. For the tests, we're going to have to say "We're being asked to evaluate a test for neuropathy. The test that has been done is X, Y and Z. The test that is being proposed is X1, Y to Z. The question we have is," and we can work out over the next day what those specific questions are going to be.

And the answer comes back, "Yes, this is a state-of-the-art test, the cost is reasonable," or "it should cost $5 a test" okay, then we're in business. The thing comes back and says "this must be" -- what's the guy's name?

DR. MICHALEK: Albers.

DR. HARRISON: "This must be Albers. Because he's the only guy who thinks that this is worth doing" you know. And we say "Whoa, wait a minute now. Let's discuss this, and ask Dr. Albers to" --.

MR. CAMACHO: And these are sent to people that you know.

DR. HARRISON: Well, I'm not just --

DR. CAMACHO: They're state labs. Every state has a lab that has --

DR. HARRISON: No. What I do is, I've served on two study sections. I mean, I can find someone who evaluates, who's in the neurology research area and ask them if they'd be willing to look at something.

The rest of you all can do the same thing.

DR. CAMACHO: We could send to like every state lab.

DR. HARRISON: It's not going to be a state lab.

DR. MINER: Another consideration for tests as well, though, is time. Because we only have about 2-1/2 days of time.

DR. MICHALEK: So if it's a test that takes four hours to do, it's just infeasible.

DR. MINER: Right.

COL MARDEN: Something we probably need to do sooner rather than later is to look at what pieces of information we really need to gather from this last set of exams, and start filling that matrix in. And if the technology doesn't agree, it doesn't exist to answer that question; then what's the best way of archiving stuff to answer the question in years from now.

Because when I see some of these proposals, I'm seeing pixels instead of the whole picture, and that's probably my problem rather than -- I'm sure the picture exists in Joel's mind, but I don't have it firmly fixed in mind. So that's probably something that I recommend that we do, is what we need to know.

DR. STOTO: Could I address that. It seems to me that the genetic studies kind of come into that category.

I don't know now; is there no genetic information that's been kept?

DR. MICHALEK: None; except maybe semen. And urine -- is it true there are some cells in urine?

DR. HARRISON: Yes, what you're saying is that there are some samples that could be used, but no genetic studies have been done.

DR. STOTO: But the plasma, they lose the genetic information by throwing away the red blood cells.

DR. MICHALEK: The other point is that the specimens that are in the freezers are irreplaceable, so you only get one shot at using them. Whereas in the year 2002 we have the chance to draw fresh specimens, directed at a specific purpose.

DR. HARRISON: In fact those semen samples are stored as single samples; they weren't aliquotted, were they?

DR. MICHALEK: No. Single chunk of frozen semen.

DR. HARRISON: And man, you've never seen a mix of enzymes like you have in semen. I mean, once you thaw those things, they're just going to start chewing on each other.

DR. MICHALEK: Yes, you have to act -- I mean, you've basically committed yourself once you thaw it; there's no turning back. There's no turning back.

DR. STOTO: So --

[Simultaneous discussion]

LTC BURNHAM: But again, this shows you the importance of between now and December, because '02 is the last chance.

DR. HARRISON: That's why, I really suggest that if you think this can be done in one of your labs, that -- it's a serious project, though, because you're talking about a huge amount of technician time because you've got all these samples coming at -- you know, there's no way to store them and they've got to be handled a long time --.

You've got to grow the things, you've got to freeze them away properly so that you know that you'll be able to revive them; and then the storage conditions are not your -70, -80 freezers; your storage conditions are liquid nitrogen or liquid nitrogen equivalent temperatures. So you talk about much more expensive storage than the samples that you have.

On the other hand, ten years from now when a technique has been discovered to sequence the entire genome in 24 hours, somebody is going to be able to thaw those boogers out and just go to town.

VOICE: Clone Jack Spey.

(Laughter)

DR. STOTO: That gets us into a whole another level of IRB concerns, of confidentiality concerns.

MR. CAMACHO: Why do we have to worry about an IRB concern now? If you're collecting the material --

COL MARDEN: You have to tell people why you're doing it.

DR. HARRISON: Yes, you have to do it beforehand. You can't do it at post hac. In fact -- no, I'm not going to go there.

DR. STOTO: Just to collect genetic information and store it is a serious confidentiality issue that needs to be addressed. It may be worth it, but --

MR. CAMACHO: I tell you what we're going to do; this is for this test maybe in the immediate future, and for tests down the road -- we don't even know, they might save a lot of lives.

COL MARDEN: If you don't tell them what you're using it for, you can't use it.

DR. HARRISON: Let's also consider that next year the police call, the police call the Air Force because Major what's his name has been accused of killing his next door neighbor. "And we have a DNA sample, we want to do a match. We can't find the major, but we know you've got his -- cells."

DR. STOTO: Or 50 years from now, his grandson is accused of something or other.

DR. HARRISON: Yes. You know, might be Thomas Jefferson all over again.

(Laughter)

COL MARDEN: No lie; when they dug Zachary Taylor up to see if he'd been poisoned, they had to get the family's permission.

DR. HARRISON: And the reason that this works so well in Utah is because their state laws -- they have designed their state government to do genetic studies. You know, I can't quote you anything, but all these laws have been put in place just to provide the kinds of protections that we're talking about.

DR. STOTO: But are the vets going to trust federal government in this regard? We'll ask Jack.

MAJ SPEY: 81 percent of the Air Force officers that served in operation Ranch Hand went on to make the military their career. For 80 percent of 1185 people, 80 percent of those people have served in this study. So that's 40 years for some of us, that we will have given to Uncle Sam in uniform and to science in our second career, if you will.

One of the suggestions was made, since we're talking about an additional study, and I'll address this to the doctors: A thank you test. The mean average age in 2002 of the cohort, both comparison group and Ranch Hand cohort, is going to be in the neighborhood of 67 years old or somewhere in that general neighborhood.

Without going into a big expense, looking at all the lab work, much of which is way over my head and all the rest of us that have sat in the vampire room and had blood sucked out of us until we --. But just one little test that says it's not being done but is important or that I wouldn't go to a doctor or a hospital to have done for myself -- I'll be 65 when this next cycle starts -- but might be useful for our longevity. I just throw that out -- as not part of the protocol and it can't be expensive, you can't run us through sumari {ph} or anything like that and check our brain, because you might find vacuums, but -- just something that might be of value to our health in the future. It's just something for some of you to think about. Thank you.

COL MARDEN: Cholesterol, PSA -- you know, I'm thinking of prev-med kind of stuff.

DR. HARRISON: That's an interesting thought.

One of the things that makes that a difficult thought is that they do damn near everything as it is.

(Laughter)

DR. HARRISON: Trying to -- as you were talking I was saying "Dang." I mean, this is --

MAJ SPEY: There's a couple of them I'd like to have repeated, but --.

COL MARDEN: Don't go there.

DR. HARRISON: Yikes. Well, does anyone have -- yes, Joel?

DR. MICHALEK: I'd just like to make a proposal, and that would be that I write a -- actually rewrite all six of those proposals with a lead-in paragraph or two, explaining why we're considering this; and I'll talk through exactly what I just said to Mike Stoto about, whether this is relevant to the physical exam or isn't it, why are we considering this, what does it have to do with our previous findings, how will it contribute to the study?

I think those are the pieces that are missing, right?

MR. CAMACHO: Yes. You sent this to somebody --

DR. MICHALEK: Because a person who sees these and doesn't know the context won't know what's going on. So I'm going to write a paragraph, a lead-in, and I'll coordinate that with each of the authors to make sure they --

LTC BURNHAM: He was going to give us that tomorrow. Separate questions for tests and separate questions for study.

DR. HARRISON: Yes. What I'm proposing to the committee, what I've suggested, is that we have essentially a protocol for how to -- you're asking us a question about tests on the one hand and about investigative studies on the other. And I'm suggesting that we need some defensible way of providing you feedback on that; and being a small motley crew, I don't think that we have sufficient expertise amongst us to advise you on all of the things that you're proposing; and so I'm saying that we'll get a mail review.

And what you're saying is that you're going to clean up the proposals and give them to us so that what we send out is something that's reviewable, and that's fine.

DR. STOTO: But the criteria that he has in mind in rewriting them are exactly criteria we need to ask the referees, did they meet these tests?

DR. HARRISON: Fair enough; and yes, by sometime tomorrow morning -- I'll try tonight to just write up two separate sets of questions that would go as a cover letter with these things to reviewers.

Does that sound okay?

MR. COENE: And then we'd have a paragraph from Joel on each one of them and then the proposal.

DR. HARRISON: Joel will have whatever he puts together.

DR. SELVIN: Would it be heresy to suggest we're making too much of this? I mean, it's $16 million to get the guys out there, and they're asking for five new measurements. I don't know -- it doesn't seem to me that big a deal. Now I'm just a statistician, I don't really understand what all these tests are. But Joe said they're relatively inexpensive, they're unobtrusive.

DR. MICHALEK: Well, that's a legitimate point of view, because in years past we would have taken -- you know, ten years ago we would have just gone ahead and done these, and then tell you the results later. Now we're trying to give you a heads up right from the start and give you a chance to --

DR. HARRISON: Yes, and I'm trying to handle what you're doing in a responsible way. I'm trying to make sure that our acts are clean all the way through.

Now, --

DR. STOTO: I guess I heard that they may not all be that cheap.

DR. SELVIN: Well, those guys can decide about the money.

DR. HARRISON: Well, it's not just that. Drawing blood from a person's arm is probably one of the most trivial things that I can think in medicine. But it's invasive. And it shouldn't be done for a single wrong test. And that's not my moral position; that's just the position of clinical research in the United States.

LTC BURNHAM: That's OPRR's position.

DR. HARRISON: And so, no matter what the relative cost of this test is versus the overall cost of the project, we're duty-bound to make some judgment as to whether or not it's appropriate and whether or not it's appropriate.

I agree with you, they can decide whether they can afford it, but we have to render some kind of an opinion on whether or not it's appropriate.

LTC BURNHAM: I thought somehow or other we had communicated that what we would like is a yes or a no, and then also prioritized. If you had to pick four of these to prioritize, and then we'll get what we can afford.

DR. HARRISON: Yes. And all I'm saying is that I'm trying to throw a little bit of a funny, funky review in there so that we can say that we did, under the circumstances, the best that we could. Now what we've said is that for this kind of thing -- well, not for the test, but certainly for the investigator-initiated studies, that it would be best to have an RFP, to have it evaluated through NIEHS or NIDDK and all the rest of this business, but that's not happening.

So what do we do as a compromise?

DR. STOTO: I think the plan we talked about is a good one.

DR. SELVIN: It just strikes me as overkill; but you know, I'm a beginner at this.

DR. GOUGH: We certainly don't want to have a test that, unknown to us, has a record of producing misleading results.

DR. SELVIN: I would agree with that.

DR. GOUGH: And I think that --

DR. HARRISON: The other thing is that if you were to -- I admire this study. I feel proud to have been involved in it. And if you were to throw in just one funky test, one test that lacked credulity, one test that would --

DR. STOTO: You mean one more funky test.

DR. HARRISON: I mean one test that scientists in that area would laugh at, you place the whole study in danger. I mean once you see one thing wrong, you figure that you're just looking at the tip of the iceberg. That's the way people are.

DR. STOTO: Another thing which is consistent with all this is, one of the big problems with this study is they measure so many things that occasionally things pop up as significant just because you've measured so many things, the multiplicity problem.

DR. MINER: Well that, of course, is out of the barn.

DR. STOTO: Well, but you don't want to make it worse.

DR. HARRISON: Let's finish up, because we're kind of just filling up time now.

DR. STOTO: Where did these six proposals come from? I presume you guys worked them up and asked for people. It's not like these are --

DR. MICHALEK: Well, there's a very definite trail for these. Number one, we've been working with James Albers for almost ten years on this peripheral neuropathy issue, and we have coauthored a paper in submission -

- and he's telling us his professional judgment on what to do next. And that is your electrophysiological measurement. That's where that came from.

DR. STOTO: I'm not questioning that. The question is, you didn't make some announcement that you're open to proposals?

DR. MICHALEK: No. These are non-open -- nothing, no. These are recommendations like Albers' from a colleague. The same is true of James Dwyer.

DR. STOTO: So I guess I wonder whether there are even studies in this other category of investigator-initiated things.

Well, the genetic ones, they came out of their friends; and they also, it sounds to me like the real issue in the genetic ones is do we keep the red blood cells?

DR. MICHALEK: Right.

DR. STOTO: So it's kind of like the other test.

DR. GOUGH: Well, the issue is whether we give $180,000 to Dr. del Junco to do her study, too.

Whatever.

DR. HARRISON: You know --

DR. GOUGH: The blood cells I might agree with.

DR. HARRISON: My whole reason for wanting the RFP and wanting review and stuff is that I really don't feel comfortable with the way this is done. And the reason that the NIH has reviewed panels and the like is because anything less than that is apt to give you this going from one acquaintance to another acquaintance to another acquaintance, and you may not really be getting -- in fact, I can almost assure you that you're not getting the very best science that's possible in any of these given areas.

You get that from competition, and this is not competitive. But we can't have that.

DR. STOTO: Right, so I guess we should just reflect that and then say --

DR. HARRISON: so what I'm saying is, that the worst part would be if one of these studies -- if one of these proposed studies was really, unbeknownst to us and certainly unbeknownst to Joel and colleagues -- if one of these studies was really useless, to be just blunt. If it turns out that these cytochrome studies have been done up the wazoo, the relationships are already known, the hypothesis has already been disproven, and none of us knows that literature so we just -- well, Mike knows it, but --.

So that's all I'm looking for with this little mail review, is to just be able to get a couple of people to look at things like this and --

DR. STOTO: I don't disagree with that at all; I'm just saying that I think all these things really are in the same category rather than test versus investigator-initiated things.

DR. HARRISON: Okay. All right.

MR. CAMACHO: I'm on to, it seems three things going on here. One of these particular studies, that's one thing. You've got to have people look at this and say "I agree with that" and other things. As far as what tests, I still think we should be taking samples that, if things change down the road, at least we got to 2006. Some other studies, and we do another kind of RFP out there, if there's money or whatever, that the samples are out there and able to be used.

DR. STOTO: That's essentially one of the proposals. I think the genetic studies are morphed into that proposal. And that whether or not Debbie del Junco gets funded for analyzing it is kind of a separate issue altogether.

DR. HARRISON: Are you saying that you think that the Epstein-Barr is something that's on the table now? Or are you just saying that preserving white blood cells or the buffy coat -- it's called a buffy coat.

DR. STOTO: I don't know the science there, but I guess preserving genetic information, preserving genetic material -- genetic material is on the table, it sounds to me like, and maybe there are different ways of doing that that need to be compared to one another.

MR. CAMACHO: If we keep the whole blood -- I don't know anything about medicine -- right here it is, and this is my blood sample, my own blood sample. 20 years, 30 years, 40 years, 50 years -- can't they get all the DNA they want out of that?

DR. HARRISON: If what you want. But let me, for example, just --

DR. CAMACHO: We're back to this again.

DR. HARRISON: Let me throw what might be a little bit of a twist. This population is too small to do this, but population studies right now are done with mitochondrial DNA. If you do a regular DNA extraction you're not going to have mitochondrial DNA; you just have chromosomal DNA. Mitochondrial stuff stays out.

So let's suppose that five years from now or eight years from now someone looks and goes "Oh, dang! What we need to finally solve this problem is to compare such-and-such gene on the mitochondrial genome in these two cohorts" and you don't have the samples.

DR. STOTO: I guess the other aspect of it, I understood, was that the red blood cells are frozen, they're dead.

DR. HARRISON: The white blood cells.

DR. STOTO: The white blood cells are frozen and then they're dead. But this other technique actually would preserve them so they could be --

DR. HARRISON: Would preserve live cells. Or let's say that suppose five years from now you decided that it really was worth studying the protein produced by -- you know, the cytochrome protein produced. So you start the cells up, you turn on that gene, and you isolate the protein. It offers you everything but the person, as opposed to --

MR. CAMACHO: That's what I was trying to get at. I'd want to see something preserved out of it. If I was a soldier, I'd want this.

DR. HARRISON: The disadvantage is a considerable difference and expense. And so if you could only do a little something, then you'd just freeze the buffy coat. If you could do a little better, then you might do this Epstein-Barr transformation.

DR. CAMACHO: It's getting off into the -- I am for that cost.

LTC BURNHAM: Is this an ongoing cost that you would have to pay this company forever, until they --?

DR. HARRISON: It would -- well, once the cells were transformed, grown up and frozen, they'd be in a freezer analogous to but more expensive than the freezers you've got your other samples in.

LTC BURNHAM: That's my point, though. So we'd have to pay them every year to keep that --?

DR. HARRISON: Well, or they'd be sitting there with your other freezers.

COL MARDEN: Or pay for the power.

DR. HARRISON: Yes, they'd be sitting there with your other freezers. And then at some point someone will write a proposal -- so for each man you'll have a rack of five ampules in liquid nitrogen-level temperatures, and someone will write a proposal and it'll get approved by whatever mechanism, and you'll pop one vial out of each little straw. You'll pop one vial out, keep it frozen, and ship it off to whoever has given the proposal.

DR. STOTO: Sounds expensive.

DR. HARRISON: It is. It is. I make no bones about it.

MR. CAMACHO: Maybe there'll be conversion techniques ten years from now.

DR. STOTO: Well, it's expensive between now and then to maintain it, yes.

MR. CAMACHO: Think of how expensive it could be if down the road in one of these new little conflicts we seem to always run into that somebody started throwing gas or toxins around. And then somebody, looking at all the wounded soldiers, somebody said "Wonder if this will parallel the dioxin? Jesus, can we go back and do that?" That alone would be worth it. To me it would be worth it. It would be worth it to me.

DR. HARRISON: Well, why don't we think about these things?

DR. STOTO: I think it's worth asking. I think it's worth asking the question. I don't want to prejudge the answer, but --

COL MARDEN: What would a frozen sample of the 1918 flu be worth to us today? A bunch.

DR. CAMACHO: Oh, sure.

DR. HARRISON: In fact, we went and got it, didn't we? Where were --

DR. SELVIN: Alaska or Siberia?

DR. HARRISON: Yes, it was someplace.

DR. HARRISON: So I don't think we've got anything else to do today, do we?

DR. GOUGH: Well, it would be --

DR. HARRISON: We don't have anything else to do today, do we?

(Laughter)

DR. GOUGH: Could Jay -- who can tell us how much these things cost?

DR. HARRISON: Do you know what you could probably do tomorrow morning? You could probably call up the administrator at the University of Utah, GCRC, General Clinical Research Center.

I've got even better than that. Call Jeffrey Cheung at the NIH, and tell him we need this information. He's area code 301-435-0768 and tell him that we're talking about preserving cells the way they do at the University of Utah; and can he either tell us or put us in contact with the right person to get the cost.

MAJ SPEY: I'll drive him out there.

(Laughter)

MAJ SPEY: We're leaving at noon.

DR. MINER: Would you repeat phone number? Make sure I got it right?

DR. HARRISON: Oops. I was just with Dr. Cheung yesterday.

301-435-0768.

DR. MINER: Thank you.

DR. HARRISON: He won't be surprised.

MR. CAMACHO: This little letter we're supposed to -- where is the focus? Who's getting this letter eventually?

DR. HARRISON: This is to be inserted into the minutes.

It's not a letter. What is it they were supposed to do?

MS. JEWELL: Just a statement for the minutes.

DR. GOUGH: To continue the --

DR. HARRISON: Oh, the continued funding.

MR. CAMACHO: Preservation of the records and the samples and archives -- yes.

DR. HARRISON: What time do we convene in the morning?

MS. JEWELL: 7:30, Continental breakfast, 8, meeting.

DR. HARRISON: All right. Thank you. [Whereupon, at 5 o'clock p.m., the meeting recessed, to reconvene at 8 a.m. the following day.]