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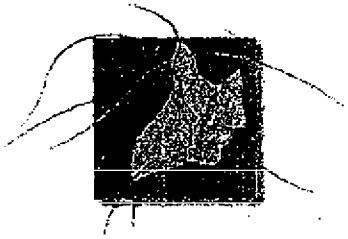
U.S. Food and Drug Administration

THALIDOMIDE: POTENTIAL BENEFITS AND RISKS



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TRANSCRIPT

THALIDOMIDE: POTENTIAL BENEFITS AND RISK

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P R O C E E D I N G S (8:35 a.m.)

DR. GROFT: Good morning, everyone. If you'll take your seats, we can get started. We

have quite a busy agenda for the next two days, with lots of speakers and some real tight time constraints that we'll be working under, so I would like just to get started.

To give us a welcome from NIH is Dr. William Harlan, the associate director for disease prevention within the NIH.

I'm sorry. My name is Steve Groft, and I've been the coordinator with Terry Toigo for the meeting. There's a little anxiety up here with this, but we're getting it together.

DR. HARLAN: Good morning, and welcome to the conference on "Thalidomide: Potential Benefits and Risks." I want to express my appreciation to those who have collaborated with us in this effort. The Centers for Disease Control and Prevention and the Food and Drug Administration have joined with several of the research institutes here at the National Institutes of Health to put on this program, and we appreciate their active participation in the development of the program, and in the program itself.

The meeting is convened really to look at the novel and potential important actions of thalidomide. It's interesting that we have to look at the unique attributes of this particular drug in order to see it utilized in the future. In essence, the discovery and development process of drugs has been revised somewhat. Ordinarily, a drug is licensed for a potential benefit, and as time unfolds, the full scale of adverse effects of the drug are known, as well as potential new uses. These potential new uses can be elaborated under the protection, if you will, of the licensure of the drug itself.

On the other hand, what's happened with thalidomide, as you know, is the fact that it was not licensed has put a particular onus on it. The very severe adverse effects are very clearly a detriment to some of the investigation that has occurred. It's particularly important, then, that one look at the potential benefits, and that these benefits meet a higher standard, I think, a standard that will remove the onus of the very severe adverse effects that occur.

There are a number of applications under study at the present time. There are about 20 applications. Nine of the institutes and centers at the National Institutes of Health are actively investigating uses for the drug. Twenty of the General Clinical Research Centers also have protocols investigating the potential uses of the drug.

It's a particularly apropos time for the meeting to occur. As you probably know from the reports last week, one of the advisory committees to the Food and Drug Administration has recommended that thalidomide be used for leprosy, and I think that provides an opening for all of us to look at the potential uses that are developed here.

Before we start the meeting, I would like to express a note of appreciation to Dr. Steve Groft, who was the introducer this morning, and will be the moderator. Steve has done a wonderful job of directing the Office of Rare Diseases. As a pharmacologist, he has a long interest in the pharmacologic actions and in looking for new and novel approaches to treatment of disease with pharmacologic agents. He has shepherded this meeting along, has

worked with the other federal agencies, with industry, and with others to develop the program, and he is to be congratulated for this effort.

Steve, I'll turn the program over to you.

DR. GROFT: Thank you very much, Bill.

Almost a year ago, we established an interagency working group to look at what was going on with thalidomide. At that time, several of the meetings that have been held were not conducted, were maybe on the planning stages, but we had representatives from the Centers for Disease Control and Prevention, the Food and Drug Administration, and the NIH.

Initially, our plans were to come up with a common research clinical protocol, to guide the research, or perhaps even some research guidelines to have as a direction for the research. It became pretty obvious, after looking at the pharmacological actions of thalidomide and all the uses, that one protocol was not going to suffice for all of the research that was underway or was planned.

So at that point, we decided that perhaps the best thing to do would be to conduct a workshop where we could present the potential benefits and risks associated with thalidomide. So here we are today, almost a year later. I think our first meeting was last October. It has taken some time for us to get the direction that we wanted to go, and arrange the speakers and logistics.

As Dr. Harlan mentioned, it's sort of fortuitous that last week the FDA's advisory committee met and came up with the recommendations. Between Dr. Woodcock and Dr. Jonathan Wilkin, we'll be hearing the results of that, as most of you have already read in the paper.

Since last year, the Centers for Disease Control and Prevention conducted a workshop on preventing birth defects due to thalidomide. Cynthia Moore from CDC will be here to present the results of that meeting, and as I mentioned, Dr. Wilkin. There were also about three other workshops or parts of different scientific meetings that discussed thalidomide during the past year, so we'll be hearing from various people who participated in those workshops and those sessions as the meeting goes along.

I think it's important to realize that this is not by any stretch of the imagination a consensus development conference. It's not a technology assessment conference. We're here really to exchange ideas of where the research is going. What are the opportunities for research? What are the emerging opportunities that we haven't even thought about, but because of the action of thalidomide may prove to be beneficial to a select group of patients?

We also want to discuss risk communication and management of the risks associated with thalidomide. I think everyone here realizes what went on approximately 40 years ago, and none of us want to repeat or even anything close to what occurred at that point. However, there is concern that this is a product that can be very beneficial to a select group of patients, and we really should look at it in great detail.

We also want to discuss the methods of monitoring for safety and adverse effects in both the research environment and the community itself. With perhaps the arrival of the product on the market, plans have to be in place for adequate monitoring of this and prevention of pregnancy.

I think, looking back over 40 years ago, it has been two generations since the product was kept off the market by Dr. Kelsey and her colleagues at FDA here in the United States. In those two generations, it is probably 50 percent of the U.S. population who really don't have a clear understanding of what occurred, and what the effects of thalidomide were on the unborn.

We have quite a task in front of us. All of us -- the health care providers, the researchers, physicians, pharmacists, health educators, the pharmaceutical industry -- I think anyone who has a tendency to get close to thalidomide, adequate warnings have to be made and will be made. We'll be hearing from several of the manufacturers here at this meeting of their plans, how they're going to provide the information to individuals who will be using the drug.

We'll be looking for comments as we go along. Really, the hallmark of the workshop is, there will be time for questions as you go on at the sessions, especially the breakout sessions. We look for your input. We look for your advice as we move along.

Not that we have all of the questions answered with thalidomide. It doesn't boil down just to a safety consideration of trying to avoid pregnancy, or the neurotoxicity associated with thalidomide. We also will be discussing the need for analogs, with less potential for teratogenicity and neurotoxicity. We'll be discussing that in great detail at one of the breakout sessions tomorrow.

The issue of mutagenicity has been raised in several publications, and we will want to hear a little bit about that, if it really is a concern, or if it's something that we should not be really concerned about, or do we need results from additional studies.

The neurotoxicity, is it something that's permanent, or is it transient? Is it dose-dependent? We'll want to talk about that a little bit.

Then another issue is the window of susceptibility as far as teratogenicity. If someone should have the misfortune to take the product while they're pregnant, we know that between days 35 and 50 after a woman's last period of this extreme sensitivity. What happens after that if exposure occurs? We'll want to discuss that as well.

So there are a number of questions that remain unanswered. This gives us an excellent opportunity, I think, if everybody can go a little informal as we go along. The speakers, even though they're up here on the stage and in the various breakout sessions, most of them will be around for the two days. If you have any questions you don't have a chance to ask them here, please just catch them in the hallways and talk with them. I think, from my conversations, they're willing to answer the questions and discuss them with you.

With thalidomide, as with all drugs, we all have to make a benefit/risk decision. I think that the point of the workshop here is that we want to provide a clear understanding of what those potential benefits and associated risks are for thalidomide, and then come up with different methods of communication that will provide that information to the public, all the health care providers and their patients, so that they can make a good decision, and we don't have any unfortunate accidents that have occurred in the past, and in fact have been reported to be occurring now in several other countries in which thalidomide is marketed. We do want to stay away from that as much possible.

I'd just like to go over a couple of things logistically for the meeting. We don't have any floor microphones, but what we will have will be people coming up and down the aisles after each speaker. Some forms have been provided in the package. If you have any questions, please fill them out, and we'll bring them up front, and then try to coordinate them as we go along for each of the sessions. So if you'll do that, that would help out quite a bit.

We prepared a selected bibliography of thalidomide. I culled through, I guess, about 4,500 references from around 1962, and selected around 1,600. So in about a half-hour or so, or after the first break, there should be a copy of the bibliography out over here. My apologies if I've slighted anyone whom I didn't pick as a reference that you may have published, but we tried to get an adequate representation of the literature. That will be available. Karen Patrias from the Library of Medicine helped with that, and I'd like to thank her.

If all of you have got the abstract book, it contains the agenda. I don't know if you've had a chance to look at it, the agenda and the various abstracts from the speakers who were able to get a copy of the abstract to us at the time of printing. There may be others available as the meeting goes on, if they were not included.

In the abstract book, as well, there's an informed consent document that's being used for research purposes. So most of the investigators who are doing research with thalidomide probably are using this, or some form. The template has been accepted by the FDA, and used extensively. Then there is the patient brochure that's being provided to patients as well.

Most of you, I know, did sign up for breakout sessions. Stay in those sessions. Tomorrow, we'll list where they are, which location. Right behind us on top there are three lecture rooms that will be used, the main auditorium, and then Conference Room A will also be used. If you have signed up, stay with it. If you haven't signed up, there will be sheets there in the back at the registration desk for you to sign up, so please do so. It will be helpful for us in planning everything.

The cafeteria is on the main level, upstairs, if you need that. It's open until 2:00, so watch your afternoon coffee levels or caffeine levels. If you need it, then get one before 2:00. The elevators are out to the left here. There are restrooms to the left on this floor, and upstairs, if necessary. As the meeting progresses, if any of you have to leave, there is a telephone that you can summon a taxicab. The registration staff of Prospect Associates with Carol Sadler will be willing to help you with this.

I believe those of you who are eligible for CME credit, there is a form provided. Fill it out and complete it, and turn it in to the registration desk after the meeting, and we'll see that credit is provided to you.

So at this point, I'd just like to thank several people who have been working with us all along. First, Terry Toigo from FDA, who has been the co-chair of this event, trying to put things together, and Dave Banks, who works with Terry. So thank you to both of them, and to my staff -- Anita Pikus, Mary Demory, and Beth Clay -- for sort of giving me the time to devote to this effort.

When we started this, we envisioned a very small workshop, but as things have grown and I've identified more and more uses, the breakout sessions got larger and larger, and it required quite a bit of effort. I thank them for all the help they gave to us.

Thanks to Bill Hall of the Office of Disease Prevention for assisting and putting the meeting together as well, and then finally, to all of those of you who came today, not just the members of the public, but the scientists, the lawyers, the health care providers, the clinicians, and others. Thank you for giving of your time and sharing your experience with thalidomide. We've got quite a way to go, so I think with everyone working together --

We can't get enough publicity for thalidomide, but I think it has to be positive, with the benefits and risks, and the message has to go out that this is a potentially beneficial product, but the risks are so serious that we don't want to have this become another 1957-1962 era.

So thank you. I think we'll get started now, leading into Dr. Kelsey, who back in the 1960s -- if you look at her abstract, we're about three days short, I think it is, of when the application was submitted to the agency, so it's quite a good time to have the meeting.

Dr. Kelsey?

DR. KELSEY: It's a pleasure for me to be here today and recapitulate a bit of the past. I joined the Food and Drug Administration as a medical officer in August of 1960. I spent the first months going around various areas of the Food and Drug Administration getting familiar or getting introduced to the type of work that was done there. On September 1st, I reported to the Bureau of Medicine as a reviewing medical officer.

The thalidomide application was filed shortly after September the 8th. Although it was usual to give applications around more or less in rotation, since I was new, they selected an easy one for me.

Now, at that time, the bureau was, of course, much smaller than it is now. I think, if we could have the first overhead, that would perhaps bring that out. I don't know if you can read it, but in essence, there were seven full-time medical officers and four part-time medical officers. The total applications were about 300 a year. Now, there are over 200 medical offices.

Now, I should explain, however, that the applications really were quite a bit different from what they are today. A lot of them were for fairly ordinary drugs, minor molecular modifications of long-used drugs, or a new mixture of old drugs. It was rare that a really new and exciting drug came in, and it was in those applications that the best clinical and animal studies were performed. In general, at the time, drug testing was not considered a very scholarly pursuit by most people. Many of the studies in support of new drugs were written really more as promotions than as scientific studies.

The ground rules in those days were that after an application had been submitted and filed with the agency, the agency had 60 days in which to decide that the drug was safe for the proposed use or uses. There was no requirement for efficacy, and this of course was one reason why the applications were so much smaller.

In fact, the thalidomide application was four volumes in size, as I recall. That was about standard. I think I remember one that was 11, and one that was one or perhaps two. Now, although I guess they're mostly computerized, it's a matter of 100 or 200 volumes.

The applications were reviewed, as they are now, by a chemist, and a pharmacologist, and a medical officer. The chemists were in the same little prefab building that we were in on the Mall between 7th and Independence, where the Museum of Science and Industry now is. The pharmacologists were in another bureau altogether, in the Department of Agriculture.

The medical officer really had the choice. They could do the pharmacology themselves or they could ask for a consult from the pharmacologist. I chose the latter course.

We had, as I said, 60 days. If we hadn't communicated with the company before that, they could have automatically assumed that it was okay, and marketed it. So very close tabs was always kept on the date.

We did get our letter out on November the 10th, although I said the application was received on the 8th, or some little time before it got logged in. I think the official date of acknowledgement was September the 15th. So we got our letter out on the 10th of November. In this, we declared that the application was incomplete and inadequate, and could not be filed. Then we gave the reasons for our decision.

We all had fairly serious questions. The pharmacologist felt that the chronic toxicity studies had not run for a sufficient length of time. He also felt that there were inadequate absorption and excretion data. The chemist found all sorts of problems or shortcomings with the manufacturing controls. She had concerns about the asymmetrical carbon atom, and wondered what was known about the D and the L forms, and in what proportion they were present, and so on.

She, fortunately, had been educated in German, and a lot of this application consisted of German reprints with an English translation. She of course could read the original German, and did find at least one error in the translation. I, who know no German, or just enough to

pass a Ph.D. exam in it, was very impressed by this.

I had some problems. The data to submit safety was very sketchy and anecdotal. The claims were quite fulsome, you might say, almost. It was of course perfectly nontoxic. It lacked hangover effect. It was nonhabituating, or addicting, and so on. But one by one, these claims sort of were modified somewhat.

I was particularly -- and all of us were -- concerned about the fact that you seem to be able to give enormous amounts, both to animals and humans, without any effect of perhaps drowsiness or sedation. In fact, one of the claims or one of the mentions in the brochure included several cases in which persons had tried to commit suicide, and been unable to do so. You've probably heard a later comment that, had thalidomide been on the market, Marilyn Monroe would be alive today.

Well, pretty soon it was acknowledged that, like all other drugs of its class, there was indeed some hangover effect, but we were concerned about this nonabsorption. We felt there might be conditions of the nontoxicity, which we felt was surely due to nonabsorption, and we thought there might be conditions, illness or another drug or something like that, that might change this so much more would be absorbed, and toxic effects might appear.

We did not know, for some years later, that a solution of liquid form of the drug had been marketed in Germany, particularly for use in children. When the British company thought they would market a similar one, their pharmacologist was horrified to find out how very toxic this compound was. I can still remember his anguish when he described experiments he had done. It was a micronized preparation in a sweet solution.

Despite his findings, however, it was marketed for awhile in Britain. As I understand it, the preparation was taken off the market because of some toxicity in humans, but we didn't know this.

The application was resubmitted again on January the 17th, which meant that by mid-March we would have to give them another opinion. We were continually concerned about the lack of data on metabolism, excretion, absorption, and this curious lack of toxicity. Then, at the end of February -- the 23rd, I think it was, actually -- we picked up a number -- it was actually the December 30th number -- of the British Medical Journal, which contained Florence's article posing the question, did thalidomide cause peripheral neuritis?

This was a little late in getting to us, because the mail was on strike. It was actually a shipping strike, I think, and we did not get our British and other foreign publications by air mail in those days. However, this did come in time. When we questioned the company about it, they said they had just seen that, too. They were sort of surprised, and were going over to Europe to find out more, and would let us know when they came back.

Now, what we didn't know, again, was the German company had been questioned about peripheral neuritis as early as the winter of December of 1959, before our application was

even submitted. The same person that asked them about it this time gave a paper -- I believe it was in May of 1960 -- describing a number of cases of peripheral neuritis, some of which seemed pretty severe.

The British actually answered the first report by saying that they were aware of it, and had put some reference to it in the material that they distributed with the drug. Our company was not obliged to submit foreign supporting material or material of that type at that time, so we were not aware of this side effect.

They had independently discovered it about May of 1960, and there is good evidence that the German and the British company had a sort of gentleman's agreement to keep the matter rather quiet until the American company had a chance to get the drug on the market. So we were inclined to believe that the American company had not heard of this earlier.

The company did report to us on their trip to Europe. They said that indeed there did seem to be some cases that neither in Germany or in England was it considered of great moment, and that both companies felt a little note on the labeling would suffice.

There were even questions early on whether the drug should continue on an over-the-counter status, as it was in some parts of Germany, and other parts of the world. It was a little time later that the over-the-counter drug status was changed, and the drug became prescription-only.

But it's difficult to exaggerate how popular this drug was at this time. I think it was the third largest-selling drug in Europe. As I mentioned, it was considered so safe that it was over-the-counter in many areas.

We were concerned about the peripheral neuritis, even if the companies did not seem to be. We sought some outside consultations with neurologists, Dr. John Tower at NIH and Dr. Webb Haymaker in the Army Walter Reed Hospital. They both felt the same. They felt that peripheral neuritis could be serious, painful, and often irreversible. The risk of developing this would not be justified in a drug that was used simply as a hypnotic and sedative, since there were other drugs on the market for this purpose.

We continued to feel it might be a serious matter. One of the questions we raised at this time was what would happen if the mother took it through pregnancy, and this drug was taken for quite long periods of time, what would be the effect of the drug on the child?

This was not a shot in the dark, because at that time the Food and Drug Administration and the American Academy of Pediatrics had been concerned about the effects of drugs when taken during pregnancy, and were in the midst of preparing guidelines for the testing of such drugs. There had been a number on the market that had been shown to have disastrous effects -- ananoptrine, chloramphenicol, to name a few.

I'd had a little experience some years previously when I worked on the anti-malarial drug project during World War II. We were given a little time for research, and we were

interested in the metabolism of the effective anti-malarials, quinine and Atabrine. We established that the quinine was very rapidly metabolized by the liver of the rabbit, but we found that the fetal liver had no such activity, and it did not appear till shortly after birth. This, of course, was the same situation that causes the chloramphenicol problems. The baby simply doesn't have the enzymes to protect itself against the chloramphenicol as the adult did.

The answer always was, if it had had an ill effect, surely it would have been known by now. That, of course, is a common excuse about any adverse effect. But, interestingly enough, it had. A German in Bonn, Germany, a pediatrician and a geneticist, had been struck by the increase of phocomelia cases in their hospital. They felt it must be due to some recently introduced substance, and they wrote around to a number of other hospitals in Germany. Most of them reported the same thing, that they had had an increase in this very unusual adverse effect.

They then thought they would find out the experience of other countries where thalidomide had been used. Most of them had indeed seen this increase. They were thrown off, ironically, because they were under the impression that the drug was released in the United States. The promotional material said it was widely used in North America, and it had of course been marketed in Canada.

They wrote to three centers in the U.S. where statistics were kept on birth defects. There wasn't really any indication of an increase. This is, sadly enough, what put them off the scent. It wasn't until November of 1961 that Lenz discovered the association.

Now, the first report of phocomelia was announced at the end of November of 1961. The company immediately phoned us, and told us the news, and said they didn't really believe it, but as a precaution they would put a halt to clinical studies going on in this country. But they did want to continue some that they had just started on its possible usefulness in cancer. That seemed no great problem to us, the benefit/risk ratio being entirely different.

In March, early March of 1962, they told us they were withdrawing the application immediately, as they believed there may be some truth to this association. There were some weird differences in wording of their two communications that led us to think it might have been more widely used in this country than we had gathered from the new drug application, so we asked for a complete list of the doctors they had sent the drug to, and were very surprised to find that actually over 1,000 doctors had been given the drug.

Most of these were recruited after the application had been submitted in September, in the expectation that it would be rapidly approved. They were told, in essence, "Don't really worry about recording the results. We just want you to try it out, and see if you want to use it in your patients."

We then visited, or had the company visit, every one of these doctors, and pick up what remaining stocks they had -- and there were indeed quite a lot -- and find out if they had had

any phocomelic or abnormal births amongst the patients they had given the drug to. In all, we found about 10 or 11 cases that we thought might be due to the trials in this country. There were an additional seven patients or subjects where it was clear that the drug had been gotten from a foreign source.

Now, the thalidomide tragedy in Europe actually didn't cause a great stir at the time in this country because there really were, except for those few, no victims. The one person who was concerned was Dr. Helen Taussig, who was the professor of cardiology at the Johns Hopkins Hospital. She had heard about the outbreak from an ex-resident of hers who was now in Germany, and he had urged her to come across and see some of the victims, many of whom had cardiac defects.

Before going, she had contacted another ex-president who was working at the Food and Drug Administration, and when she got back she invited both him, Dr. John Nestor, and myself to hear the results. They were essentially published later in the JAMA after she gave a talk to the American Academy of Physicians.

She also spoke before the House committee, but it really wasn't until mid-July when the article in the Post came out, authored by Morton Mintz, that the country realized the enormity of the problem. Almost immediately, the long-awaited Kefauver-Harris bill was passed, in October. This not only required proof of safety, but also proof of efficacy. It also included a last-minute addition that patient consent must be obtained from all subjects in the clinical trials in the future.

Meanwhile, FDA had hastened to strengthen the investigational drug requirements, and essentially published early in July, what was finalized in early March, with the addition of this efficacy and consent requirements.

So these were the two immediate effects of thalidomide, the strengthening of the law and the regulations, both offering greater protection both to subjects of trials and to the public getting drugs later.

It also stimulated other countries to bring new laws. Many of them had laws such as we did back in 1930, before 1930, when a manufacturer could simply put a drug on the market if he felt it was safe when used as labeled. The onus was on the government to remove them. But many of them introduced laws similar to our 1962 ones, and one of the great forward steps has been the harmonization, the efforts being made to bring the requirements of Japan, the European countries, and the United States into harmony. This of course will add to more rapid marketing of good and safe drugs, and protection against unsafe ones.

It also increased greatly the efforts to monitor birth defects. It caused a great increase in the science of teratology, or means of testing drugs for adverse effects in pregnancy. So those were some of the immediate good effects.

I would say, however, that thalidomide never faded away. I mentioned that we permitted

certain trials in cancer to proceed. Some years later, when an application was submitted for leprosy, we felt that was a reasonable use, since there was great need for such a drug in this distressing disease, and the patients would be under pretty good control.

I look forward to hearing advances that have been made in the understanding of a pharmacology and the metabolites of the drug, and the many proposed new uses for this fascinating, but rather difficult drug.

Thank you.

(Applause.)

DR. GROFT: Thank you very much, Dr. Kelsey. It almost is a history of FDA regulatory action since the 1960s, so reliving quite a few moments in FDA history.

Our next presentation will come from Dr. Janet Woodcock, who is the director of the Center for Drug Evaluation and Research. It's on her desk that Dr. Jonathan Wilkin will be sending the application to consider for approval.

So, Dr. Woodcock?

DR. WOODCOCK: Thank you, Steve, and good morning to all of you. I also want to join in thanking Steve and Terry Toigo, who I think have really put in a tremendous effort to have this workshop come off in such a timely manner for everyone's consideration of this product.

What I'd like to talk about today -- if I could have the lights down a little bit -- is to bring the history up to date on this, and talk about the challenges in the clinical drug development that thalidomide has presented, and currently presents, because we are seeking everyone's help in dealing with the orderly investigation of thalidomide for various conditions.

Could I have the next one, Steve?

Now, what I want to talk about is, first of all, why is there interest in thalidomide? I mean, some people really asked this with a note of incredulity in their voice. Why would you possibly be interested in such a product with its history? Second, what are these challenges in development? Third, I'd like to really appeal for help from all the sectors that really need to help in this -- patients, academia, industry, media, government, and the public.

First, why the interest in thalidomide now? What has happened? Well, in the midst of the tragedy that Dr. Kelsey described, some leprologists made a serendipitous discovery that some of their patients with a type of reactive syndrome in leprosy had, as they described, a dramatic response when they were given thalidomide for sedation. So in erythema nodosum leprosum, or ENL, they observed a rapid resolution of some of the symptoms in patients who had been put on thalidomide.

Over the years, this kept the drug alive, so to speak, in investigation. I'll go into that a little bit later. But the drug continued to be used. As Dr. Kelsey said, there were investigational applications for clinical investigations.

Today, we have great interest in thalidomide for a wide variety of conditions. We have life-threatening conditions, such as graft-versus-host disease, AIDS wasting, and interest in various malignancies. There are a wide variety of immunologic disorders where there's interest, where it is believed that thalidomide may be helpful, including various types of lupus.

Behcet's disease. We heard from a Behcet patient at our recent advisory committee last week. Sjogren's syndrome, Crohn's disease, and rheumatoid arthritis. Many of these conditions on this particular slide are very prevalent in young women.

In addition, there are a lot of other conditions. A wide variety of serious dermatologic conditions, most of which I cannot pronounce properly, but are very, very serious for those patients who are afflicted; tuberculosis; various types of aphthous ulceration, including ulcerations in patients infected with HIV; and the ocular disorder, macular degeneration. This is a very wide and disparate set of conditions where there is interest in studying thalidomide.

Unfortunately, while there is great interest, there are also serious challenges. What contributes to these are, number one, historical factors, and, number two, the current situation.

Historically, after thalidomide was taken off the market around the world, and failed to be approved in the United States due to the actions of Dr. Kelsey and her colleagues, it was, as I said, investigated for use in leprosy. For over 20 years, it was used in the United States under an investigational new drug application that was held by the Hansen's Disease Center in Carville, Louisiana, and was used there for the treatment of ENL.

Now, this group had extreme difficulty over the years in obtaining a consistent product, obtaining a stable source of product, and obtaining a product that was a consistently defined, pharmacologic, high-quality product.

Now, what happened is, other uses began to be explored over time, extrapolating from what was felt to be the very striking effectiveness in ENL. Other uses began to be explored. What happened in the U.S. was the Hansen's Disease Center was used as a source for other clinical investigators who wanted to hold INDs and perhaps administer the drug to their patient or do a clinical trial. These investigators also were subject to the same whims and problems with drug supply as was the Hansen's Center.

I personally was an investigator who sought to obtain thalidomide for a young woman, a patient of mine who had Behcet's disease. It was at a time of difficulty of supply of obtaining thalidomide. I was unable to obtain it, possibly partly because it was a young

woman of childbearing age, but my patient subsequently died of the complications of her treatment.

So this created a lot of problem in the development of thalidomide. There was no real source available. The investigators had single investigator INDs. There was no overall development plan for thalidomide.

HRSA, the Health Research and Services Administration, who ran the Hansen's Center, developed a progressive financial burden of supplying this thalidomide to folks, and of tracking who they had distributed it to. FDA became increasingly concerned about the quality of the drug being distributed. We felt it probably varied in dose significantly. We often were called to participate in testing of the tablets to ensure their quality and uniformity, so the situation was not good for investigation of thalidomide.

Recently, in the last several years, HRSA, because of the current fiscal environment, made a decision to cease supplying the drug outside of the ENL use. At the same time, there became interest in use in AIDS patients for the indications that I mentioned. There began to become access issues of actually being able to get thalidomide for patients who didn't have other alternatives, with AIDS wasting, and severe aphthous ulcerations.

Because of all these issues, buyers clubs sprang up, or began to offer thalidomide illegally through basically mail-order, or going in and obtaining it in various buyers clubs, clinics, or what have you. So distribution of the drug through non-medical channels in the United States began to occur.

At that time, FDA put together the FDA Thalidomide Working Group to try and coordinate regulation. By this time, there were many INDs scattered throughout the various divisions of FDA, where the drug was under study for all these conditions.

The working group was to coordinate access programs to make sure that those who needed access to thalidomide, investigators and patients, would obtain it under controlled conditions, where the possibility of adverse effects could be minimized. To that end, the working group developed a model informed consent for individual investigators to use with their patients, to make sure they would be fully informed, and also a patient brochure that could be given out.

We also, because of the HRSA decision, held discussions with some companies that had begun to develop interest in actually clinically developing thalidomide. We brought those companies in, and had discussions with them, because it appeared that the most prudent path would be to get the drug evaluated and studied in the clinic for these various indications, see whether or not it worked, and at the same time ensure a consistent supply of product that is a high-quality product.

We also either talked the buyers clubs into not distributing thalidomide or, in one case, took legal action against a buyers club to stop illegal distribution of thalidomide. Regardless of

this, though, I still hear that thalidomide continues to be available through various channels without having an IND.

Recently, as you heard, there was submission of an NDA for thalidomide in the treatment of ENL. The last step last week in that process was the recommendation of the advisory committee that thalidomide is safe and effective for that condition. Then this conference, I think, is the next step.

The challenges, though, remain. The challenges for all those conditions that I mentioned on the earlier slides, and the other ones that are going to be discussed over the next two days, is getting the drug properly studied.

For sponsors, there are liability risks, of course, involved with thalidomide that have in some extent decreased the interest in this pharmacologically active agent. For investigators, there has been an ongoing challenge -- when we talked to the NIH investigators, they said it was the same for them -- obtaining a stable supply of high-quality clinical supplies, and funding the necessary studies. For patients, it's really balancing needs for access to this drug in these serious conditions against the need to really study the drug in controlled trials, and get the information.

There are additional issues that will be raised at this conference. We need to get to some agreement on what would be required for both safe and respectful inclusion of women of childbearing potential in these clinical trials. There is need for some, if possible, common methods of toxicity evaluation, so we can accumulate safety information across all the trials, and develop a database of safety that will pertain to thalidomide in general. We need to establish reliable sources of product, and we need some public input of where we're going with this.

Where are we going? We've heard repeatedly over the past few years from patients with serious diseases that they need effective treatments that have been shown to be effective, but we've also heard recently from the advocates for children that, of course, as the use of thalidomide would increase, the possibility of fetal exposure rises.

On the other hand, and in addition, we have to consider what I said earlier about buyers clubs and illegal distribution. We understand in this country how difficult it is to absolutely keep drugs out of illegal distribution channels if people want them. That's been well-proven. So severe restrictions on thalidomide availability that are intended to decrease the risk of fetal exposure may, paradoxically, lead to wider availability or use under absolutely uncontrolled conditions.

Some of this buyers club thalidomide just has a label on it. Otherwise, they're just plain tablets in a vial. Somehow we have to balance those issues I just mentioned.

A lot of it, I think, is information for the public and risk communication. That's where the media are extremely important, and the professional organizations. I did an informal survey,

and FDA has done a formal survey, although small. The bottom line is, most people 35 and under have never heard of thalidomide. They have no clue. Most of the reproductively active people in this country have no reaction to the word "thalidomide."

The illegal distribution, as I said, the product isn't well-identified. It might just have "thalidomide" on it, but people have no idea what that means. We have to recognize that among various people with serious conditions, pill-sharing, sharing of medications, is a very common practice. How can we inform the public to make sure the public is protected, even as clinical investigations go on?

In summary, what I believe is that thalidomide needs to have standard clinical drug development, like any other drug, for these conditions. It needs to be evaluated in clinical trials, so we can tell is it effective in these conditions, and what its safety profile might be. The teratogenicity is pretty well understood, although the nuances are not understood, but I think we know enough about that to know it should not be used in pregnant women. But there are many other safety issues pertaining to the drug that need to be explored in the various diseases.

The needs of seriously ill patients for access to treatments must be met, and met safely. We need to have, jointly, a common understanding of where we're going, and public information is vital to the safe use. The public must be made aware.

These are my version of the goals of this workshop. I hope we can accomplish all these goals as we go through the various sessions.

I thank you very much.

(Applause.)

DR. GROFT: Thank you very much, Janet. I think your goals are pretty much consistent with what everyone will be working towards.

I would like to acknowledge Dr. Marlene Haffner, who is here from the Office of Orphan Products Development at FDA, who has taken some actions on giving orphan drug designation to thalidomide for several of the uses, and probably would welcome an application for more uses for thalidomide. So hopefully, the provisions of the act have stimulated the development of thalidomide a little bit.

Our next speaker comes to us from Mexico, sort of the FDA equivalent in Mexico. **Dr. Guillermo Bierzwinsky** will relate the activities in Mexico related to the use of thalidomide in HIV wasting.

DR. BIERZWINSKY: Thank you, Dr. Groft, for inviting me to this meeting.

This is our volcano, which is about 80 kilometers outside of Mexico City. The name is Popocaqutatal. It's fuming. The issue we are dealing with today is also fuming.

Thalidomide was first synthesized by Kunz in 1956 in Germany. It was initially used as a sedative in various countries. I'm going to repeat information that has already been mentioned. Reports of peripheral neuritis in 1960 delayed approval of thalidomide by the FDA. In late 1961, the possible association between unexplained fetal abnormalities and the use of thalidomide was raised by Lenz at a meeting in Westphalia. The manufacturer withdrew the drug from the market in 1961.

The tragedy of thalidomide is largely responsible for the strict sanitary regulations applied presently for approval of new drugs in several countries. However, positive actions of thalidomide have also been observed. In 1965, Sheskin, in a Jerusalem hospital, serendipitously noted improvement in the inflammatory reaction of leprosy patients known as erythema nodosum leprosum. Since then it has become the drug of choice for its treatment. In Mexico, thalidomide was licensed for this indication in 1988.

It has also been successfully used for the treatment of other difficult ailments, like Behcet's disease, lupus erythematosus, graft-versus-host disease, ulcerative colitis, and esophageal ulcers in AIDS. This has already been mentioned.

More recently, there has been interest in the use of thalidomide in the treatment of certain aspects of the clinical picture in AIDS patients. Mexico has the third place in the number of AIDS cases in the American continent, and the 11th in the world.

It has been shown the thalidomide has no antibacterial effect in cases of erythema nodosum leprosum. These and other observations suggest that its beneficial effects are exerted through a direct action on the immune system, as supported by the suppression of guest-versus-host disease observed in animal experiments and in humans.

It has been reported to selectively inhibit the production of tumor necrosis factor alpha by human peripheral blood mononuclear cells, primarily by accelerating the degradation of TNF alpha messenger RNA transcripts. Also, thalidomide inhibits in vitro both TNF alpha messenger RNA and TNF alpha protein, as well as the expression of HIV-1 in infected cell lines in peripheral blood mononuclear cells of infected patients.

Human immunodeficiency virus disease has detrimental effects on the nutritional status of infected patients. Progressive weight loss is a major clinical feature and a diagnostic criterion of AIDS, and contributes to its morbidity and mortality, independent of the CD4-positive T cell counts. Weight loss in this patient is at the expense of body cell mass, predominantly of muscle protein -- wasting or cachexia -- and may occur in two patterns during the late clinical stages of HIV disease: one, acute, severe, and remitting weight loss, mostly related to opportunistic infections; and two, chronic, progressive weight loss, the wasting syndrome.

At the Instituto Nacional de la Nutricion Salvador Zubiran in Mexico, a randomized, double-blind, placebo-controlled trial was designed to evaluate the efficacy of thalidomide, a selective inhibitor of tumor necrosis factor alpha, in the treatment of wasting syndrome in

patients with advanced HIV disease, and to assess the effects of thalidomide on peripheral CD4-positive T cells, plasma levels of tumor necrosis factor alpha, and HIV viral burden in peripheral blood mononuclear cells.

Patients included were adults with an advanced HIV disease who were under antiretroviral therapy without an active opportunistic infection, and with over or equal to 10 percent weight loss in the previous six months. Patients were stratified by severity of weight loss.

Here in the graphic, you can see, most of the patients were in the category three, where the weight loss was between 10 percent and less than 20 percent, with a CD4-positive T cell count of less than 100 for most of the patients in both groups, the placebo and the thalidomide group, 11 patients. There were 14 patients in each group.

>Patients were stratified, as is shown, by severity of weight loss and CD4-positive T cell counts, and assigned in a random and double-blind fashion to receive thalidomide 100 milligrams four times daily or a matching placebo.

Patients were followed for 12 weeks, three months. Weight and anthropometric data were recorded every two weeks. Clinical events were registered. HIV viral burden in peripheral blood mononuclear cells by endpoint dilution cultures, CD4-positive T cells, and tumor necrosis alpha plasma levels were evaluated.

The efficacy of thalidomide was defined as weight gain or no progression of wasting. Between June 1992 and May 1994, 28 patients -- 24 men and two women, non-pregnant -- were randomly allocated to receive thalidomide, 14 patients, with 14 patients on placebo. Both groups were comparable in their baseline status.

Therapeutic failure occurred in 10 of the 14 patients from the placebo group, and in three only of the 14 patients of the thalidomide group. This is the therapeutic failure probability, where it shows that you can have more with placebo than with thalidomide.

Weight gain occurred in one patient on placebo, and in eight on thalidomide. As you can see here, they started within 55 or 56 kilograms, and the patients with thalidomide went up to 68 kilograms, as compared to the patients on placebo, which remain about the same weight.

The Karnofsky index was significantly higher by the end of the study in the thalidomide group. Mild and transient somnolence and erythematous macular skin lesions were significantly more common in the thalidomide group. CD4-positive T cell counts and HIV viral burden in peripheral blood mononuclear cells did not change in either group. Circulating levels of tumor necrosis factor were undetectable throughout the study.

Results suggest that thalidomide not only impeded, but also reverted the wasting syndrome, preserving the Karnofsky index in patients with advanced HIV disease. This is the median of the calculated muscle mass, which also increased from 20 kilograms to about 26, where the patients in the placebo group remained about the same, or decreased.

There was no change in this study. It could not be measured, any change in these parameters.

Based on this study and other similar reports, the Ministry of Health in Mexico approved the use of thalidomide for the treatment of the AIDS wasting syndrome in 1996, considering that at the time there were no better options available.

There is one sole manufacturer of thalidomide in Mexico. The company's name is Serral. Raw material is produced in Mexico by Diorchem, a manufacturing plant managed by investigators of the National University of Mexico and the Polytechnical Institute. The drug is not sold in drugstores. It is directly distributed by Serral, the manufacturing company, to infectologists and dermatologists, and to the Social Security Institute, the largest public health institution in Mexico.

It is supplied in boxes containing 50 100-milligram tablets. The cost of each unit is $38 U.S. The monthly cost of treatment is around $92. This compares favorably to the cost of megestrol acetate or recombinant human growth hormone. It is estimated the total annual sales are in the order of 6,000 units, that's all.

The labeling states that it should not be used in pregnant or fertile women because of the risk of fetal malformations. A pregnancy test must be performed and found negative before treatment is initiated. Contraceptive measures must be used during treatment. Dr. Fost will have something to say about these requirements.

Adverse reactions reported with the use of thalidomide in these high doses have been frequent, but effects have been mild and transient, mostly skin reactions. In the Mexican study, there were two cases of severe skin reaction, requiring discontinuation in one case. Neuropathy developed in one patient, and the drug was also withdrawn.

This is to show you the toxicity. One case was a serious disseminated rash, and two cases were a severe disseminated rash, and neuropathy.

Also, the percentages of efficacy. The placebo was 29 against 79 percent.

In conclusion, it can be said that thalidomide seems to delay and reverse the wasting syndrome in patients with advanced HIV disease. The beneficial effects should be investigated in larger clinical trials. It remains to be determined whether thalidomide alone, or in combination with recombinant human growth hormone, can sustain its effects long enough to significantly alter the clinical course of AIDS, particularly in regard to quality of life and survival in those patients with weight loss. It can perhaps be used in other wasting diseases, as there have been recent reports of accelerated weight gain when it was used in patients with pulmonary tuberculosis.

Thank you.

(Applause.)

DR. GROFT: Thank you very much, Dr. Bierzwinsky.

If there are any questions, I don't know if anyone has passed them over, if anyone has been collecting them, so if some of the staff could come up and down the aisles to see if there are any questions, I would appreciate it if we could bring them up to the stage.

Our next speaker will be **Dr. Carol Braun Trapnell** from the Food and Drug Administration. Dr. Trapnell is with the Office of Therapeutics Research and Review from the Center for Biologics Evaluation and Research. As I mentioned earlier, she will be talking about the clinical pharmacology of thalidomide and all the potential uses.

DR. TRAPNELL: Good morning. I'd like to first thank the organizers for inviting me to the meeting.

As has been said, I'm going to discuss briefly the clinical pharmacology of thalidomide, and really just hit the high points of some of the major issues with this drug that we know of, or don't know of.

I also would like to say that I noticed in your handout that only one reference is listed for my talk. Obviously, there are more references. If anyone would like a more complete reference list, please see me afterwards. I'd be happy to provide that.

This is the structure of thalidomide. It is a glutamic acid derivative that, as we've heard, seems to have a wide variety of potentially beneficial activities, as well as potentially harmful properties.

The five topics I'm going to just highlight today in my talk are absorption of thalidomide; the issue of enantiomers, and we're all going to have to get the cobwebs out of our chemistry classes from high school to discuss this; issues with metabolism and disposition in vivo; and questions about drug interactions, as well as toxicities of the compound.

First, I want to discuss absorption. This data is from a trial that we did at Georgetown University, looking at the pharmacokinetics of thalidomide and oral contraceptive products, which I'll discuss in more detail in a few minutes. But this is the plasma concentration versus time curve that we generated from 10 healthy women who received this product. They were getting 200 milligrams of thalidomide at bedtime for three weeks.

As you can see, the peak time of absorption of the drug is actually fairly delayed. It's about at two to three, maybe even four, hours. Then it has a first-order elimination that gives it a half-life of between eight and 12 hours.

I think the interesting thing, from my perspective, is that the patients begin feeling quite drowsy within 30 minutes or 45 minutes of swallowing the capsule. So clearly when we're up here at the peak concentrations, we are well above the level that is needed for at least sedation. I think it's fair to say we don't actually know what the concentrations really are that we need for the beneficial effects of this product for really any indication that we are

interested in evaluating today.

I think the same is true in reverse. We also don't really understand what levels produce toxicity, although certainly with the teratogenicity, it has been reported that one dose given at the right time in embryogenesis can produce harmful effects.

Now, the issue of enantiomers is that at this nitrogen in the structure, this ring can either go up out of the screen, or go down into the screen. These are so-called R or S or DNL enantiomers. They are mirror images of each other. The drug is actually administered as a racemic mixture, so half of what someone swallows is the R isomer, and the other half is the S isomer. This is actually very common in drug administration. Usually when there are centers in the molecule that can have either the molecule going up or down, it's given as a racemic mixture. I think most of that is because of the ease of the chemistry. I also think there hasn't been a lot of interest until more recently in what the potential effects of the isomers as individual compounds can be.

Now, what happened is that there was some published information in animals that suggested that one of the isomers could be the toxic isomer, and the other isomer could be the isomer responsible for the activity. I think there was some interest in thinking, well, if we could just give the S isomer alone, could we somehow get away from all the toxicities that we're seeing with the drug?

What happened in response to that was a group in Sweden led by Erikkson did, I think, a very elegant study which was published in the Journal of Chirality in 1995, where they gave to an in vitro experiment, using human blood -- they put the R isomer into the petri dish, if you will, and watched it disappear, and at the same time watched that the S isomer was formed de novo. So somehow in the blood, the R isomer was converted to the S isomer as part of its metabolism. As you can see, out here at about four to six hours, there's really equal amounts of both isomers in the preparation.

A similar thing was observed when the S isomer alone was put into the preparation, and we had increasing levels of the R isomer, so that there were equal amounts seen at about four hours or so.

Now, he did the same thing then in patients to see if the in vitro findings could be proven. Indeed, I think in the subject he reports in the paper, the same paper in Chirality, you can see that administering the R isomer does essentially give you the same concentrations of both isomers, although of course the formation of the S isomer in this time profile is a little bit delayed, because the R isomer has to get into the bloodstream. Again, the same thing is seen when the S isomer is given as the only compound.

Just to get another point about the metabolism here, this is the structure of thalidomide that I showed you earlier. Again, you have to understand that there are two compounds actually being administered, the R and the S. What happens is, this drug is hydrolyzed to a series of metabolites in humans. There is some hydrolysis. There is some metabolism. We actually

tried to work with this compound in the lab to do some in vitro drug metabolism studies, and had just a heck of a time keeping this compound as thalidomide because it really loves to break down into all these different products.

Now, the point about this is that we don't actually know what is responsible for both, again, the activity and the side effects of thalidomide. It could very well be that a couple of these compounds would be more active for activity, and a couple may be the ones that really produce the toxicity, but it is very hard to work with this compound, because the breakdown products occur very quickly, and they are hard to measure in the serum. When you're doing a clinical study, actually there has to be very good care taken to how the blood samples are handled, because the breakdown of the parent can occur very rapidly once the drug is pulled out of the blood.

Now, to touch on the drug interactions topic, there was a question about whether thalidomide could affect the pharmacology of concomitant therapies that it was being administered with. In particular, there was a paper published regarding a compound called taglutamide in 1980 by Wiener which implied, really, the taglutamide could induce the metabolism of other compounds in the rat model that he studied. Taglutamide is very structurally similar to thalidomide. So the question was, could thalidomide affect the metabolism of other compounds?

There is no data available that we could find, but we felt that it was important to ask this question, particularly in regard to oral contraceptives, or hormonal contraception, because women of childbearing potential who are receiving thalidomide as parts of clinical trials were being advised to use some kind of hormonal contraception as one of the contraceptive measures to prevent pregnancy.

Of course, if thalidomide was inducing metabolism, what could then happen is that the oral contraceptives would be more rapidly eliminated, and could potentially then not be as effective in preventing pregnancy. Obviously, if the woman is taking thalidomide when that is happening, that is not a good interaction that you want to see, so we performed at Georgetown University a Phase I crossover evaluation in 10 healthy women who had had surgical sterilization, who are between the ages of 21 and 45.

Interestingly, what Dr. Woodcock said -- one of our subjects was young woman who is in her early 20s who had had her children early, and then had undergone a tubal ligation. She told me when she went to the library to ask the librarian to get some information about the drug, the librarian, who I assume was a woman in her 50s, from the study, just about fainted on the spot when she told her she wanted to do thalidomide. My patient could not understand what the big deal was because, again, I think she had never heard of the drug, which is what Dr. Woodcock said.

But these women all were surgically sterilized. Our study design was that, on study days 1 and 22, they received two tablets of the Ortho-Novum 1/35 product, which contained together 70 micrograms of ethinyl estradiol, and 2 milligrams of norethindrone. As you

know, Ortho-Novum 135 is a combination tablet of these two drugs.

We obtained blood at regular intervals for 24 hours after each dose, which was then used to determine the pharmacokinetics of these two compounds. Then on days 2 through 21, we administered to the patients 200 milligrams of thalidomide at bedtime every night. The product that we used was supplied to us by Andrulis Pharmaceuticals, so we used two 100-milligram capsules. We did this as outpatients, because it was not really realistic for us to keep our subjects in the clinical research center for three weeks.

We wanted to be sure that we had good compliance with therapy, so we used something that clinical pharmacologists like to talk about, MEMS caps on top of the prescription bottles, to make sure that patients were either taking or not taking the drug, so that we could better understand our data at the end of the study.

This is what a MEMS cap looks like. It's basically a larger top that goes onto a standard prescription bottle. Inside this cap is a little computer chip that records, on the computer chip, when the bottle is opened and when it is closed. It records both the date and the time. The way you use these caps is, you of course have to educate the patients that these are being used, that they are part of the research protocol. Then you obtain from the company that you rent these from software and hardware that can be loaded onto any standard IBM-compatible computer or PC.

It has this reader, that looks a little bit bigger than a mouse, where you invert the cap onto this little part of this device, and you instruct the computer to read it. Within about 10 seconds or so, the data from the cap is actually downloaded into a computer file, and you can then read it on your computer screen.

What you get when you read the caps, you can get the readout in various forms. This is a format from a study that the patient was being asked to take the drug twice a day. You can see, you actually get a very interesting readout of both the date of administration and the times of day that the caps were opened and shut.

In this particular example, this patient had very good compliance. In fact, in our thalidomide study, we had 97 percent compliance with the therapy, which I thought was very good, given that most of my patients were saying they were a little bit sedated from the drug.

What we found in this study when we evaluated the pharmacokinetics is that the baseline ethinyl estradiol area under the concentration time curve compared to the same information after three weeks of thalidomide was essentially unchanged in these 10 subjects. These dots represent the individual patient area under the concentration time curve, and again at baseline, and after three weeks of thalidomide. You'll notice here, there's a fairly large distribution of area under the concentration.

Results within the 10 patients, that actually is very well-reported for ethinyl estradiol. There's a lot of intrasubject variability, but, as you can see, there's no change in the kinetics

of this compound with thalidomide. Similarly, we found the same thing with norethindrone. The scale here is in different units because we gave the drugs in different units, but again, no change in the area under the concentration time curve for this compound in the presence of thalidomide.

The toxicities of thalidomide have already been mentioned. Here is just a sum of them. Sedation, I think we could say, is a pharmacologic effect. I was impressed during our trial how well this drug works as a sedative. In fact, one of my patients asked me where she could get more of it because she's never slept so well in her life. So I think that's something that really does need to be taken into account for patients who need this drug for other reasons.

Of course, the teratogenicity has already been discussed by Dr. Kelsey and others, and the peripheral neuropathy will be discussed in more detail as well.

I think, again, it is important to note we do not know the mechanisms for these toxicities. We don't know if it's thalidomide and/or one or more of its metabolites. I think clearly this is an area of research that needs to be done for this drug.

In conclusion, I'd like to just say that I believe there's adequate thalidomide pharmacokinetics available for most purposes regarding the design of larger trials, and to carry out bioequivalence studies in the face of more than one manufacturer of this product.

I think the enantiomer was put to rest by the nice research by Erikkson's group, and that for humans it's really not clinically relevant, that there's no reason to go to the trouble of giving one isomer over the other because the human makes it a racemic mixture anyway, so there's no reason to even ask the question any further.

I think we can also safely say that thalidomide does not affect the pharmacokinetics of either ethinyl estradiol or norethindrone.

Some areas of future research we'll discuss in more detail tomorrow include understanding the pharmacokinetic and dynamic relationships, better understanding of the pharmacologic mechanisms of action, and the impact of the hydrolysis and metabolites in vivo. It clearly, as I said, affects the way samples are handled from clinical studies.

Finally, I just want to acknowledge my collaborators, Jerry Collins from the FDA, Steve Donahue, Darrell Abernethy at Georgetown University, Debbie Birnkrant from the FDA, and Dr. Norman Fost, who worked with us on the design of the Phase I study. Thank you very much.

(Applause.)

DR. GROFT: Thank you very much, Carol.

As she mentioned, tomorrow we will have quite a bit more time available to discuss the

pharmacology in The Analogs of Thalidomide. So those of you with an interest, you're welcome to attend and participate in that session.

Our next speaker, **Dr. Norman Fost** from the University of Wisconsin, Madison, will discuss the ethical issues related to the use of thalidomide in fertile women and the variables that enter into a benefit/risk decision. So we're anxious for your comments.

DR. FOST: Thank you. I'd like to thank Dr. Groft for the opportunity to talk at this really excellent conference.

In the interest of time, I will adopt the method of Hubert Humphrey, who was said to talk at 500 words per minute, with gusts up to 1,000.

No one wants to have a child with phocomelia. All reasonable people will take all reasonable precautions, if properly informed. No one opposes high standards of disclosure and informed consent for patients. No one opposes high standards for education of physicians and pharmacists.

The question is whether coercive measures are warranted to prevent the birth of even a single child with phocomelia; that is, whether it's appropriate to impose restrictions on the liberty of women who have obviously legitimate and understandable interest in access to this drug for the many, and growing, number of conditions.

It's important to remember that a zero risk is not achievable. There is no system that will prevent the single birth of a child with phocomelia. So the goal of my comments will be to try to find some middle ground that properly balances the interests of future children in not being born with this deformity, and second, the interest of women in getting reasonable access to the drug.

I will not today, in the interest of time, be saying anything about the interests of embryos or fetus; that is, an embryo or fetus who might be affected but does not come to term. There are issues there, but we don't have time to get into them.

I'll be discussing solely the interests of children; that is, future possible children who may be born with phocomelia and who obviously have an understandable interest in avoiding this harm. I will make the point that these interests arise, obviously, before the child is born; that is, if these interests are to be protected, they have to be addressed before the child is born.

Balancing these with the interests of women, who have interests not only in access to treatment once the drug is shown to be effective for whatever condition is at issue, but women as a class who have an interest in being included in clinical trials, so that if and when the drug is approved for marketing, there is information available about safety and efficacy.

Gender and pregnancy are obviously not trump cards; that is, while women have very compelling interests in being protected, and in procreative privacy, these are not absolute values. The point, obviously, is that the interests of women and of mothers and the interests

of the future child have to be balanced.

I think we can reject extreme positions. On the one hand, the moral claim that a woman, or a man for that matter, should have unrestricted liberty to expose future children to harm I think can be rejected. It's important to mention it because a recent Institute of Medicine report on access to drugs by fertile and pregnant women took that nearly absolutist position; that is, seemed to suggest that there should be no restrictions on women who have a legitimate need for access to drugs during pregnancy that might expose a future child to possible harm.

A more middle-ground position, as illustrated by the recent proposal of the National Bioethics Advisory Commission on the cloning issue, in which they recommended legislation that would restrict the access of women and men to cloning technology for the time being until safety issues are resolved; that is, who thought that legislation was appropriate to protect the interests of future possible children against the possible harms of cloning.

I happen to disagree with the recommendation, but it's an example of a governmental body recommending legislation that imposes some restrictions on the procreative privacy of women, and of men.

Similarly, the absolutist position that the child's interests should always take precedence -- that is, that the goal here should be a zero-risk environment, that the goal here should be to ensure that no child is ever born with this deformity -- I don't think can be sustained. Just one Supreme Court decision that takes the view that interests of future children cannot be absolute is the Johnson Controls case in which a company in Milwaukee that prohibited women from working in a work place where batteries were made on the grounds that future children would be exposed to established dangers from exposure to lead -- that this was an unreasonable restriction on the liberty of women; that is, the interests of children were not the only factor, that women's access to jobs, and so on, had to be balanced in.

As Judith Ahren, an attorney at George Washington, has said, "A woman has no legal or moral duty to be a procreative saint."

Let's first discuss, then, the interests of children. Children obviously have an interest in not being disabled and being severely disabled. Postnatal phocomelia, if it were to occur, would constitute child abuse. That is just to imagine the hypothetical example that if a woman or a man took a drug, and if suddenly their child's arms and legs would fall off, we would consider that an unreasonable risk to expose the child to.

Even if there were a compelling argument for the woman to take the drug, there would at least be a claim that the child has an interest here to be protected, and there should be some regulation or perhaps some restrictions on it. Maybe not an absolute restriction; it would depend on the reason. But we would take measures to try to reduce the interests of this, even restricting the liberties of people who had access to such drug.

The purpose of such laws in the postnatal setting is not punishment, but prevention; that is, the purpose of child abuse laws is to prevent children from risk of harm, although in some severe cases, even criminal penalties might be warranted.

Well, if postnatal children have an interest in having their arms and legs intact, these interests obviously exist for future possible children as well. This is reflected in many aspects of our laws; that is, damage that occurs while a fetus is in utero can result in liability in some jurisdictions if the child is born alive. Preconception damage can result in liability; that is, if DES were to cause damage in a second generation, there might still be liability if it were prescribed under negligent circumstances; that is, the fact that the child had not even been conceived at the time of prescription would not be an argument legally against a claim.

The interval between when the agent is administered and when the injury occurs is morally and legally irrelevant. Just to make the analogy, someone who puts a bomb in a school yard, even if it's timed to go off in 100 years, we would still say there's a strong moral argument for restricting this activity and there would be legal prohibitions against the activity. The fact that children had not been conceived yet would not be an argument for saying that there are no interests here to be protected.

The cloning example, again, is an illustration of a proposal to restrict a technology for the time being, while safety is unknown, to protect children who are not yet even conceived. So the point I want to make is that children have interests which can be legally protected, not only before they're born, but before they're conceived.

Women's interests, on the other hand, as I said, include access to treatment for effective drugs for life-threatening and disabling diseases such as the ones that we'll hear about. They have an interest as a class in being included in clinical trials; that is, even women who might not presently benefit from access to thalidomide have an interest as women as a class being included in trials, so that if the drug is shown to be effective for a clinical condition, down the road physicians can intelligently and safely prescribe it.

Women also have an interest in procreative privacy, apart from their interest in access to the drug for treatment; that is, they have an understandable legal and moral interest in being left alone with regard to procreative decisions, and even exposure of future possible children to risks.

Let me first just say a few words about the procreative privacy issue. The procreative privacy issue arose legally in full force with Roe vs. Wade, which, it's important to remember, had to do with the right not to procreate; that is, the claim in Roe vs. Wade and most of its progeny to protect the interests of the woman not to have children -- not a positive right to procreate, but a negative right to, if you will, avoid procreation, to be left alone.

This is not the same as an affirmative right to create a child under any conditions of harm. We do have other legal trends, which we'll probably hear more about tomorrow, on ways in

which the law has restricted the liberty of women when harm to a future possible child was at issue. In some jurisdictions, for example, women have been forced, compelled by court order, to undergo a Caesarian section medically indicated to protect a child from harm of being born vaginally.

There is also a federal case which refused to acknowledge that; that is, which overruled a court which did that. But there are cases that have gone both ways, including two state supreme courts. In contrast, the Johnson Controls case, as I mentioned, set some limits on how far the state can go in restricting the liberty of women.

But I think the point is that morally it would be wrong -- I think we would all agree -- to knowingly bring a child into the world under conditions of probable misery such as that associated with phocomelia, or at least extreme disability. At least it would require some compelling reason to justify doing that; that is, there would be a moral responsibility to take reasonable steps to avoid that.

Now, with regard to the woman's interest in treatment, which is the central issue here I think, I would suggest that it's important to distinguish the following variables, and this is the heart of my comments. What degree of restrictions are appropriate, and what kind of access women are entitled to have to thalidomide is not one question. It's many questions, depending on a number of variables. I've tried to identify them here.

First, whether or not the disease for which treatment is being sought is serious or trivial. Now, at the moment, all the disorders for which treatment are being sought are serious, life-threatening, seriously disabling, associated with extreme suffering, such as AIDS, cancer, Kaposi's sarcoma, and so on.

It's important to point out, though, that the drug will almost surely turn out to be -- will probably turn out to have efficacy for diseases which may not be life-threatening. Rheumatoid arthritis is one example. Rheumatoid arthritis, of course, can be associated with severe suffering, but there can be milder forms of rheumatoid arthritis.

So the first point I'm trying to make is how compelling the woman's interest is in having access and how weighty that claim should be against the interests of the future child will depend on the severity of the illness and the amount of suffering involved. We would not think, for example, there were a compelling reason if thalidomide were shown to be effective for acne or mild asthma.

Second, the likelihood of benefit would be morally relevant. If the drug has been shown to be proven effective, a woman has a much stronger claim for access to it than if it's in a Phase I trial where efficacy is statistically unlikely. The vast majority of Phase I trials never show efficacy and never wind up going to market. So the claim for access during that phase of testing would be less compelling.

Third, it would depend on the alternatives. If, just hypothetically, asthma turned out to be a

disease that was responsive to thalidomide, the claim for access to it for that, even if proven effective, would be less compelling if there were other effective drugs that the woman had not yet used. That is, obviously when it's a last resort, the claim is much more powerful.

Two other variables that are relevant but I think perhaps not as important are obviously the probability and severity of harm to the child. I'm not going to dwell on that because I think everyone would agree that the embryopathy, the phocomelia, everyone would agree, is a severe degree of harm and warrants strict scrutiny.

The importance of the pregnancy might be a relevant variable; that is, there might be a more compelling argument for a woman who is trying to have her first child than one who -- maybe third is not a clear enough example, but a woman who is trying to have her 10th or 12th child. The argument could be made that her claim for procreative freedom in that circumstance would be less compelling than a woman who is seeking to have her first child.

So I've tried to identify some of the morally relevant variables that might guide us in deciding how strong the claim is.

Now, other variables would have to do with the amount of intrusion on the woman's liberty to protect the child. That is, there are different remedies for promoting the safety of the future child. I've just listed four of the common ones here just for points of discussion. The drug could be restricted to just infertile women; that is, women who were surgically sterilized. That would obviously be too severe a restriction. It would be too severe an incursion on procreative privacy and would force too many women to be denied access.

One could require abortion for affected fetuses. I won't dwell on it because it's morally complicated and legally untenable in our country, but it's a method of protecting children that would almost surely be rejected.

Everyone would require strict informing and consent standards; no one is against that. The question is whether that's a sufficient amount of protection, whether that's too loose of a standard to protect the interests of the children.

The most controversial, and I think where most of the discussion needs to occur, is over the question of possible, for example, weekly pregnancy testing, which would be an almost fail-safe mechanism; that is, restricting the supply of drug in exchange for a negative weekly pregnancy test. I think comments of Dr. Woodcock were very appropriate on this point; that is, the trade-off here, if you required something as strict as weekly pregnancy testing, which would be a near fail-safe mechanism, the problem there is if it's perceived as too restrictive by a majority of women, it will drive them underground. It will drive them to buyers clubs.

So the question is, what kind of restrictions here in terms of frequency of pregnancy testing will attract a sufficient number of women -- that is, make it acceptable -- without driving them outside of the system?

Let me just close by trying to apply these principles to two specific examples. For a Phase I

study, such as the thalidomide/birth control pill study that Dr. Trapnell mentioned, I think there was a conclusion that obviously there was no benefit to patients. Even in other Phase I trials for therapeutic intent -- that is, for diseases -- since most Phase I trials fail, I think the point could be made that there's no clear benefit, and therefore the claim of women to have access in this would not be compelling. They are not being denied anything which involves a likely benefit.

If gender is important to assess biologic variables in dosing and so on, then it would be reasonable in a Phase I trial under this kind of analysis to require very strict standards, namely infertile women at that stage of testing.

In contrast, if efficacy were established -- that is, if Phase III testing had been completed and the drug were shown to be effective for any of the conditions we're talking about -- if there were no alternatives, no alternative therapy, there was now a high likelihood of benefit and obviously a severe risk of harm and disability for the child, if pregnancy were avoidable through not just contraception but through some kind of periodic pregnancy testing, there would obviously be an obligation to take reasonable measures not to bring a child into the world under conditions in which he or she, presumably, would rather avoid.

The question is mainly, I think, a political one, as Dr. Woodcock phrased it, or a sociologic one, of what degree of pregnancy testing, what frequency would attract or be acceptable to a sufficient number of women?

In summary, balancing is clearly required. We cannot take a position that women should just have unrestricted access to this; no one has suggested that. But, on the other hand, we cannot take the position that a zero-risk environment is what is being sought here. It's impossible anyway. Even if you had daily pregnancy testing and restricted access to the drug, the drug would still find its way into the open market, as Dr. Woodcock made clear. We will never have a world in which there is zero risk of exposure of fetuses or of future possible children. So the goal here is to find some reasonable middle ground that will get that incidence as close to zero as we reasonably can.

Thank you.

(Applause.)

DR. GROFT: Thank you very much, Dr. Fost. You've really given us something to think about in further discussions as the meeting progresses.

Dr. Wilkin has arrived. Last week, as many of you read in the newspapers and probably saw on TV, one of the FDA's advisory committees looked at thalidomide for the second time, and Dr. Jonathan Wilkin from the division will present the summary of that meeting.

DR. WILKIN: Thank you very much, Steve. I appreciate the invitation to this important meeting that you and Terry Toigo have crafted. I think we'll look back on this meeting in the future as an important exchange of information at the beginning of a new era in therapeutics

and clinical pharmacology.

We did have a meeting just down the street five days ago. It was a meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee, which hereafter I'll refer to as DODAC. That will shorten this presentation by five minutes. We considered Celgene's NDA new drug application, thalidomide for ENL.

The Federal Advisory Committee Act establishes the legal framework for all of the FDA advisory committees. They provide scientific and technical expertise. They advise and make recommendations. They do not decide finally on regulatory decisions. That goes to the people who work at the agency. But the real asset is that they do provide this independent expert scientific advice.

The DODAC group has approximately three to four meetings per year. There's a fixed membership, with three-year rotations. There are nine dermatologists who serve on the committee, four ophthalmologists, one biostatistician, one consumer representative, and for the particular meeting that we had last week, we did invite obstetrician/gynecologists from other committees, and neurologists from other committees. But the only person from another committee who came was a member of the Antiviral Drugs Advisory Committee. In addition, we often have special government employees who are previous members of committees who come and sit in on the deliberations.

Approximately two to three weeks before the meeting, the committee will receive a briefing package which will consist of the sponsor's summary of safety and efficacy, the FDA's summary of safety and efficacy, data from the clinical trials, the FDA reviewer's reviews, and often articles from the literature.

The types of issues that will come before an advisory committee are many and varied. There have to be at least 25 really great reasons. Some of the ones that we thought about when thalidomide was coming to the advisory committee are it's the first product in a class, it's a new molecular entity, it's never been approved at the agency. Products that have attracted significant public interest and controversy were all here today. Any product under review with significant safety or effectiveness issues -- and again, we thought it was important to have outside advice on these points.

Now, the advisory committee meeting has identifiably separate portions. There is an open public hearing, where anyone can sign up. There is a format for this, but one can sign up and get 5 to 10, sometimes 15 minutes and present their own opinions on the issues that are before the committee, or perhaps issues that might be related to that particular area of the FDA but are not really being discussed that day. It's truly open.

Then there is the part where the committee will listen to the FDA presentations, the sponsor's presentations, invited speakers. That's the open committee discussion. There was no closed session for the thalidomide meeting. In our particular committee, the usual reason for a closed session is where we are updating them on the drugs that are in-house at the FDA

that we're considering.

So the meeting began on September 4th with an open public hearing. We heard statements from the American College of Obstetricians and Gynecologists, the American Leprosy Foundation, the American Academy of Pediatrics. Then there were brief introductions by the agency, and then we moved to the sponsor presentations.

After lunch, we came back and had a second open public hearing. American Leprosy Missions presented a statement, as did American College of Medical Geneticists, the Teratology Society, National Organization for Rare Disorders, National Women's Health Network, and American Behcet's Disease Association.

This was followed by the FDA reviewer presentation. Then after that we had two invited speakers. Dr. Cynthia Moore from the CDC discussed elements of strategy to prevent birth defects due to thalidomide exposure, and Dr. Colin Crawford presented information on thalidomide neurotoxicity in ENL.

On September 5th, we opened the morning with a committee discussion. Then there was a statement by the Thalidomide Victims' Association of Canada. Then the committee received the questions and deliberated on them.

One of the aspects of the questions as presented to the committee was that we knew that the term "erythema nodosum leprosum" is actually used ambiguously in the literature. It can refer to the entire systemic syndrome of ENL or just to the cutaneous lesions. So the questions were originally crafted in a way that the chair could go either way on this. For question one, the chair exercised his prerogative of altering the question. He limited it to: Has the efficacy of thalidomide in the treatment of cutaneous ENL been demonstrated?

I should tell you that this is still in draft format. The chair needs to sign off on this, but this is the initial draft from advisors and consultants -- nine yes votes, one no vote.

Question two: Has the safety of thalidomide been adequately described in the treatment of the systemic ENL syndrome, or any subset of ENL, such as cutaneous ENL? The vote was three yeas and seven nays.

Then, really, the pivotal question three: Do the benefits outweigh the risks? The interpretation of this is, does the committee recommend that Celgene's thalidomide be approved for the systemic ENL syndrome, or any subset of ENL, such as cutaneous ENL? The response to this was eight yes, one no, one abstention.

Everyone, I think, outside of the agency focuses a lot on the outcome of the questions. I think there's a tendency to under-value the rich insights that emerge in the discussion. We at the agency spend a lot of time going over all of the discussion points that were raised by the committee.

The discussions seem to begin among the committee members with restricting the

distribution of erythema nodosum leprosum, but it evolved. They discussed that the distribution system might be a better, safer system than the IND mechanism, actually, and in the end they came up with not restricting distribution to ENL. That's an example. I'm not trying to be exhaustive and encyclopedic in all the comments that I thought were important. I'm just trying to give you an idea of some of the types of comments they made.

The comment emerged to use the actual photo of an infant in the package insert or the packaging for thalidomide, and that there needs to be a really good monitoring for neuropathy.

They thought that there were a few other things at the end that were still needed. There's a study ongoing by the sponsor in the Philippines, E003/P, and they would like to have those results, when that study is completed, presented to DODAC. Also, they would like to have some information on studies that are performed to learn more about neurotoxicity. They are encouraging sponsors to develop safer congeners. For thalidomide, they would like more pharmacokinetic information, specifically information on metabolites, elimination, and storage.

So, what is next in the regulatory process? Well, after we have an advisory committee meeting, we then have an internal meeting at the FDA, a debriefing meeting to go over the responses to the questions, and also all of the insights and discussion points that emerged at the meeting. That will be done this week.

This is a new molecular entity, and you may know the system is that the office director, the Director of the Office of Drug Evaluation V, will be signing off on this particular application. He'll be taking everything that he has on his desk into consideration -- all the reviews, the information that emerged at the advisory committee meeting, discussions with others in the agency. I'm sure he'll be looking for ideas that come from this meeting as well.

Thank you.

(Applause.)

DR. GROFT: Thank you very much, Jonathan.

Are there any questions? I don't know if the people have collected questions. We have a couple of minutes for questions before we break. If there are any, if you could stand up and identify yourself and project as well as possible, we'll try to pick you up.

PARTICIPANT: (Inaudible.)

DR. GROFT: Jonathan, did you get the last part? Oh, I'm sorry.

PARTICIPANT: Do you want me to say it again?

DR. GROFT: Would you, please? Yes. Why don't you come up here to the microphone, and

I think by the afternoon session we'll try to get a floor microphone.

PARTICIPANT: The first question. It was mentioned in passing that there is some ongoing cases of phocomelia in countries from thalidomide currently. I wondered what some of them were.

The second question was, is erythema nodosum in leprosy patients the same as it is in ordinary erythema nodosum, in that the nodular manifestations occur primarily, or at least initially, on the legs?

DR. WILKIN: Well, I'm a dermatologist and not a leprologist. There are leprologists here, and I'm sure later in this meeting you might be able to get some more definitive information on the distinction of erythema nodosum leprosum.

Erythema nodosum is different from erythema nodosum leprosum. They are two different inflammatory types of reactions. I think it might be possible to have erythema nodosum and erythema nodosum leprosum occur in a patient with leprosy, and perhaps they well could make the distinction between the two entities. The old-timey name for erythema nodosum was actually erythema contusaformi, because, as these lesions resolve, they leave what looks like a bruise. I'm not sure if that's the way the lesions of erythema nodosum resolve.

But we have Dr. Yoder and Dr. Ray and others here who might be able to speak to that.

DR. GROFT: I think the second part of the question, with the occurrence of phocomelia in other countries -- Dr. Bierzwinsky?

DR. BIERZWINSKY: Well, thalidomide is being used in Mexico for the treatment of erythema nodosum leprosum. We have had no reports of phocomelia, which means that people are being careful about which people are taking it.

DR. GROFT: I don't know if anyone has any other comments.

Dr. Trapnell?

DR. TRAPNELL: We actually had information sent to us when we were starting our study that there are cases apparently occurring in Brazil, but I have no scientific data at all. This was just mailed to us, really, at random.

DR. GROFT: For Dr. Trapnell: What are the inter-species differences in metabolism, pharmacokinetics, pharmacological effects, toxicity of thalidomide?

DR. TRAPNELL: Frankly, I don't think it's really been studied well enough to be able to delineate that with total certainty. A lot of the metabolism studies in animals were done after the teratogenicity issues were discovered in humans. There is a lot of different metabolites in animals that are found; many of them are found in developing embryos and fetuses.

But I would have to say that, at this point, that's probably one area of research that we need to do so that we can develop better animal models to be used to assess the human toxicity.

DR. GROFT: Dr. Bierzwinsky, is thalidomide going to be approved for other indications in Mexico?

DR. BIERZWINSKY: If there is enough scientific support, and clinical trials are conducted in Mexico which show benefit, then it would be approved for new indications, yes.

DR. GROFT: Dr. Fost, would you comment on the advisory committee's decision in the context of risk versus benefit for a condition as rare as ENL?

DR. FOST: I don't know enough about what, if any, prescribing or distribution restrictions were put on it. Obviously, the condition is a serious one, and serious enough to warrant some access. The question is, under what degree of restrictions? I'm not clear on whether the advisory committee -- what distribution mechanism you recommended.

DR. GROFT: We've got several others that I don't know if we'll have enough time to get through.

DR. WILKIN: Would you like a comment on the distribution?

DR. GROFT: Go ahead, sure.

DR. WILKIN: There was a presentation by Dr. Lumpkin at the advisory committee meeting on the different possible types of distribution schemes. The one that is most rigorous can be found in 21 CFR, the Code of Federal Regulations, 314.520. It's a mandatory restricted distribution.

I have to say, though, that while these were discussed, nothing was concluded at that meeting. It was merely just presented to the committee as different choices.

DR. GROFT: Dr. Wilkin, please clarify your comment on the photo of the infant. Do you mean an infant with phocomelia?

DR. WILKIN: We may hear more about this from Cynthia Moore or others. I think the committee had the notion that if there were a photo in the informational package that went to patients who would be taking thalidomide, that that might be more compelling, more educational than just simply a line drawing.

DR. GROFT: Then again, why are there no teratologists or neurologists on the committee?

DR. WILKIN: The neurologists on the -- there is an advisory committee. Our advisors and consultants staff person contacted that committee, attempted to obtain neurologists to attend and vote, but no one agreed to come.

We did have Dr. Crawford, a neurologist, and of course the sponsor had Dr. Cornblath at the meeting. So they provided expert advice to the committee.

DR. GROFT: Dr. Fost?

DR. FOST: At the risk of seeming self-serving, I think it would be desirable to have qualified ethicists on some of the advisory committees when there are obviously major ethical issues.

DR. GROFT: Dr. Kelsey, was the January 1961 NDA denied because of neurotoxicity? This is a multiple-part question.

DR. KELSEY: Could you repeat the question?

DR. GROFT: Was the 1961 NDA denied because of neurotoxicity?

DR. KELSEY: We delayed approving it, not that we ever did. The neurotoxicity was certainly our first concern, and it increased. We had an advisory committee, too, in September. They actually didn't think it was too serious; it could be dealt with by labeling. They also felt the teratology would have been disclosed. As I mentioned, it had been suspected before this.

Then after that meeting, we got much more reports on the severity of this peripheral neuritis. My opinion is that we would probably have never approved it on that basis alone, but we didn't have to make that decision once the word of the teratology got around. So I say, yes, it concerned us very much.

Remember, the proposed uses were as a sedative and a hypnotic.

DR. GROFT: We're going to have to cut the questions off now in order to keep the meeting moving. So if you did submit a question, please gather one of the panelists with you and present the question to them. Or, if we have time, as the meeting progresses, perhaps we can bring these questions back in tomorrow.

One other bit of housekeeping. If any of you would like to make a presentation at the open public session tomorrow, please sign up out back. I think we referred to it earlier. It's important for us to know what the time constraints will be, if necessary, for tomorrow afternoon.

We also have received the bibliography that was put together by the National Library of Medicine, and that is available outside as well.

So if we could reconvene in about 10 minutes, at five of.

(Recess.)

MS. TOIGO: I guess we'll get started, if everybody is ready. My name is Terry Toigo, and I'm with FDA's Office of Special Health Issues.

This meeting is described as an open scientific workshop. Given the meeting's scientific focus, some have asked what's the purpose of this panel? A public perspective? After all, like NIH and CDC, FDA is a science-based agency, where scientific facts and not opinions must prevail, and where scientific facts represent the impartial arbiter of conflicting views and our best protection from human error.

As a consumer protection agency, FDA must make certain that the public's interest is protected as those scientific facts are being discovered. In that regard, we must constantly be mindful of the impact of our actions on the people we serve, people from all walks of life who often have differing views about what FDA can and should do.

Although our constituencies are diverse, we nevertheless strive to be responsive to all citizens. One of the most effective ways in which we can live up to this principle is by inviting the public to actively participate in our deliberative process.

Thus, the purpose of this panel is to give all of us an opportunity to hear from you, the public. We'll hear from health care practitioners, an advocate for women's health, a thalidomider, and a patient advocate.

What might we learn from this panel? I think we will learn that each participant has a unique point of view. Some may be personal, some may be legal, and some may be societal. I think we will also learn that although individuals and the groups they represent may differ in their perspective, they are each working towards the same public health goal. In this case, that is to maximize the benefits and minimize the risks associated with this potentially therapeutic but dangerous drug.

The panel reminds us of the various constituencies who may be affected by our actions and that it is very important for researchers, industry, and the government to be mindful of these varied needs when making policy decisions or designing a clinical trial or recruiting patients to a clinical trial, or developing an educational program for a drug targeted at multiple audiences. The public's views must be included.

I'd like to thank the panel members for taking their time to share with us their perspectives. I'd also like to thank my co-chair, Steve Groft, for his flexibility in working with his sister agencies and others to accommodate the various agenda needs of this meeting.

Finally, I'd like to thank the staff in the Office of Special Health Issues, and particularly David Banks for his dedication to the many unanticipated tasks that accompanied this meeting.

That being said, I'd like to introduce the panel members of the public perspective.

Dr. Leo Yoder represents health care providers for leprosy patients, and he was formerly the

chief of the Medical Department at the Hansen's Disease Center in Carville, Louisiana. Dr. Yoder has extensive experience treating leprosy in the United States and Africa.

Mr. Randolph Warren represents the Thalidomide Victims' Association of Canada, an association created to empower and enhance the quality of life of Canadian thalidomiders.

Mr. William Zellmer represents the American Society of Health System Pharmacists, where he serves as the vice president for professional and public affairs.

Dr. James Allen represents the American Medical Association, where he serves as the vice president for science and technology.

Ms. Cynthia Pearson represents the National Women's Health Network, where she serves as executive director and oversees all program and policy projects.

Finally, Mrs. Nancy Paller, who represents herself in her role as the mother of an HIV-infected young man with aphthous ulcers.

That being said, I'd like to start with Dr. Yoder. We're going to try to keep these to 10 minutes, so you'll have the light. At nine minutes, the yellow will go on.

DR. YODER: Thank you, and good morning. I come to you, as has already been stated, as a physician who has been involved with Hansen's disease, or leprosy, for about 20 years. The last 15 years of those were at the Hansen's Disease Center at Carville, Louisiana.

In that situation, we are the referral center for the United States, and we tend to see many of the more complicated and difficult cases of ENL. In that role, I have lived through this difficult experience, these ill patients, sometimes for a number of years, and have experienced not only the physical pain but also the psychological distress, and even depression, that goes with this illness, especially in some of the more ill forms.

When I was asked to give this talk, I was asked to talk about what I would say to a patient for whom I was prescribing thalidomide. Basically, that's what I intend to do for just a few minutes. At least I will try to touch on the areas that I would discuss with a patient who would have come to Carville or to me and I was considering putting that patient on thalidomide for the first time.

Just a few facts about the disease itself. Leprosy is a disease with a spectrum. You can have very mild disease, very few bacteria, limited disease, and it may not even be of major consequence; to the other end of the spectrum, where patients have generalized disease, they have a lot of bacteria, they have many nerves involved, and it can be a devastating illness.

This disease is caused by bacteria, Mycobacterium lepri. Part of the problem with this disease is not only that it's a bacterial infection which persists for a long period of time, but it's an immunological problem as well, and especially also the fact that it has a predilection for certain specific cooler parts of the body, namely the nerves of the hands and feet. Also,

some other organs are affected in the lepromatous type, the type which I indicated has the diffuse type of disease -- namely, the eyes, the testicles, and sometimes joints and other areas can be affected as well.

A group of these patients who have the generalized former disease get what we have talked about here this morning as ENL. We don't have time, obviously, to go into a lot of the things that we could talk about.

But primarily I would point out to you as a patient who has this problem that this is an immunological problem. It's a problem with the immune system. It is not a treatment failure. It's not a drug reaction. Incidentally, this often occurs sometime after a patient has been on treatment for a period of time, sometimes maybe a year or two. He cannot be present at the time the patient is diagnosed.

But often the patient is started on treatment. We have good antibacterial drugs. We can kill the bacteria actually fairly rapidly with some of the drugs, but the bacteria do not clear from the patient rapidly. They stay around for a long time. The dead bacteria stay around even for several years at times. It is this immune response of the body to these dead bacteria that are around that cause this problem that we know as ENL.

These patients not only have a skin eruption, but I would note in response to a question that was asked earlier that it is quite different than simple erythema nodosum of the lower extremities, which you've seen in other disorders.

The skin lesions can look very similar, but these can occur in any part of the body -- the face, the extremities, all over the trunk. It is associated often with fever, pain. You can get swelling of the glands. These patients often are rather acutely ill. These skin lesions not only are painful, but they may ulcerate. So it is a generalized severe illness in many patients. It can be in a mild form, but we're primarily talking about patients who are fairly ill.

I want to show just a few slides of what it looks like. I hope the slides are on. I think we went one too far.

This is a typical skin eruption. These look like the erythema nodosum you may have seen in other disorders, but they are tender and painful. Usually an individual nodule will stay for a week or so, and then they do resolve with a slight darkening pigmentation of the skin as they go away. But untreated, you will get new crops of these.

A second patient with a similar type of problem, and the same patient with these lesions on the face. These look like they might be almost ulcerating. A little different type of lesion -- this young lady had typical eruption of the upper part of the body in the extremities, but also had these blistering type lesions at the lower extremities.

This is another patient with sterile pustules which may ulcerate. Finally, a young lady who I remember so well some years ago was referred to us and was actually in our institution for several years. Because she had persistent and chronic ENL, she suffered all the side effects

of prednisone, which I will mention again in a moment. She even ulcerated on her face.

That's the end of the slides.

The treatment options for this disorder in leprosy patients are quite limited. There are only a few that are useful, other than in the mildest cases. The mildest cases can be treated with simple analgesics, but that is basically a drug called clofazimine, number one, which is a drug that is of some benefit. However, it is slow-acting and benefits patients primarily if it is given at large doses for four to six weeks, and importantly causes significant pigmentation of the skin, which persists for a long time and is therefore unacceptable to some patients, especially young women.

The second drug that is very effective is prednisone, or what is commonly known as cortisone-type drugs. These drugs will work and have been used for many years to treat this disorder, but the problem is that you have to give them in fairly large doses, often in this country 60 to 80 milligrams a day. This disease tends to be chronic, and therefore you have to give it a long time. You need to give it in fairly large doses, which produces significant side effects such as thinning of the bones, diabetes, cataracts, glaucoma, and other things.

So one of the main reasons I would give thalidomide to you is to avoid these side effects from prednisone, which is really the only good alternative.

Thalidomide, in our experience, works. It allows people to return to work. It allows them to get off of their prednisone, or at least in much-reduced doses, and therefore is a god-send to many of these people who really have no other alternative.

It has been recognized by the treatment of choice by many leprologists for many years. There is a rather extensive body of literature. In our experience, it has been found to be very effective.

We do not, however, ignore or forget the serious disadvantages and side effects of this drug. If I were going to give this drug to you, I would certainly start out by telling you the serious birth defects that can be caused if it is given to women of childbearing age. Therefore, pregnancy is an absolute contraindication, and under the present program -- I am not giving you this as necessarily my opinion of how it should be done. Under the present program, under the IND that we have, it cannot be given to women of childbearing age anywhere in the United States, except at Carville.

Therefore, we can give it as outpatients only to men or to women who have been surgically sterilized or women who are postmenopausal. This does limit access of the drug to some women who would certainly benefit from it.

There are a number of other side effects that every patient would need to know about. One, of course, is sedation, particularly in the larger doses. Patients would need to be warned about the fact that they should not drive or engage in other hazardous activities which would endanger them if they were sedated.

Neuritis, which has been mentioned, which will be talked about some more, we would talk about at some length. We're also dealing with a neurologic problem with leprosy as well. So patients are very much warned about the possibility of new numbness, tingling, any change which might indicate a problem with the nerves, and that we need to be advised so we can do appropriate testing and evaluation to see if indeed this is due to the Hansen disease or leprosy itself, or whether there might be any reason that it might be connected to the use of thalidomide.

There are less common, less serious side effects associated with it -- sometimes dizziness, constipation, swelling of the extremities -- which are usually mild and do not necessitate discontinuing a drug.

So I would say in conclusion, with many years of experience and the experience of other people who have used this drug, we have found it to be very effective in use in these patients which would allow them to avoid the serious side effects of prednisone and allow them to continue their reasonably normal activities of work or whatever they might be. If properly monitored and given according to instructions and used only by the patients for which it is indicated, I think the risk can be minimized to an acceptable level.

Thank you.

(Applause.)

MS. TOIGO: Thank you, Dr. Yoder. I can say I've learned far more about thalidomide in the last two years than I did as a pharmacist in the outpatient pharmacy in the Staten Island Clinic, where once a month we had a Hansen's disease clinic.

Our next presenter is Randy Warren.

One more thing. If you have questions after the speakers, Carol is going around collecting. So if you flag her, she will get them.

MR. WARREN: My name is Randy. I'm 36. During her pregnancy, my mother was prescribed thalidomide to alleviate severe morning sickness symptoms. My mother took thalidomide twice, two teaspoons total. Thalidomide caused my birth disabilities, necessitating 32 operations over my life and eight years accumulated time spent in the hospital before I was 16, in a different city from where my parents lived.

When I was 12 years old, I looked at my chart on my hospital bed and I read the words, "congenital anomalies as a result of the drug thalidomide." I learned, and I continued to learn what happened to me and to my friends 40 years ago.

Today, I describe myself far more professionally, as a founder and CEO of the Thalidomide Victims' Association of Canada. I represent the 125 Canadian survivors of the drug that violated our mothers and betrayed their doctors. Many of our mothers and fathers were doctors and pharmacists.

I speak for thousands of unborn babies, murdered as they were to grow. I speak for the 50 to 60 percent of us born who died young. There are 5,000 of us alive today.

I came here today to dazzle you with my eloquence and the triumph-over-tragedy stories of my brother and sister thalidomiders. That's what we call ourselves, thalidomiders, lest we forget. But I kind of feel somber and resolute. I grieve, yet I feel conviction and a sense of purpose. It's been a really, really tough week for us.

In 10 minutes, I want to say so much. I want to tell you of brave women raising children expected to live to be only 10 years old, and then 20 years old, and now we're told 55 years. But I know these children, now adults, and I am one. We want to enjoy our grandchildren and great-grandchildren, those of us who can have children. Some of us, I know, will live longer. But nobody can really say what can happen to us until we're all gone.

We thalidomiders, we're a family. We were all born together in the same few years, whether we're from Japan, Australia, Germany, Great Britain, Sweden, Brazil, or Canada. We even look alike. We know each other, and we understand each other without words. We want you to understand us. After all, today is yesterday's tomorrow. We are you. We're your brothers, we're your sisters, we're your mothers, we're your fathers. We're the people that you marry; we're the people that you broke up with before you intended to get married.

We feel. We laugh. We cry. We love, and we are loved. Yes, we suffer. We're degenerating. We're deteriorating in ways we were never warned of by doctors or scientists or persons who develop artificial limbs to make us look like everybody else. But these things should have been easy to predict.

We who know pain and uncertain futures extend ourselves, our empathy, to those who suffer from other unjust diseases and conditions where thalidomide might help.

Thalidomide, I have heard, takes people out of wheelchairs, and so much more. But please respect and remember the fact that thalidomide put me in my wheelchair. Thalidomide gave many of us shortened arms, or no arms, meaning we can't hug back. We can't comb our own hair. We can't even touch our own backs.

We of the Thalidomide Victims' Association of Canada will never accept a world with thalidomide in it. We cannot. But we cannot fight thalidomide. It wins every time.

We're forced to prefer regulated thalidomide over illegal thalidomide available on street corners, without warnings. We who know suffering cannot deny quality of life or longer life to others who suffer. We demand mandatory compliance with strict distribution systems. Thalidomide must never be a drug of choice, but always of need or last resort.

We demand forced research into new analogs to replace thalidomide, with all of the benefits but without the teratogenic and disconcerting nerve damage side effects. When the new analog or drug is developed, we demand the removal of thalidomide from this planet.

Thalidomide must always be called thalidomide -- no glory names, just thalidomide. As you, the United States of America, prepare to license the drug, we beg you to remember us. As much as we need to be involved in this process, you need us as a moral compass, as a picture of what can happen, and what did happen.

We can help. Let us help. We have a right to help and to be heard.

We thalidomiders must educate about what happened so it never happens again. We insist we be involved as constituents of this drug in monitoring the distribution process and in educating potential patients, prescribers and dispensers, and the public at large. We demand media act responsibly in reporting the benefits of this drug. Always be balanced, and also always be sure you're giving legitimate hope to hurting people and not false cures.

We insist that doctors and pharmacists who are the prescribers and dispensers be certified to use thalidomide by attending workshops and seminars cosponsored by us. We caution that off-label use increases the likelihood of American thalidomide children being born. We know that there will be more thalidomide children with licensing.

We believe patients considering thalidomide must have access to all information of all side effects, with warnings being given in consistent, plain, simple language. Patients must make their own, however, risk-aware choices.

Our role is clear. We're going to be watching. We will be educating, and we will be reminding. We will be waiting for the day thalidomide is a historical painful memory.

So everybody has been asking me over the last couple of weeks how do I feel, or how does my mom feel. Well, I feel proud of my 125 thalidomide co-survivors who reasoned a position of compassion through their fear. But we are afraid. By not opposing regulated thalidomide, we now have expectations. We expect patients to act responsibly. We expect that the appropriate authorities will stop the illegal distribution of thalidomide. We expect to be heard.

People pause today during pregnancy before they take a tablet, before they smoke, before they take a drink, knowing that it could possibly affect the fetus. Nobody knew that before us. We are a legacy, and we've given a lot to this world. We would hope some respect back.

Now as it appears that thalidomide is about to be regulated, our fears fall to hidden agendas in other countries where thalidomide is relegated to secret access programs or emergency distribution programs. Let's bring thalidomide to the forefront so that we can all speak about it and so that we can make those determinations whether the benefits actually outweigh the risks.

On a final yet opening note, it will be in the interests of future children and mothers to talk with us. We will be there. I hope that all of you take the opportunity to talk to me regarding the friends that I have around the world in various countries who are thalidomiders and learn our experiences.

I spoke last night with several of the American thalidomiders who are shy and didn't want to be pursued by paparazzi or gimmicks. They are quite pleased with the position that we have taken, which we constructed with them. They are members of our association as well.

The very final note I have regards our collaboration with drug companies. In particular, we have had some meetings with Celgene Corporation, and this is part of our approach to attack thalidomide from every angle. We believe we have a voice in every aspect.

I want to remind the FDA that we're going to be there. We're going to be watching, and we're going to be communicating on a regular basis. We want to remind other drug companies that may come forward that they may come forward with thalidomide, but learn from consultation with us what the safest mechanisms for distribution will be.

So I pause now, as everybody should before they take the drug thalidomide. I pause, hoping that everybody will read the warnings that are constructed in plain, simple language. Hopefully everybody will go and find a video with a testimonial from a survivor. Learning from us, just seeing a North American survivor I think will be the best mechanism to protect women and children.

(Applause.)

MS. TOIGO: Thank you, Mr. Warren.

Now we'll hear a perspective from the pharmacy profession.

MR. ZELLMER: Good morning. It's a pleasure to be here at this very important conference. My name is William Zellmer, and I work for the American Society of Health-System Pharmacists.

The teratogenicity of this medicine obviously requires extraordinary measures to prevent fetal exposure and birth defects. In this regard, the situation is similar to that associated with the use of isotretinoin, or Accutane. Practicing pharmacists can play an important role in a system that is designed to ensure the appropriate use of thalidomide, but that role is much broader than currently exists in the distribution system for Accutane, where pharmacists have a fairly limited function.

Because the pharmacist is at the final point in the health care system before the patient receives the medicine, the pharmacist should be expected to do at least these four things, I believe: first of all, verify that the patient, the thalidomide patient understands the risks associated with the medicine; second, verify that any patient who is a woman of childbearing age is practicing birth control; third, advise all patients about the side effects of the medicine and what precautions to take if they occur; and four, advise patients about what to do with any unused dosage units.

Now, these are points, of course, that will have been made with the patient before he or she sees a pharmacist. But the pharmacist can provide a valuable service by reinforcing the

information, answering any questions that have occurred to the patient since seeing the physician, and in general ensuring complete patient understanding.

Given the risks associated with the use of thalidomide, it is entirely appropriate -- entirely appropriate -- to impose on participating pharmacies compliance with specific procedures designed to ensure the product's safe use. Any pharmacy that demonstrates that it understands these requirements and is prepared to comply with them should be allowed to handle the product. Thalidomide patients will be using other prescription medications, and it will be a great convenience to them to be able to obtain their thalidomide at their regular pharmacy.

I have been briefed by Bruce Williams of Celgene about his company's current thinking about product distribution. As I understand it, those plans include the following critical points. First of all, the participating pharmacy would enroll in the thalidomide registry system, which would signify the pharmacy's understanding of the distribution process and its agreement to comply with the stipulations of that process.

Second, the participating pharmacy would obtain the product through a designated wholesaler distribution channel which would verify that the pharmacy is registered with the system.

Third, the pharmacist would verify that the patient has read and signed an informed consent form.

Fourth, the pharmacist would enter certain information about the prescription into an online adjudication system which would verify that the patient is registered and it would authorize dispensing.

The fifth point in this system is that the pharmacist would dispense only a 28-day supply in the original package, which would contain written patient information.

The sixth point, no refills would be dispensed. Each new supply of medication for the patient would require a new prescription.

Now, these provisions appear to be well-conceptualized, and I think that Celgene should be commended for its initial planning on these matters. There is precedent for successful pharmacist participation in systems of this nature in the Clozaril treatment system of Novartis.

However, I encourage Celgene and public health officials to expand their preliminary thinking to include the following two points. First of all, I think it would be quite appropriate to require the participating pharmacist to engage in a substantive, relevant dialogue with the patient covering the points I mentioned earlier. Second, I think there should be recognition of the additional professional service of the participating pharmacist through an appropriate level of compensation by the drug manufacturer.

Oral counseling of patients by the pharmacist is becoming a standard of practice. It can play a critical role in fostering patient adherence to treatment and patient understanding of the risks of treatment. There are currently many barriers to oral counseling by pharmacists, and the profession is attacking them.

For example, later this month the National Pharmacy Practitioners Organization in the United States, representing pharmacists in all types of practice sites, are sponsoring a major consensus conference that will analyze the barriers and what can be done to expand the practice of pharmacist oral counseling.

It would be unfortunate for thalidomide patients if the pharmacist is not encouraged to assume a meaningful role in ensuring safe use of this medicine after it is approved for marketing. Meaningful responsibility for the pharmacist will entail significant, professional time well beyond that required for handling the typical prescription. This should be recognized by the manufacturer through appropriate compensation to the participating pharmacy.

In summary, pharmacists have a potentially important role to play in ensuring that the public health benefits of introducing thalidomide to the market outweigh the risks. In the interests of the patients who will be using thalidomide, I urge the manufacturer of the product and the public health community to capitalize on the pharmacy profession's willingness and ability to make this potential role a reality.

Thank you very much.

(Applause.)

MS. TOIGO: Thank you, Mr. Zellmer. I think we'll all be interested in hearing more about the barriers to oral counseling.

Our next health care practitioner organization that we'll hear from is the American Medical Association, and Dr. James Allen.

DR. ALLEN: Thank you. I'm pleased to have a chance to be here this morning and to participate in this meeting.

The title of the presentation is "The Physician's Perspective." I think a disclaimer is in order -- truth in labeling, if you will. Let me say that this is a physician's perspective. We have already this morning heard from many other physicians; we will hear from more this afternoon, as well as tomorrow. I think it represents a real diversity.

Second, what I'm about to say will represent simply some of the concerns that might be expressed by some of the physicians who are in practice, as opposed to those who are primarily doing clinical research or are in academic settings or working for pharmaceutical companies, or for the federal government agencies or others.

It's not even an AMA's perspective. I say that because, although the AMA does have a considerable body of policy on prescribing issues and practices, there are none that refer directly to this situation, to the drug thalidomide itself, or to the circumstances that we're discussing today.

From the AMA perspective, however, this is an extremely significant meeting. The whole process is one that is extremely important. We laud this and are very grateful to be able to participate in this discussion, a discussion that started in the past, is continuing today, and will need to continue in the future.

The title of the workshop, "Potential Benefits and Risks," captures the essence of the issue. How do we establish a system to maximize the potential benefits, and minimize, or even eliminate, the risks? The task that has begun in the past, as I said, must continue today and through into the future, must be an open process that involves all interested parties.

Given the tragedy of the birth deformities that occurred in the early 1960s, it is a real tribute to both the perceptiveness and the tenacity of physicians and scientists who perceived the potential for other uses of thalidomide and have been investigating these uses very vigorously over the ensuing decades.

Dr. Woodcock was absolutely correct this morning when she stated that good clinical trials are absolutely essential. They are, and they must continue. The use of thalidomide for appropriate clinical trials should not be a problem if the clinical investigators are well-informed and dedicated to reducing risk for patients. The issues of informed consent, patient and family education, pregnancy testing and prevention, and appropriate follow-up can be reasonably well controlled in well-monitored clinical trials, although issues such as pill-sharing and noncompliance certainly do exist.

The more critical questions arise with approval of the drug for marketing, particularly as information continues to accumulate about the potential utility of thalidomide for a much broader range of diseases and conditions, as we have heard at this workshop, or will in the next day or two, and for a much larger patient population.

Therein lies the real problems in terms of application in the clinical setting. The March 26, 1997 conference at the Centers for Disease Control and Prevention, titled "Preventing Birth Defects Due to Thalidomide Exposure," apparently will result in a set of recommendations that might guide the setting of restrictions around the availability of thalidomide. These will, I understand, be presented later this afternoon in a discussion here.

Certainly there are models. The Accutane issue has been mentioned, and other drugs also can be considered as models that might be applied in some way, or modified as appropriate for use with thalidomide. Certainly these restrictions probably can be appropriately worked out.

In essence, the type of control mechanisms that might be implemented with thalidomide

include the following: restrictions on the labeling; provider education and certification, and that goes both for physicians and pharmacists, and perhaps other providers; product packaging and dispensing that restricts access and the amounts that would be prescribed, as we heard earlier; careful patient selection and verification of that selection; for women with childbearing potential, the requirement for pregnancy prevention and monitoring.

Most reasonable people would support these general guidelines as being a very good first step. There are many details that need to be worked out, however, and resolved before these general guidelines, or something similar, could be put into place. I think that discussion will continue this afternoon.

Physicians in practice will have concerns about any system, however, that is too restrictive or onerous in terms of paperwork or time required, or just the hassle factor. I think this is especially important, given our current setting when managed care organizations are requiring physicians to see more patients per hour, to spend less time with them and to follow a variety of other practice restrictions with an intent to limit the cost but that also limit the ability of the physician to provide the best care for each individual patient.

The AMA, and most physicians in practice, feel strongly about the flexibility for physicians to prescribe the pharmaceuticals that are most appropriate for their patients. The freedom to use drugs for off-label indications is extremely important, and it always has been in medical practice in our country, and it should not be abridged, even in this special instance.

I believe this is particularly important, given the wide range of disease conditions for which thalidomide is currently being studied, and may well be found to be an appropriate indication. It is highly likely that medical knowledge will run well ahead of the FDA regulatory process to approve a drug such as thalidomide for new indications.

Another potential issue is any system of physician selection and accreditation before being allowed to prescribe thalidomide. Certainly education is appropriate. But the greater the indications for use, the more difficult it will be to have a functional accreditation program for prescribers. An accreditation program also implies a process for decertification or loss of accreditation. This needs careful discussion. Who will have control over such a system? My initial reaction is that this should be handled through state licensing boards rather than through other mechanisms.

Another issue for physicians is writing the specific diagnosis on the prescription. While this would be an important part of a verification program for appropriate patient selection, it also is a potential source of information about patients and their illness that physicians are reluctant to provide because of concerns about patient confidentiality and breaches of confidentiality.

In conclusion, I want to come back to the purposes of this workshop, an examination of benefits and risks, and keeping these in perspective. Part of this examination is evaluation of access when indicated, with appropriate safety precautions to address the serious concerns

about uncontrolled use of thalidomide. One of the access issues is to assure that the safety system is not so onerous or overbearing that physicians and patients are discouraged from using it, or, just as bad, that it is circumvented.

Finally, our focus today is on decisions within the United States. We all must be mindful, however, that today we truly live in a global environment. We must develop the best system for our country, but we need to share our knowledge and experience with our counterparts in other countries of the world as we learn also from our international colleagues and their experiences.

Thank you.

(Applause.)

MS. TOIGO: Thank you, Dr. Allen.

Our next speaker is **Cindy Pearson** from the National Women's Health Network. We at FDA are fortunate to have frequent input from the National Women's Health Network, and this is one more opportunity.

MS. PEARSON: Thank you. I've added a couple of remarks to my prepared comments, and I'll do my best to keep myself on time.

We're really glad to get the chance to participate in an interdisciplinary, open public scientific meeting, and commend both the NIH and FDA for putting in the extra effort that's required to pull off a meeting like this, but I have to say I am very puzzled at the fact there are no mikes on the floor, and want to throw out a challenge to the organizers to get mikes on the floor. We have such a wide range of people, both on the panels and in the audience, that it would be a shame to miss the opportunity for interactive dialogue back and forth. I hope the organizers will see the light, and bring us some mikes.

I've also added a little introductory remark about, why is the Network speaking today? Terry is right. We often give comment to the Food and Drug Administration, and had a chance to do that last week at the advisory committee meeting. But what is our role today? We have already heard from a thalidomider, from a physician taking care of leprosy patients, we will hear from someone speaking on behalf of a person with AIDS, and we've heard from a bioethicist who talked about balancing the rights of fetuses and women. What can the Network add to that?

Well, if things were easy, I'd like to say, well, we're a feminist organization, so I'm here to tell you the feminist point of view. But I can't do that, because Randy Warren is a feminist, as all of you who have heard him speak know. Dr. Fost, the bioethicist -- his remarks were obviously informed by a familiarity with the feminist literature of reproductive rights.

So what do we add? Well, the Network represents, for those of you who don't know us, the organized women consumer response to the felt need by the majority of consumers, male

and female, for safe drugs, especially those that are used over a long period of time by healthy people, and most importantly for information about all the drugs that are used, whether for short or long-term, and by healthy people or people facing a serious condition.

We in the Network, and many in the women's health movement, see part one of the thalidomide story as part of the beginning of our movement. I want to read to you something I wrote three years ago on the occasion of Dr. Kelsey's 80th birthday. After telling the story much as she told it this morning, I said that "The Kefauver-Harris amendments to the Food and Drug Act created the regulatory groundwork for many of the advances of the women's health movement.

"By the late 1960s, feminists began to insist that women had the right to information about their bodies, and the drugs, devices, and medical procedures that doctors recommended. Without the requirement that safety and effectiveness information be submitted to the FDA, the women's health movement would have had a much harder time making that information available to women."

That's what I think I have to offer you today, not just a feminist perspective, but a perspective of a movement that wants as much information as possible, and for individual patients and consumers to play as large a part in the decisionmaking role about their health care as they choose to.

So what do we face now? We face a situation with thalidomide where this one drug brings us face to face with a series of problems that have never adequately been solved in our society. We have to talk about the way to move forward with thalidomide in the context of these unsolved problems, which range from unplanned pregnancy, physician behavior, and stereotypical assumptions. So I'm really casting a wide net, not just what happens in the exam room in a conversation between a physician and a patient, but what happens outside it.

Well, first of all, should we even try to grapple with these very hard problems that no one has found a way to solve yet? The question of whether or not we should try is obviously the question about is there enough evidence of efficacy of thalidomide to even make the conversation about can we deal with the hard problems necessary? Others have talked about that, and in the interest of staying on time, I'll skip that part.

So, given that there is a vote of at least one advisory committee, after much discussion and thought, that the benefits of thalidomide outweigh the risks of thalidomide for one particular use, let's start to talk about the problems we face.

One problem is physician behavior. As a consumer, I feel like it's important for consumer viewpoint on physician behavior to be heard. We know that we all benefit, as we've just heard from a physician's perspective from the appropriate off-label use of medication. But any of us who are students of the history of medicine know that at times people have been hurt by the inappropriate off-label use of medication.

We know that most physicians do a fabulous job of getting to know and talking with their patients, but that some physicians sometimes do an inadequate job of thoroughly counseling their patients about the risk and benefit of treatments that are being advised to them.

So our recommendation as a consumer group is that we together craft strategies that support the good behavior of physicians; that physician education materials be developed that lead physicians to the logical conclusion that off-label use should only be reserved for the most serious of conditions, where there is substantial evidence of benefit; that patient counseling is of the highest importance; and that whatever fights physicians have to have with the people who are standing outside their doors with stopwatches need to happen, so that the patient gets enough time.

Written informed consent should be required for thalidomide. That's out of the norm. Written informed consent is usually reserved for surgery and experimental drugs, or drugs under investigation. But on this one, we believe that written informed consent for both male and female patients is absolutely necessary.

We also believe that tracking systems should be put into place which are not too burdensome to the individual physician, but can evaluate the appropriateness of use of thalidomide, and at least the reproductive outcomes of the use of thalidomide.

So if we can begin to address some of the problems of physician-patient interaction, then let's next turn to addressing the problem of unplanned pregnancy, which the 200 or so of us in this room can't completely solve because, as those of us who working in family planning know, over half of all pregnancies in the United States were either unplanned or unanticipated. That means either someone didn't expect to get pregnant or was actively trying not to get pregnant.

So given that that's the context in the United States right now, a pregnancy test before the first prescription of thalidomide should also be mandatory. Every ovulating woman should have a pregnancy test before she begins taking thalidomide. That's just a must. Many women are very in tuned with our bodies, and know pregnancy signs, and can recognize them early, but not everybody. So that's a must.

Then the discussion and use of contraception. That obviously is also a must. We've heard no disagreement on that, but I just want to throw in a word that, although Medicaid and managed care organizations are very good about covering all approved methods of contraception, private third-party insurance is not. A substantial number of insurance programs do not give coverage for contraception, particularly reversible contraception. So physicians may have to play a role of the social worker in making sure that women are able to get, and start using, the contraception that we want.

I want to take a minute to talk about repeated pregnancy tests as pregnancy prevention. This is like cancer screening. Early detection is not prevention. Now, I am not at all saying that everyone involved in the use of thalidomide wouldn't want a woman using thalidomide to

know as soon as possible that she were pregnant, nut if she's already using thalidomide, even if it's not to the day in which the organ systems are at risk, I can't believe that that woman isn't going to feel that she's already exposed her fetus, that the primary prevention opportunity has been missed. So let's certainly talk about repeated pregnancy tests, but be clear about what we're using them for.

Then, in my less than one minute left, I want to talk about stereotypes. I said that the consideration of the use, the mainstreaming, of thalidomide would lead us to challenge stereotypes. The first stereotype that needs to be looked at and examined and challenged is that all women who ovulate and have open fallopian tubes are at risk of pregnancy.

I'm here to tell you that's not true, that people who are involved in the provision of thalidomide need to respect the reality that some ovulating women are celibate; some ovulating women are lesbian; some ovulating women are sexually active with men, but are not having reproductive sex. That needs to be treated respectfully, and physicians involved, clinicians involved, in the care of people who are considering thalidomide need to be sensitive to that.

The second, and contradictory, stereotype is that young women who are ovulating are not having sex because they should not have sex. Now, most of us probably realize that that's not true, that there are shockingly young women who are sexually active, but many of them cannot be honest about their sexuality with an adult, even with a supportive and caring clinician. So physicians and clinicians need to make sure that both young women and their parents understand that contraception is a necessary part of the use of thalidomide.

I would also like to challenge what is often the most uncomfortable stereotype for us to look at, but based on the history that we've heard from Dr. Yoder, and some of the comments we heard at the FDA meeting last week, the stereotype is still in force and directing the actions of some people. That stereotype is that women, or at least some women, can't either be trusted or can't seem to manage their lives in a way to use contraception consistently.

I find it shocking to learn that for over 20 years the federal government has required premenopausal women to either be sterilized or hospitalized to use thalidomide. I think that is unacceptable. Whatever else happens with the mainstreaming of thalidomide, that needs to change.

Now, it's true that no woman can protect herself against sexual violence and rape. All women who are ovulating, however they describe their sexuality of choice, should be given a prescription for emergency contraceptive pills so that they can immediately institute contraception if they are raped.

But beyond that, I think we have to accept that free-living women in the outpatient world, after adequate counseling and adequate logistical support in getting contraception, can make good decisions to use and keep using contraception. We should encourage women and expect women to choose the most effective contraception that is acceptable to them, but we

should not take away their freedom of choice as to what that most effective contraception that works for them is.

I guess I'm way past my time, so I'm just going to stop without any grand sum-up here, and hope that we'll have a chance to talk more in the question and answer period.

(Applause.)

MS. TOIGO: Well, Cindy's always good for the challenge. As an organizer, I guess we'll have to work on the microphone issue. It was a risk/benefit decision, I suppose, and we thought that the public session tomorrow would allow us to get the questions that we didn't get today, but I think we heard you.

Our final speaker is **Mrs. Nancy Paller**. I will let her tell you her story.

MS. PALLER: I'm really honored to be able to participate in this panel, and to be able to give you a mom's perspective on thalidomide.

In November of 1991, I took a vacation to Cancun. I was trying to recover from the loss of my husband, who had died earlier that year from a long illness. He had been sick for nine years. The first five years, he had intractable rheumatoid arthritis, and was almost bedridden. The last four years, it had been compounded with lymphoma, and he was incredibly sick, and very, very much in pain.

But when I returned from this trip, I was feeling good until I saw the three messages on my answering machine. The first message was, "Hi, Mom. This is Richard." Richard always told me who he was, even though a mother knows her son. "Hi, Mom, this is Richard. I'm sick and they're going to put me in the hospital."

The second call was, "Hi, Mom. This is Richard. I'm in the hospital, and they don't know what's wrong with me, but they're going to put me in intensive care."

The third call was, "Hi, Mom. This is Richard. I'm in intensive care. The nurse just brought me the phone. They say I have something like septic shock, and I can't breathe, and they're going to put a tube down me so I can breathe."

There were no more messages.

I was terrified, and I dialed the phone, and I called Santa Barbara from Chicago. I found out not only was he out of intensive care, but he was back home and doing well. He had stabilized, and he was okay. But I thought about that call, and I thought about why would a 25-year-old boy go into shock from an appendectomy that happened six months ago? It didn't make sense.

So the next day I called him, and with that call, I found out that my son was gay, and that he had AIDS. He was well enough by January of 1992 to come and visit me in Chicago. I

learned to know and love his partner, Dan. I learned a deeper respect for my son, and a greater love than I had ever known before.

I visited them in July of 1992, and it was an uneventful trip in Santa Barbara, if Santa Barbara can ever be uneventful. He was in great health and totally stable. But by the end of the summer of 1992, he had been attacked by CMV, wasting, and upper rectal ulcerations.

Early December 1992, we decided we couldn't wait to celebrate Christmas. I needed to go the beginning of December, because we didn't think he would live until Christmas. He was down to 130 pounds, and he was practically bedridden. All the way home on that five-hour trip from Santa Barbara to Chicago, I was sure -- I knew I would never see my son again.

But late December, his partner, Dan, had smuggled some thalidomide in from Brazil. He started it immediately. They told me about it, but I'm a registered nurse. I worked ICU/CCU. Thalidomide was a bad drug. This isn't going to help. I thought maybe it would act as a placebo, at the most. So each day I called, and each day he was getting better. Each day he was getting stronger. Each day they told me it was working.

My question, as a nurse, was is this real improvement or is this wishful thinking? So we decided to plan for my next trip. We decided I would go out there in May of 1993. It was his birthday, it was Mother's Day, it would be great. I could only travel to Santa Barbara when I saved up enough vacation time, and enough money to fly there, so the anticipation was nerve-wracking. Would he look as good as he sounded? Would he be as good as he said he was?

When I got off that plane, it was more than any mother could ask for. He picked me up, driving in his red Z, dressed like a Southern California, weighing 180 pounds, and looking like a Greek god. He still had his little donut that he had to sit on, but he was driving. I thought, maybe my life stories don't all have to end the same way. Maybe people can have a bad illness, and still live.

But while I was in Santa Barbara, I found out that our Brazilian connection had gone dry. As a nursing skeptic, I thought, well, it's not going to matter, but as a mother, I froze. Richard did start to deteriorate immediately. He was dying again.

While caring for my husband, I had been faithful to my orthodox medical treatments -- only the prescribed, only the tried and true, only the protocols we knew, only by the book. But with my son, I throw away the book. I mean, I went through the streets of San Francisco looking for thalidomide. I even bought good marijuana, but that's another story.

(Laughter.)

MS. PALLER: I was not going to let my son die. I became a mother with a mission. Let me tell you, don't ever get in the way of a mother on a mission.

I called my senators, I called the Congressmen, I called the President, and I called the FDA.

The FDA responded quickly. They responded proficiently, politely, and, most of all, positively. They immediately started my son on an independent study providing him the thalidomide, and allowing it to be administered by their local physician whom they loved and trusted. He had a rapid response, and within two days, I received a call that Richard had driven to Burger King, and was on his second Whopper. It was wonderful.

Because of thalidomide, Richard had a chance to experience so many things that he would not have experienced otherwise. He was able to go with Dan to Catalina, and even to Hawaii. He was able to spend quality time with his partner, Dan, who loved him and cared for him, and stayed with him to the end. He was able to develop and share the knowledge that love is the only important thing. His last words were, "Love is all there is." He was even able to see his mom remarried in May of 1994.

But in July of 1994, Richard lost his battle to AIDS, with multiple complications. But because of thalidomide, he had been able to live the last year and a half of his life with a quality of life and a standard of life that the normal AIDS drugs could not provide for him.

My wish is that other mothers and fathers and friends don't have to see their loved ones life shortened or compromised because of the lack of a drug that I personally have seen make a difference in someone's life. If administered sooner, or with better medical assistance initially, who knows what that drug could have done? I know the alternative was worse.

My wish is that thalidomide be made available to others, so that they too may benefit.

(Applause.)

MS. TOIGO: Thank you, Nancy.

We have a couple of questions here. I'll read them for the group. This is for Mr. Warren. "Considering Dr. Fost's presentation, which emphasized proven efficacy, do you think your or the public's interests were protected by the fact that the first NDA was considered under orphan drug status or by off-label use?"

MR. WARREN: To be critical, as far as I'm concerned, the first application should have been an honest application that was involving HIV/AIDS wasting.

MS. TOIGO: This is just a comment by a physician in Texas: "In the 1960s on TV in West Germany, I saw a program on a medical museum or display of anatomical specimens of deceased thalidomide babies. Does any of the panel know of this museum, and could that TV program be used for educating the public? I know I will never forget the program."

Any comments from the panel? Okay. This is also for you, Dr. Allen.

DR. ALLEN: Let me just respond briefly. I don't know anything about the museum, but certainly, to the extent that there is useful information that could be put into educational programs for health care providers, for professionals, or for the general public, I think it

would be very useful.

I think we're going to need a much wider range of discussion than we've had to date, with a lot of fairly graphic examples. On the other hand, we certainly want to avoid any scare tactics or, you know, sensationalism. So it's got to be well-handled. If there is useful information out there, it ought to be looked at very carefully.

MS. TOIGO: Thank you, Dr. Allen.

Did you have another comment, Randy?

MR. WARREN: I was just going to comment why there are not a lot of thalidomiders present at the fight. It's simply because of that sensational aspect. Throughout history, persons who experience phocomelic disabilities have been the fodder for sideshows.

MS. TOIGO: Thank you.

"Ms. Pearson, what of a married couple with religious objections to contraception?"

MS. PEARSON: Whoever you are, you're mean, coming up with the hardest case. I don't know what to say. I know that in general it's wrong to give government or medical authorities the power to run other people's life. I know that I personally, as an individual, probably share the feeling that most of the rest of you as individuals share, is that it would be morally wrong for people who are, for their own reasons, uncomfortable with contraception, and yet having vaginal intercourse, to use thalidomide.

So balancing those two things is a terrible quandary.

MS. TOIGO: Thank you.

This is also for you from Dr. Fost, who has identified himself on the question. "The purpose of repeated pregnancy testing is to withhold the drug unless the test is negative. Used this way, it is a prevention program."

MS. PEARSON: If you think that requiring another pregnancy test changes behavior beyond the requirement of counseling and education and contraceptive and the facilitation of getting the contraception, you could be right. I'm not sure there's evidence that requiring repeated pregnancy tests changes behavior.

MS. TOIGO: Thank you.

"Mr. Warren, what is your position regarding the research and potential approval of other drugs that may have significant effects on the fetus, especially those that work on blood vessel formation?"

MR. WARREN: I think our position would be consistent with the position that exists now.

Some teratogenic drugs may be effective in the short term, but our goal should always be to eliminate them. Further than that, I think that the distribution system that I've actually had the privilege of reviewing and having some comment into that thalidomide hopefully will undertake should become the model for the industry.

MS. TOIGO: Thank you.

This one has two questions. "Is there a possibility to develop thalidomide in a time-release capsule, which would make distribution less cumbersome?" I'm not sure someone on the panel wants to address that. I guess there is always the possibility to develop something. It's just developing it.

Then the other question was related to developing a different version of thalidomide. I think thalidomide analog discussions are going to take place in the clinical pharmacology section tomorrow.

This one, I think, goes to Mr. Zellmer, in terms of commenting on it. "How will the FDA and drug manufacturers' very restrictive drug dispensing scheme address the limitations placed on patients whose pharmacies are not participating or approved by FDA or the manufacturer when the patient's insurance company or health care provider mandates the use of that pharmacy? What about mail-order pharmacies, and what about rural and underserved areas?"

MR. ZELLMER: Those are very good questions. I'm afraid I don't have specific answers to the situations posed there, although I think, as I understand sort of the thinking that the manufacturer has gone through in devising the registry system, they would be equipped to find a source for the patient who is registered with this system.

The point I was trying to make is that pharmacists are in a critical spot in the health care system to reinforce all of the information I think we all agree patients who are taking thalidomide need. I find it hard to contemplate that that can be done well with a mail-order type pharmacy.

It also strikes me that the uses that are being contemplated immediately and long-term for thalidomide are with patients who are going to be taking many medications, and probably have an established relationship with a pharmacy, so it makes sense for thalidomide to be available at their pharmacy.

With respect to insurance coverage, yes, I think this is a big problem. That was one of the reasons I was advocating that, for the additional professional services from the pharmacist that I believe should be fostered, the compensation would come from the manufacturer to the pharmacist, and that essentially the price of the product would build that into it.

MS. TOIGO: Thank you.

I've been reminded that our afternoon session starts at 1:15. So if we don't leave for lunch

now, I'm going to have to pay for it.

Thank you all, and thank you very much to the panel members.

(Whereupon, at 12:25 p.m., the meeting was recessed for lunch, to reconvene at 1:15 p.m.)

AFTERNOON SESSION (1:20 p.m.)

DR. BIRNKRANT: Good afternoon. This afternoon's session deals primarily with safety monitoring and adverse events seen in patients who receive thalidomide. Both sessions this afternoon actually cover this broad topic, which is of critical importance in the clinical development of thalidomide.

The first session deals with IRB-related issues. I'll give an overview of some regulatory considerations in the safe use of this drug. The other speakers for the first session will deal with neurotoxicity. The second session will focus primarily on pregnancy and embryopathy-related issues.

Our first speaker is **Dr. Melody Lin** , who will discuss the role of the institutional review board in the protection of human subjects involved in thalidomide research. Dr. Lin is from the Office for Protection from Research Risks at NIH.

DR. LIN: Thank you very much. Good afternoon. I'm delighted to be here, and I'm very honored to represent the Office for Protection from Research Risks, also known as OPRR. My title of the presentation is "The Role of the IRB in Protection of Human Subjects Involved in Thalidomide Research."

I have three objectives for my presentation. First, I would give you an overview of the ethics and the regulation of human subject research. Second, I would like to describe the IRB review process, and the informed consent process.

There are three ethical principles that guide the ethical conduct of biomedical and behavioral research. The three ethical principles are the respect for persons, the principle of beneficence, and the principle of justice. These three ethical principles provide the guidelines for the protection of human subject research.

The principle of respect for persons acknowledges the dignity and autonomy of the individual, and for those with diminished autonomy, it requires special protection. Therefore, it is important to give informed consent prior to research.

The principle of beneficence obligates us to maximize the benefits and minimize the risks. It is required to carefully examine the research design and the risk/benefit assessment.

The principle of justice requires us to treat the patient fairly. The principle of justice requires equitable selection of the subject, in light of research settings. Not any given group or class of subject can be automatically included or excluded unless a comparative justification is

given.

The Public Health Service Act requires the Department of Health and Human Services to issue a regulation for protection of human research subjects, and it is codified as 45 CFR 46. The 45 CFR 46 requires additional protection to vulnerable subject populations, such as pregnant women, children, fetuses, and prisoners. It is important for me to point out, in addition to the Health and Human Services regulation 45 CFR 46, FDA has similar regulations. One of the differences is, the Health and Human Service regulations regulate research, and the FDA regulation for implementing protection of human subjects regulates the product approval for marketing purposes.

This slide summarizes the policies and the regulations for the protection of human subjects. Prior to research, there needs to be committee review of the research protocol. That is what we call an IRB. It also requires a risk and a benefit assessment of the protocol, and prior to research, we need to have the subject give informed consent. Therefore, the IRB is the cornerstone of the American system of protection when involving human subjects in research.

The IRB review process. This slide lists all the criteria for IRB review, such as the objective research by grant of the research, subject population, subject selection. What are the potential risks, and whatever has been made to protect against risk, potential benefits, risk/benefit ratio? Are there any alternatives? Subject compensation needs to be addressed, and investigators' credentials.

What is the objective of the research? The IRB needs to look into that. Are there any preclinical and clinical data to support this proposal in the subject population, such as age, sex of the subject, and the anticipated number for subject accrual? What is the inclusion and exclusion criteria? For instance, in the thalidomide research, should you exclude pregnant women? Are any subjects vulnerable, such as children, pregnant women, and fetuses?

Selection of the subject. What kind of method do we use to identify what kind of subjects are acceptable, and is the recruitment process free of coercion?

Potential risks. What are the potential risks, discomfort, and inconvenience associated with thalidomide research? It is important to point out, the risk is not only a physical risk. The IRB needs to look into the psychological, social, economical and legal risk from participating in thalidomide research.

Potential benefits. What are the benefits to subjects? What are the benefits to society? Are the benefits maximized to the greatest extent possible?

I wanted to talk a little bit about the informed consent process. These are three slides listing elements of informed consent. The title of the research study should be informed consent, and then the participation should be voluntary.

The IRB needs to look into the basis of the subject selection. The purpose of the study needs

to be in the informed consent, and to explain what kind of procedure is going to be done to the research subjects, and the potential risks and discomforts, potential benefits to the subject and to society. Is there any alternative to participation?

The financial obligation and compensation for participation need to be addressed in the informed consent. In case of emergency, a contact individual needs to be listed there. If the research subject is injured during the course of research, the informed consent needs to address how it's going to take care of that.

Also the assurance of patient confidentiality, and right of the research subject -- I'm sure that means right to withdraw any time -- voluntary participation or withdrawal, documentation of informed consent.

Are there any therapeutic alternatives that offer the subject a reasonable prospect of health benefit, other than the agent you'll be studying, in this case thalidomide?

I wanted to emphasize, informed consent is not just a form for subjects to sign and agree to participate in research. It should be an ongoing process. It's not just the informed consent document.

Also, of importance in the thalidomide research, I believe, is the continuation of IRB review. The IRB is the continuation review, and the purpose is to monitor the safety and to manage the adverse event. The kind of question that's raised in the continual review is, did any new information develop during the approving period that may cause the IRB to change their mind? Is the study being conducted as approved? In the FDA information sheet, these are the kinds of question that they ask for submitting for continual review.

Demographics. How many subjects have been recruited in the first year or first period of the proposed study? What kind of benefit and what kind of adverse reaction did patients experience? How many subjects withdraw and what are the results of the data? So the IRB, with the help of maybe a data safety monitoring board, can come up with a risk/benefit assessment. Are there any unanticipated risks? Is there any new information found in the literature?

Criteria for conducting continued review. Criteria for conducting continued review is just like how the IRB would conduct the initial review. The criteria are, is the risk to subjects minimized? Are risks to subjects reasonable in relation to anticipated benefits? Selection of the subject is equitable. Is informed consent adequate and appropriately documented? Where appropriate, the research primary investigator makes adequate provision for monitoring the data collected to ensure the safety of the subject. Where appropriate, there are adequate provisions to protect the privacy and confidentiality of subjects. Appropriate safeguards have been included to protect vulnerable subjects.

So these are the typical data that the IRB requires the investigator to submit for the continued review. First, to list the amount of the activity that has already occurred, such as

number of approved enrollment, number actually enrolled, number dropped out, number terminated, and number completed. Any adverse event information on their own site, or if it's a multicenter trial, in another site, so the IRB can evaluate the risk/benefit ratio.

Another information that the IRB requires for the investigator to submit for continued review is the progress in the field. What kind of advances have been made, and are there any competing products that have been approved?

In the consent process, the most common concern expressed by potential subjects is time dedicated to obtain consent. There's the assessment of the comprehension of the subject during the informed consent process.

In the consent document, the investigator needs to provide adverse event history, the progress in the field, and the concern of prior subjects. Also during the study, is the approved consent being used? Very often, in the FDA audit and OPRR investigation, we find the informed consent that's being used is not the informed consent that was approved. The IRB can always have a choice of conducting this site audit.

In summary, the IRB faces a big challenge when reviewing and approving the research involving thalidomide in research. The issue is, how to do you distribute a drug that is a known teratogen, and allow the access to the thalidomide when needed? The IRB needs to continue to balance the three ethical principles, the principle of autonomy, the principle of beneficence, and principle of justice.

My office, OPRR, and FDA will continue to work together with the IRB in protecting human subjects. Having given you my thoughts, I want to wish every success for this meeting, particularly in tomorrow's closing session.

Thank you for your attention.

(Applause.)

DR. BIRNKRANT: Good afternoon. My name is Debra Birnkrant. I chaired the Thalidomide Working Group at the Food and Drug Administration.

When the marketing application for thalidomide was submitted to the FDA back in the early 1960s, as Dr. Kelsey spoke to this morning, it wasn't known that thalidomide was a teratogen. It was reports of neurotoxicity that kept it from the U.S. market, and it was only months later that the teratogenic potential of the drug was known. It was this scenario that resulted in amendments to the Food, Drug, and Cosmetic Act, which led to higher standards of drug safety, drug study, and review.

Following last week's FDA advisory panel, which recommended that thalidomide was safe and effective for erythema nodosum leprosum, a reactive state in lepromatous leprosy, it is timely that I will discuss current safety considerations in the clinical development of thalidomide as it becomes more widely available.

This is a list of some of the publicly acknowledged indications that are under review at the Food and Drug Administration. They are aphthous ulcers in HIV-infected patients and in Behcet's patients; HIV wasting; erythema nodosum leprosum; chronic graft-versus-host disease; solid tumors; macular degeneration; rare dermatoses; and rheumatoid arthritis. This is just a partial list, but we can learn something from this list. That is, these diseases represented here are serious and life-threatening, and they are in far contrast to the indication for which the application was originally submitted back in 1960. That is, as a sedative/hypnotic.

The other thing to note is that these indications take advantage of thalidomide's purported immunological and/or antiangiogenesis activity. Lastly, I wanted you to know that these indications are reviewed in five review divisions at the Food and Drug Administration. With such a widespread review process, how can we help to ensure that the drug is used safely?

In 1994, the FDA formed a Thalidomide Working Group. The mission of the working group is to ensure consistent practices for the safe use of thalidomide, and to establish a regulatory accounting related to the use of thalidomide, so that the FDA can advise sponsors, pharmaceutical sponsors, as well as individual investigators, and so that we can coordinate the review process for this drug.

So to that end, the Thalidomide Working Group, which is made up of approximately 20 scientists within the agency, including obstetrician/gynecologists, legal counsel, IRB experts, et cetera. We developed a number of documents and a database. The documents are an informed consent document and a patient brochure.

The informed consent document contains all of the elements of informed consent that are necessary to ensure the safe use of this product in patients. This particular informed consent document details the side effects of this drug, namely the birth defects, as well as some of the other side effects. It also describes birth control measures that should be used in patients who decide to take this product.

It advises patients clearly not to share the medication with anyone else, and that only they should be the ones who take the drug. It advises patients when to stop using the drug. That is, in the setting, let's say, of an adverse event or a missed menstrual cycle. It advises them then to seek medical attention.

We also developed a patient education tool, which we refer to as the patient brochure. It is a tri-fold document in three colors, and it has the Roche's No Pregnancy logo on the front. It has recently been amended. The original patient brochure just had the "avoid pregnancy" words through the abdomen of the pregnant woman. We've now revised it to include wording that states, "Do not take during pregnancy." There is a big bold warning up front, "Do not take this drug if there is any possibility that you are or may become pregnant."

We developed this document so that the patient can carry it around with them and refer to it as needed, so that they're constantly aware of the side effect profile of the drug, and how to

use it safely. We developed this so that we could make the patients and the physicians aware of some of the serious side effects. Notably, teratogenicity, neurotoxicity, neutropenia, and others. Earlier today it was mentioned about the teratogenic potential of this product. Speakers in the next session will focus their comments on this as well.

I just wanted to show you this from the Brent and Holmes article that discusses the thalidomide syndrome, which results as a result of exposure during a critical period that's defined in the literature as days 20 or 21 to 36, post-conception, or if you add 14 days to those dates, it becomes days 35 to 50, from the first day of the last menstrual period when the developing fetus is most susceptible to the teratogenic potential of this drug, as manifested by the limb reduction defects that are a big part of the thalidomide syndrome.

This slide shows you the sensitive stage in days when this is likely to occur, but really, what I wanted to bring out from this slide is that there are other organ systems affected as well. It's just that the precise timing of the effects of thalidomide on these other organ systems is not as well worked out.

The other thing that isn't well worked out is, what happens if this drug is given outside of this critical period that's described in the literature? Also, since it's difficult to assess behavioral aspects of this drug, what happens to the behavior or to the development of children who are exposed outside of this critical period?

Because of this important issue of teratogenicity, and because we feel the benefits of testing for pregnancy outweigh the risks, we have recommended the following pregnancy testing schedule for all women of childbearing potential. The pregnancy testing is done before the patient takes the drug, during, and one month after the drug is discontinued.

Basically, all women of childbearing potential should have a baseline negative pregnancy test. Frequent testing should be done during the first month. Subsequently, if a patient has normal menstrual cycles, then the pregnancy testing can be done on a monthly basis. If a patient has irregular cycles, then the testing needs to be done more frequently. It also needs to be performed in the setting of a missed menstrual cycle, and in the presence of irregular uterine bleeding. These recommendations were sent off to the American College of Obstetricians and Gynecologists, and we are awaiting their comments.

In our database of 500 HIV-infected patients, 72 of those are women. The majority of these women fall into the childbearing potential age range. We have allowed these 72 women to have access to thalidomide, for either HIV wasting or aphthous ulceration.

The point of this slide is that we're collecting information on the various birth control methods that these 72 women have used to show that this drug can be used safely in this age group. The majority of patients had been surgically sterilized before receiving thalidomide well before actually, and not at our request at all.

The next largest category is abstinence. We accept that as a method of birth control. If a

patient tells her physician that she's abstinent, then we accept that. In general, however, we recommend two methods of birth control, one hormonal and one barrier, unless there's a contraindication. If there's a contraindication to hormones, then we recommend two barrier methods.

Moving on to some of the other side effects that I wanted to discuss today is that of neutropenia. In our database of 500 HIV-infected patients, we have 15 reports of neutropenia. This was somewhat surprising when the first few reports came in, because we were basically not aware of this side effect.

So we went back to the literature, and we learned a lot. What we learned was that, in the early leprosy literature, there were a number of reports of neutropenia in that patient population receiving it for erythema nodosum leprosum. Then we looked in the chronic graft-versus-host disease literature. In one article, where it was used as salvage therapy, 18 percent of the patients developed neutropenia. Those who were rechallenged again developed neutropenia.

More recently, in the May 22 article in the New England Journal of Medicine, where thalidomide was used in a placebo-controlled trial for the treatment of aphthous ulceration in HIV-infected patients, in that preliminary report there were also reports of neutropenia there as well.

So from our database, this is one patient, one of the 15. It's a male patient who received thalidomide for severe aphthous ulcerations. These are not merely canker sores that we all get, and heal within seven to 10 days. These are severely necrotic, debilitating ulcers that interfere with the quality of life, and ultimately lead to wasting.

This patient, before receiving thalidomide, had a normal absolute neutrophil count of more than 2,300. He was started on a dose of 200 milligrams at nighttime. Within a week -- so that's approximately 1,400 or 1,600 milligrams of thalidomide -- his absolute neutrophil count went from 2,300 to about 1,300. About two weeks later, when he had received less than 4,000 milligrams, or four grams of thalidomide, his drug had been stopped, and his absolute neutrophil count had fallen to about 1,000. It subsequently rebounded.

We're waiting to review the data from the pharmaceutically sponsored clinical trials so we can get a better understanding of the development of neutropenia in particular patients.

Lastly, I wanted to touch on a side effect that was recently reported in the New England Journal of Medicine article that I recently referred to. That is viral load changes. I guess the bottom line is, the more patients who start taking this drug for serious and life-threatening diseases, perhaps the more side effects we will be seeing.

So just let me elaborate a little bit on this case. This was a placebo-controlled trial of thalidomide for the treatment of aphthous ulceration in HIV-infected patients. The preliminary report appeared in the New England Journal of Medicine back in May. What

they found was, in those patients randomized to receive thalidomide, their viral load went up by about .43 logs. This was a statistically significant result compared to placebo.

As I was skimming through the other abstracts in the abstract book, I noticed that in Dr. Schambelan's abstract on HIV wasting, he too reports changes in viral load in that group of patients who received thalidomide for HIV wasting.

The question is, we don't know at this point in time if this is clinically meaningful. It may be statistically significant, but we're not sure if it's clinically significant yet to date, because these studies were done at a time when the recommendation to use highly active antiretroviral therapy was not made. So we're trying to apply current recommendations to a study that was started back in 1994. So we need to get more information on these patients who receive thalidomide, these HIV-infected patients, to try and determine whether, in the setting of adequate antiretroviral therapy, if thalidomide raises viral load, and if this is clinically meaningful.

In sum, I would just like to say that the goal of using thalidomide in a safe manner is highly dependent on the benefit/risk ratio for the individual patient. I think that's important to remember. In the setting of a pregnancy prevention program, with adequate monitoring and with adequate consent, it is possible that patients with serious and life-threatening diseases can have access to promising therapies while we protect the public health at large.

Thank you very much.

(Applause.)

DR. BIRNKRANT: We now begin four successive talks on neurotoxicity. Our first talk on toxic neuropathies is by **Dr. Herbert Schaumburg** from the Albert Einstein College of Medicine.

DR. SCHAUMBURG: What I'm going to do is to talk to you a bit about toxic neuropathies in general. What I think I will do specifically is defer many of the specific aspects of thalidomide neuropathy to Dr. Crawford, who has had considerable experience with this drug.

Basically, it may come as a surprise to you to know that toxic neuropathy is probably the most common disorder of the nervous system associated with exogenous chemicals. We all think of the nervous system as being very vulnerable to environmental gases and things like carbon monoxide. But at a practical level, under a toxicology clinic, the overwhelming majority of people we see are people who have toxic neuropathies.

The thing that's very interesting about toxic neuropathies is that about 95 percent of them in North America, in fact, 90 percent of all neurotoxic disease in North America is caused by physicians, okay? Again, there's a common presumption that we are living in a toxic soup, and that if you drive through the State of New Jersey, you should have your windows rolled up on the New Jersey Turnpike because your nervous system may succumb to something.

It really isn't true. In North America, Canada, the U.K., and certainly Western Europe, with the possible exception of Italy, there really is not an awful lot of environmental or industrial clinically significant neurotoxics toxicity. Most of it is caused by doctors, and it's done deliberately, as will happen with thalidomide.

For that reason, we've learned to deal with it. If you go to any large general hospital, and go to the psychiatric ward, you will see neurotoxic disease everywhere. Any of these patients who are receiving neuroleptic drugs will develop movement disorders in time. If you go to the oncology clinic, virtually all the most powerful drugs that oncologists use against cancer seem to target the dorsal root ganglion cell, and produce a sensory neuropathy. Vincristine, taxol, pedophilins, this dreary litany of all their most useful drugs -- the nervous system is the limiting factor here.

The same is true with a great many other drugs, and thalidomide has been nominated as one of these candidates. Basically, the people in our oncology clinic don't have to call me to tell them when to stop a patient taking vincristine. They just ask them, "Look, if your feet get numb, stop taking this stuff, okay?" You don't require a neurotoxicologist to come and give you a hand.

In fact, I would submit to you that far more neurotoxic drugs than thalidomide are deployed every day, and without really terribly carefully monitoring, and we are able to get away with it, and the patients do okay.

I submit to you that thalidomide can be used safely. The degree of monitoring, though, I'm sure will be an issue of debate. But if the nervous system were the sole issue about thalidomide, you wouldn't be having this meeting today. It would be settled in the back rooms at the FDA by a small group of fascists who decide what's good for the American public.

(Laughter.)

DR. SCHAUMBURG: Present company excepted, of course.

Then really, you wouldn't have to have this. It's the other issues. This was the first issue surrounding thalidomide. It's really not the most important one, because we've had a lot of experience. We just had this tremendous experience, unfortunately, with nucleoside neuropathies in HIV-positive patients. We've learned how to deal with those, and they are now used successfully. So I'm going to talk to you today a little bit about some of the basic rules, to give you some background noise for this, and maybe a bit about how to use these drugs safely.

Well, the first thing is that all toxic neuropathies, with the exception really of diphtheria and buckthorn toxin and one or two other exotic things, all toxic neuropathies affect the axon. The myelin isn't really that much affected by these things, except secondarily. The dorsal root ganglion cell is rarely knocked out, unless you take heroic doses of these things.

So we're really talking about what we refer to as toxic distal axonopathies. Well, what on earth is that? I think I will show you. I feel like an astronaut with this thing. I've already forgotten what I'm supposed to do. I'm going to show you my first slide.

This is my version of the nervous system. It's from the point of view of peripheral neuropathies. This is a spinal cord here, half of it. Here's the anterior horn cell. Here's a dorsal root ganglion cell. This is the motor cell, this is the sensory cell. For those of you who know this, I apologize, but I realize that there are a lot of people in the audience who care about this as much as I care about the bone marrow, so I'm going to be a little pedantic here.

These two very important cells, the sensory cell and the motor cell, have long cytoplasmic extensions. Basically, part of the cell sticks out in the periphery, this long wire, and that's called the axon. That is the thing. It's really part of the nerve cell. It's part of the cytoplasm, but it's also like a wire. It's a conductile apparatus.

These individual axons each are insulated like wires by little sausage-like links of myelin. What I would submit to you as a thesis is that, when you get a toxic chemical on board, like thalidomide, or if your kidneys pack in you get uremic, or vincristine -- that a toxin hits the whole nervous system. Most of these toxins get into the nervous system. They're not held out by the blood-brain barrier.

You know, the blood-brain barrier holds out huge molecules like penicillin, and to some extent diphtheria toxin. But there is an unfortunate thing about the blood-brain barrier. One is that it's deficient here around the dorsal root ganglion cell, so toxic chemicals can get in around the sensory cell. So most toxic neuropathies are sensory, okay? You rarely find somebody just getting weak from a toxic neuropathy. They will all get numb feet, okay? Weakness comes later.

Again, some toxins like thalidomide get past the blood-brain barrier anyway. I mean, that's how it's used as a sedative. So it gets in. You have to worry about this, but some don't. But they all get into this cell. What happens is, these cells actually, in addition to having their little wires conduct electricity, these wires actually have to have very important metabolites pumped down to them.

That is, the only thing the little axon gets here by itself is sugar and oxygen from the blood. All of its proteins, all the neurotransmitters, all the things that make it cook are synthesized up here in these cells. These cells are like little factories and like little pumps. They pump these nutrients down these long fibers.

So if you get poisoned, what happens is -- well, the analogy I like to use is, these pumps in cells get poisoned. Like the pumping system of an irrigation system, if the pump begins to fail, which of the metals on the irrigation is first affected? It's the longest one, it's the one that's furthest out. So it's the end of the axon that begins to die when the nervous system first gets poisoned.

Then as time goes on, and the pump begins to fail more, more and more poisoning, these axons die back toward the cell of origin. They used to be called dying-back neuropathies for that reason. We now call them distal axonopathies.

Now, the central projections of these axons also degenerate. In this case, the motor doesn't have a sensory projection, but the sensory axon here does, up the dorsal columns. So up in the grasile nucleus, you also get degeneration.

But say something happens. Say that you suddenly stop taking thalidomide, or you get a renal transplant. You're no longer uremic. Then the cells perk up. The nice thing is, in the peripheral nervous system, you can get very good repair and recovery. That's why people get better from toxic neuropathies. These cells can reconstitute themselves generally, and they regenerate, but it's very slowly. It's about a millimeter a day. So the longer it's gone on, the longer it takes to recover, okay? Okay.

Now that you've seen this, if you had to predict which of these factories, which of these cells would pack in first if it was exposed to a toxin, you might say, well, it's the biggest one with the longest fiber that's got the most work to do, the pump has to work the hardest. What's the biggest and longest fiber in the human body? It's the sciatic nerve. It comes out here above your rump, runs down to your toes. That always goes first. It's a law.

So what do you suppose happens? If your sensory ganglion cell begins to get poisoned by this toxin, the first thing to happen is your toes get numb. Then the next longest nerve is the ulna nerves. Your fingers get numb. So these things, it's an absolute rule of neurotoxicology, a toxic neuropathy has to begin in the feet, okay? Since they are diffuse -- they go all over -- it has to begin in both feet. They are never asymmetrical. These are called distal symmetrical polyneuropathies.

In fact, if you look at somebody who has one of these, what do you suppose they look like? They look like this, the next slide. You get a lot of sensory loss in the feet, and a little bit in the hand. You even get some here in the middle of the chest, because the distal ends at the intercostal nerves that run across here also die, okay? Okay. This is called a stocking and glove pattern of sensory loss, and this is really what you get.

We can have the lights on now, if you could.

The thing that's interesting about these is that, by and large -- and it's kind of nice -- is that they're very gradual. They're very insidious, as someone said. You don't suddenly wake up some morning with the stocking and glove sensory loss. You get tingling and numbing of the toes. Unless you're getting an overwhelming dose of the drug, most drugs and toxins, it goes on for weeks, even for months. In fact, people will often change their shoes, thinking, "My shoes don't fit right." It turns out that they've got a mild toxic neuropathy.

They are mostly sensory, and they all get better in time. Even the worst ones get a little bit better. They don't recover 100 percent, but they get a little bit better.

A very important concept here is that, because these are biochemical events -- the biochemical events are the first thing to go. So biochemistry goes first, neurophysiology goes kind of second, and the axons break down kind of third. So when the biochemical events take place, the people will feel the numbness, even though the axon still has integrity.

So if you can stop the poison while you're still at the early biochemical level, people can recover within a week or so. If you let it go until the axon dies back several millimeters, it's going to take a lot longer. If the axons has been allowed to die back clear up to here, it's going to take years to recover.

So there is a high premium on catching the earliest symptoms. The symptoms will always precede, in general, the neurophysiology or the anatomical changes. Unlike dealing with -- "But I have primates or rats I'm giving toxic neuropathies to" -- you can't talk to them. You have to measure the nerve conduction, okay?

Humans, you can talk to, so you get a really nice early warning system. Obviously, it's very useful to have a primate or a rat model of these things, because then you can manipulate it. You can monitor the rat model or the primate model the same way you do in humans.

You can do something very interesting to these animals. You can actually get a very early warning system in the animals by monitoring their dorsal columns. The spinal cord is actually -- this long central projection of the axon is the most vulnerable structure. You will find changes there weeks or months in neurophysiology before they happen peripherally.

You can find them there long before they can be detected by the electron microscope. So in the experimental lab, there's a very nice way of monitoring this. Unfortunately, not all toxins that affect humans are easy to make experimental models of. I've been for years trying to produce an experimental model of rat arsenic in the rat of human arsenic neuropathy. Humans get a terrible neuropathy from arsenic.

I have given rats so much of this stuff that the lab calls me, and says, these blood levels are out of kilter. The rats treat it like it's vitamin. They never get neuropathy. I'm never amazed when you can't produce an experimental animal model. For whole reasons, animals metabolize it differently. They just handle these drugs differently.

But nerve conductions and quantitative sensory testing are very good ways of monitoring these in humans, especially vibratory sense monitoring.

There are one or two other rules. In general, in the laboratory and in the industrial arena, there's a tremendously good dose-effect relationship, which is wonderful. Unlike cancer, where you give 10,000 animals saccharine, and only five of them get bladder cancer, if I took everybody in this room, locked you in here, pumped in hexane in the air ducts, within six weeks you'd all have foot drop, okay?

(Laughter.)

DR. SCHAUMBURG: I promise you, without exception. This is great, because you're well people, and you metabolize it well, and we can do very good dose-effect responses for most of these neurotoxins in the laboratory, and in industry as well. In monitoring for accrilomide or phosphate neuropathy in industry, it's a piece of cake. You can really do it beautifully. You know how much is around, you know who's going to get sick, it's very simple. Again, you get people away from it, they do improve. They don't improve 100 percent, but they do improve.

The thing that I want to leave you with, my final thought in this xenophobic monologue, is to tell you that there is one very important point, that these are drugs. Drugs by and large are not given to well people, okay? Now, there are some drugs that are given to well people, but by and large, these are not, and thalidomide is no exception. The elderly and the sick react very differently to neurotoxic drugs than do the well.

Why is that? Well, again, if you want to give these drugs to HIV people, you want to give these drugs to people who have leprosy -- many of the oncology agents are given to people who have cancer, presumably. All of these diseases are associated peripheral neuropathy. So many of these patients are walking around with subclinical neuropathies to begin with. So they get a double whammy.

But that isn't the real point. The real problem is that, in HIV patients, and certainly in cancer patients, there are very increased levels of circulating cytokines. If you have somebody with an increased level of cytokines floating around, it blows the tight junctions in the nervous system, and there's no more blood-brain barrier. Stuff is all over the place. So you cannot predict when you give something how much is going to turn up in the nervous system in these patients.

People with HIV positivity, it was impossible to do a good dose-response effect for ddC, because some of them almost didn't get the neuropathy at all. Others just came down with it for three or four days. The same is true with vincristine.

So that's the need for some kind of monitoring, or very careful history-taking, is that sick and older people, you cannot do good dose-effect responses from.

Thank you very much.

(Applause.)

DR. BIRNKRANT: Our next speaker is **Dr. Colin Crawford** from the Imperial College of Medicine in London. He will discuss thalidomide-associated neurotoxicity in the setting of leprosy, and enlighten us with how the United Kingdom deals with the regulatory process as it relates to thalidomide.

DR. CRAWFORD: Thank you very much for asking me to speak.

Dr. Wilkin made some kind remarks. He said I was an expert and a neurologist. I'm neither

of these. I'm not an expert. I have a post-graduate clinical diploma in clinical medicine, but I do have an interest in the nervous system, and I hope to show to you that somebody with a general medical training can make a contribution to this subject.

Now, Dr. Kelsey mentioned the peripheral neuritis was an important feature in stopping her from licensing the drug back in 1960-1961. Thalidomide neuropathy, as we now call it, has proved to be a very serious condition. It can lead to serious sensory and, in some occasions, irreversible sensory loss.

To such an extent, the two British pharmacologists, Darcy and Griffin, writing recently, concluded, "This side effect alone could have led to the demise of the drug, even if the teratogenic effects had not supervened. The teratogenic effects can be avoided if the drug is not given to a woman in the reproductive age. However, anybody taking the drug is at risk of developing a neuropathy."

Now, the first slide, as we have seen, as was pointed out, is a dying-back neuropathy, so the main involvement is in the distal part. It's symmetrical, and it affects the extremities of the lower limbs. Initially it's sensory, but all modalities can be affected. But sometimes only superficial sensory modalities are involved, and this may cause confusion with leprous neuropathy.

Burning pain in the feet and cramp-like pains in the calf are common symptoms. The knee and ankle reflex can be diminished. But if there is upper motor neuron involvement, then the reflexes may be increased, and the plantar responses extensor. Then if the drug is taken for a considerable length of time, there is involvement of the proximal muscles, the muscles around the hip.

As we've been told, it is an axonal neuropathy, first affecting sensory myelinated fibers. It can be detected by sonar biopsy. Unmyelinated fibers appear to be unaffected, and this may be a distinguishing feature from leprosy.

The next slide shows a patient who received thalidomide. This is the control biopsy. You can see the normal distribution of the myelinated fibers. Because the axon degenerates, as we've seen, the myelin sheath is lost, and there is a great loss of myelinated fibers.

The histogram shows a normal bimodal distribution, with the larger myelinated fibers of the 10-12 micron in a bimodal distribution. These two patients received thalidomide, and as you can see, there's a great loss of myelinated fibers. In this case here, there's a shift to the left, which suggests that there may be regeneration of some ones which don't attain their normal diameter, regenerating small diameter myelinated fibers.

The third measure to detect neuropathy is the electrophysiological studies. You may not be able to see this too well. This is a French study done in 1986. These were for patients who were receiving the drug not for leprosy, but for a variety of dermatological disorders. The control value is 16. Much of the actual involvement here is the sensory nerve action

potential. As it is an axonal neuropathy, this is the most sensitive test. Nerve conductions studies, both motor and sensory, are probably unaffected in axonal neuropathies.

This study here shows 16, and values as low as 5, 3.5. Then the correlation with symptomatology is in here. Then on the right, there is the cumulative, the total dose given to the patient. As you can see, one patient has a total dose of nine grams. That would be 100 milligrams per day for three months.

Now, the next slide -- if sensory nerve action potentials are recorded, then the frequency of thalidomide neuropathy -- and these are recent figures for non-leprosy disorders -- is at least 21 percent. The idea of doing this is to detect subclinical neuropathy. The other features, there is no minimum dosage below which it is safe to give the drug. It is not due to a hypersensitivity. A study suggests genetic factors are not significant. Although these features I should say may not be clearly significant, they may be important, but the latest paper suggests that they are not significant. So really, in conclusion, the chances of developing a neuropathy are unpredictable.

The prognosis if the drug is stopped, the motor and pyramidal involvement is reversible, but the sensory loss is permanent in 50 percent of cases. Not only that, the patient was left with a persistent, painful paresthesia which were painful and disabling. According to Dr. LeQuesne -- her married name, she was Dr. Fullerton -- these were the most distressing things about the drug.

Now, according to the published literature, and to my attempts to look through it, none of these features -- clinical, pathological, or electrophysiological -- have been applied to patients with leprosy with erythema nodosum leprosum. The frequency of the neuropathy is reported as less than 1 percent.

The next slide is not a very good slide -- you've seen better -- of erythema nodosum. It's a chronic, intractable condition. It's recurrent. It differs from erythema nodosum in being generalized.

Personally, the first case of erythema nodosum I saw was back in New Zealand, where I qualified. A child came into the ward, and had lumps on the leg. I didn't think that was very significant. I was going to send him home. Fortunately, a consultant turned up, and said, that's erythema nodosum, x-rayed his chest, and he had a going focus of tuberculosis, and he never stopped reminding me of the mistake I made.

The second experience with erythema nodosum came when I went to Nigeria to do leprosy work. I had been there about three months, I think, and I was called into the general hospital. A patient was there who had erythema nodosum -- I could pick that -- and it was generalized. It was all over the body. But the penny didn't drop. I said, this patient has sarcoidosis. About six months later, this person turned up in the leprosarium. She knew she had leprosy, and when I examined her, she had thicker nerves, and the diagnosis was obvious.

So over the years, I've thought about this in the salutary lessons to cover my embarrassment. The point is this, that, one, erythema nodosum leprosum is a generalized condition. It's not confined to the legs. The second thing is that the hospital staff -- and to me, who was supposed to be able to diagnose it -- it wasn't immediately recognized as leprosy.

Now, then erythema nodosum leprosum comes on, the viable bacterial count drops to zero, the morphological index. The thickening, the infiltration regresses. A patient with ENL is not recognized in the community as having leprosy.

Now, you'll hear tomorrow about the treatment of ENL and the fact that patients can live a normal life. So this is one feature of the disease, that they can appear as normal, and not recognizable. So they have none of the stigmata of leprosy.

Now, Dr. Wilkin made a very important point in that he distinguished between ENL lesions and the systemic manifestations. A lot has been written about the systemic manifestations of ENL, the uveitis, the oculitus, the neuritis, the nephritis leading to amyloidosis. But none of these conditions were substantiated at the meeting last week. The efficacy of the drug was for cutaneous ENL and the accompanying fever, so we're recommending a drug against a condition which is not life-threatening.

My experience with seven patients in North Nigeria, and seven in Tanzania -- I worked in leprosy for about four and a half years. You will notice the numbers are very small. The frequency of ENL in Africa is less than in the United States, because the lepromatous/non-lepromatous ratio is much lower, the lepromatous rate in Africa.

Nevertheless, I think these figures have some credibility because, in Nigeria, we had a very extensive outpatient village-type system, and one was able to monitor the lepromatous cases there being treated as outpatients, because the condition was uncomplicated.

So our figures are much lower, but I think they have a certain amount of accuracy. We would say that the frequency is about 3 percent of lepromatous cases.

Now, you'll see that 10 of them, on clinical examination, had no evidence of sensory loss. This means that a patient for ENL who is given thalidomide runs the risk of developing an intractable neuropathy, which they would not have got from the disease.

Four had sensory loss. One of these had atrophic ulcer, and the other one had mutilation of the extremities. This raised another important point. The public perception of leprosy is of a horrifying disease with people without fingers or toes, with sores on their feet, ulcerations, trophic ulcerations, blindness from corneal insensitivity, and associated paralysis of the facial nerve. As you can see, none of these are occurring, or rarely, in patients with ENL. So thalidomide is not going to prevent the main reason why leprosy is a serious disease.

However, this neuropathy can be confused with thalidomide neuropathy. You maybe have to say, the sensory loss is similar, and as we've seen, is glove and stocking in distribution. Sometimes if the neuropathy is confined to superficial sensory modalities, then the

distinction may be difficult, because invariably in leprosy, superficial sensory loss occurs.

These are distinctive symptoms, and these are not personally observed and not recorded in the literature. Cramp-like pains in the calf. All sensory modalities can be affected, so ataxia can be distinctive. The reflexes can be lost, but in less than 50 percent. Then if the drug is given for a prolonged period, you get this distinctive muscle paralysis.

However, having said all that, the most important thing is the simple clinical examination of the peripheral nervous system before the drug is started. Last week, we saw a chart from the Hansen's Disease Center, and there was no record of the baseline or any progress of sensory loss. This is because leprosy is treated as a dermatological disorder, without emphasis on the nervous system.

Any deterioration over weeks or months must be due to the drug, because sensory loss due to lepromatous leprosy is insidious, and unlikely to occur over a short period. We know this from Gerhard Hansen's original observations back in 1895.

Now, what is the reason why leprosy patients have not developed thalidomide neuropathy in less than 1 percent? One of the reasons is that the reflexes have been preserved, according to Waters. However, as you can see, it's only absent in 10 out of 22 patients. There will be retention of the reflexes if the pyramidal tract is involved. In a review article back in the 1960s, absence wasn't regarded as a diagnostic sign. In a recent patient with AIDS who developed a neuropathy, they were preserved.

I think an important feature is the next slide. This patient had a sural nerve biopsy. The control is on this side. You can see the gross loss of myelinated fibers which has occurred in this AIDS patient.

Now, another reason is because the disease has destroyed parts of the nervous system. Well, we know that there are no records of the type of sensory loss, or the precise reason. This was a comment published in JAMA.

The third reason is that, in an editorial, a signed editorial in Lancet of 1994, the thalidomide neuropathy refers to this even after careful study. Yet this reference was in 1969. It refers to motor nerve conduction studies in the ulna nerve, and as we see, the distal axon neuropathy would be the one which is most severely affected.

Now, the U.K. guidelines for the dispensing of thalidomide have been introduced in 1994 in the U.K. There is an information sheet which occurs here, and the patient is warned, if you get pins and needles, you must stop thalidomide immediately, and in the accompanying article, where there is a common and often irreversible side effect. Dr. Floeter is going to talk about these in relation, so I'll go on to the next. The idea is that stopping it may offer recovery.

The labeling contains thalidomide, but no warning of the risk of nerve damage on the label. The responsibility is for the doctor giving the drug.

We go back to this patient number four, patient number nine, who had sural nerve action potentials recorded. However, when the drug was stopped, even after a year these did not recover, and there was a persistence of sensory symptoms. So in these two cases, even under optimal conditions, the drug symptoms still persist.

Now, I was so concerned about the fact that the patients were not being warned about thalidomide neuropathy, because it wasn't mentioned in Dr. Jacobson's article, that much of what I've said was published in the Carville Star, a famous journal which was started by a Hansen's disease patient, so the patients would have to get directly the dangers because I was so concerned.

Finally, in summary, thalidomide neuropathy has not been excluded. The main measures -- clinical, pathological, and electrophysiology -- have not been utilized. Even if the U.K. guidelines were adopted, it would be very difficult to use them for patients with ENL because, even if they have no objective sensory loss, they do get paresthesia, pins and needles, they bang their nerves, and they're likely to get pins and needles. There's no fundamental knowledge about the pathology or the electrophysiological studies in patients with ENL, and that would make interpretation difficult.

Thank you.

(Applause.)

DR. BIRNKRANT: Our next speaker is **Dr. Tucker Patterson** from the National Center for Toxicological Research. He will present his research results in primates exposed to thalidomide.

DR. PATTERSON: Thank you, Debbie.

I would like first to thank Steve and Terry for the opportunity to speak with you today. I am always looking for an excuse to leave Arkansas during the summer.

I'm going to throw a monkey wrench into things -- no pun intended -- and switch gears a little bit, and talk about an animal study instead of a clinical study. But this project is about two years in the making. We've been interested in our laboratory for a few years, looking at the antivirals used to treat AIDS.

About two years ago, we made some phone calls, maybe hoping for a new drug that may be coming out to test in our primate in hopes of developing some type of animal model for peripheral neuropathy. Someone said, well, have you thought about looking at thalidomide? We said, well, should we? So this is kind of a culmination of that work.

I'm going to present to you the data that we have so far. Like I said, this has been two years in the making, and this data is, I guess, hot off the press, so to speak, so hot we haven't even got our hands on some of the data yet. We're still waiting on it to come in, but I will present to you what we do have, and show you what we're continuing to analyze.

For lack of a better title, the neurological testing of primates, and like I said, trying to really develop -- stepping out on a limb, I think, would be what Dr. Schaumburg would say -- trying to develop a peripheral neuropathy model in an animal. Most of the work was done in our primate colony at NCTR, and that is located in Arkansas, although some of you that have traveled down county road to our facility may argue that point. We do have a primate colony there, which houses a little over 100 primates, where we can do several different behavioral parameters, testing of the monkeys.

So what we wanted to do, of course while we're here this afternoon, because there are two things that limit the use of thalidomide that we know of -- the neurotoxicity and of course the teratogenicity -- the incidence has been as low as .5 percent reported in the literature, or as high as 60 percent. This seems to be a cumulative dosage or a time factor. So we wanted to try to implement both a high dose and a chronic study in our animals, to see if we could induce neuropathy.

Why use the rhesus monkey? Of course, its comparable teratogenic doses, the rhesus monkey has -- about a one milligram per kilogram will cause embryopathies similar to what's in humans. But of course, even though this drug has been around for 40 years, there were not really any well-defined toxicity, especially neurotoxicity, studies done. When I looked at the literature, I was very surprised with the lack of the data that was there. So we had to try to come up with a very comprehensive study. We wanted to make this -- and hopefully it will be, when we're finished with all the data -- a very comprehensive study on thalidomide.

From the literature that is there, the monkey may be the most sensitive species to use. It's been very hard to produce peripheral neuropathy in other animal models, as Dr. Schaumburg talked about, with the rat very resistant to a lot of the drugs, and not showing any effects of neuropathy.

Also, the animal, the rhesus monkey, allows us to measure very complex behaviors. We have the operant test battery that's set up there at the NCTR, and I'll talk about that a little bit more later, but it allows us to measure very selective behavioral alterations. We wanted to look at the neurotoxicity and neural behavioral effects of the chronic treatment of thalidomide in our monkeys.

Our model, we had six control animals, and five animals on a low dose or a high dose of thalidomide. Again, as I talked about before, a lot of these variables were unknown, so we did do a preliminary study before this chronic treatment was started, to see what type of doses we could get away with in the monkey. We didn't know if the monkey would be totally sedated, and not respond to the operant test battery. Also, we wanted to see if we could achieve clinically relevant plasma concentrations with thalidomide in our monkeys.

We found that 10 milligrams per kilogram per day gave us very good plasma concentrations equivalent to what you see in the clinic, so anywhere between one and two micrograms per mL peak plasma concentrations with a 10 milligram per kilogram per day dose in the

monkey.

Then we tried to push the ceiling there, as we typically do in toxicity studies, trying a clinically relevant concentration, and then seeing what we can get away with. So we went 10 times higher than that, and gave 100 milligrams per kilogram per day. I'll show you some of the plasma data in just a minute, but we were able to get away with once-a-day dosing with these animals.

What do we want to look at? We tried to look at as many parameters as we possibly could, not only at the NCTR, but with some collaborators that we have outside the NCTR. Of course, our behavioral assessments -- how do you detect a peripheral neuropathy in a monkey? Of course, electrophysiology studies, as well as the neuropathy, are indicators of neuropathy, but also are behavioral assessments, as I have listed at the top. We wanted to look at blood chemistry and hematology. Not a lot of that has been reported in the literature. Someone talked this morning about the lymphocyte subpopulation, and we're also examining that parameter. Sperm analysis, pancreative analysis, we have the ability to do there, and also looking at metabolites of thalidomide.

With our operant test battery, we can look at five different aspects of CNS function: motivation, color and position discrimination, time estimation, short-term memory, and attention, and learning. Of course, initially I was concerned about the sedative properties of thalidomide, and were these animals going to be so drowsy or lethargic that they wouldn't be able to perform on the OTB?

These animals are tested about 50 minutes a day, Monday through Friday, in the operant test battery. These parameters are examined. If you see that an animal is not motivated, that's going to reflect on all the different parameters that come after that. So first we test the animal to see if they are motivated, see if they are willing to work for a food reward. We saw no differences there in motivation. This data is still being analyzed. Actually, we were looking at it Friday, that some of the statistics were just coming out. But right now, we don't see really any predominant effects of thalidomide on these parameters of behavior.

As far as our plasma data is concerned, we were real pleased with that. The yellow symbols down here are the mean of the five animals, plus the standard deviation error bars there. The red at the top are our high-dose animals. We have -- which I'll show you that data in the next slide -- we had one animal that was a little bit of an outlier in the low dose. But we're very pleased with the concentrations that we're able to achieve in the animal. Also, you see that it's pretty consistent over a 24-hour period.

This data was collected around 15 weeks into the study. These animals were dosed for 18 weeks, and most of this data is at 15 weeks. We did spot check periodically along the way to see what type of concentrations we were getting. They all fell in this range by about three weeks after dosing.

This is a very busy slide, but this shows you every animal that was in the study. Each

symbol represents a different animal. You can see, we had the one animal here in the low dose. That was a little bit high for the low dose, but everybody else was grouped pretty tightly. So this kind of answers one of the questions, I think, posed to one of the speakers this morning about pharmacokinetics in different species. We were able to achieve clinically relevant -- you'll see typically in humans about a one to two microgram per mL heat plasma concentrations. It was pretty linear. We were anywhere from 10 to 15 micrograms per mL here with the high dose.

I want to tell you a little bit our dosing procedure. We did use an HCL citrate buffered vehicle, because thalidomide does undergo hydrolysis, even at a neutral pH. We tested this, and it was stable for up to 21 days in the refrigerator. We mixed this thalidomide suspension with corn syrup to mask the taste to the monkeys. We found out we could get away with about 100 milligrams per mL concentration. Anything higher than that, and the monkeys seemed to have a taste aversion to it.

Some of these animals, like the high-dose groups -- we had 10 kilogram animals, so they're getting as much as one gram of thalidomide per day. This is over 18 weeks. So a cumulative dose is anywhere from 100 to 125 grams during the study.

The next thing we wanted to do was look at electrophysiology in these animals that were being treated. These animals served as their own controls before the study began, but also, we did have a control group that we did the electrophysiology on.

We looked at perineal and sural nerve velocities, as well as amplitudes. But by far the most sensitive, or most consistent measure, I should say, that we had was the F-wave. You see the baseline here is around 17. There was about a 5 percent prolongation of the F-wave. The nerve was stimulated at the ankle, and the measurement was taken at the extensor digitorum brevis. A slight prolongation there, you see with their high dose. I would see a similar trend. If you look at the control animals, it was about 17 for each parameter. You see that it took out to 17 weeks before we did start seeing something.

We're not going to get too excited about this data yet -- this is about a 12 percent prolongation of the F-wave -- until our histological analysis is done, to see if that confirms it. We have had some studies in the past in rats, where we're trying to look at peripheral neuropathy, that the histological analysis was the only thing that actually confirmed the peripheral neuropathy, that no behavioral alterations were seen.

These are our analyses in progress. We're still looking at the behavioral data. As I said before, the preliminary data looks like there is not really much of an effect in the operant test battery with both doses of thalidomide. Lymphocyte surface markers are being examined, especially the CD26 and CD54. We're interested in these biomarkers because Dr. Neubert at the Free University of Berlin has shown in marmosets that there is some alterations with these biomarkers. We want to see if we can replicate that in the rhesus, or is this something that is species-specific? Also, our histological analysis, we're waiting on that to come back. Hopefully, that may verify this F-wave prolongation that we've observed.

Also, our colleagues at the Division of Drug Analysis in St. Louis are looking at the metabolites in the plasma forensics. They also looked at the parent compound and the antimeric ratio. They did see a slight predomination of the R over the S in the plasma of these animals. This was a racemic mixture of thalidomide that was given to the animals, supplied to us by Celgene. We sent it to the Division of Drug Analysis in St. Louis to confirm the purity. They checked it against their gold standard, and it was 100 percent pure.

Also, some pancreatic analysis that we're doing, because we do have that capability there, someone interested in our institution in that, looking at some mutations or some epigenetic effects.

So right now, a very conservative conclusion, that we are able to achieve clinically relevant concentrations in our primates with thalidomide, and also very high levels of thalidomide. Interestingly enough, I never saw any signs of sedation or drowsiness or lethargy in these animals, even with the high dose. These are very well above clinically relevant concentrations, and we were kind of surprised about that. But also, there has been some studies that have shown about two grams per kilograms in a dog could not cause drowsiness. So maybe it's something to do with species, or just the animal itself.

There is a slight prolongation of the F-wave. The data suggest a trend in that. We're hoping the histology will back us up in there. There are really no overt signs of sedation or toxicity at this point with these clinically relevant plasma concentrations.

Just to give you an idea of the people involved in this project, hopefully we tried to implement some of what Dr. Woodcock talked about this morning, trying to garnish as much information as we possibly can from these studies. We had a neurologist from the VA Medical Center there in Little Rock doing our electrophysiology for us.

A colleague at Morgan State University there in Baltimore is looking at lymphocyte subpopulation for us. Also, our colleagues at CDER -- as I said, this project would have never gotten off the ground, probably, without discussions with Dr. Birnkrant and her colleagues at CDER, and also in-house with our Molecular Epidemiology Group and Pathology in NIOSH.

I'd like to acknowledge specific people involved, Dr. Slikker, our division director, and Dr. Paul, our behavioralist, and also Mr. Glenn Newport. Without him, there's no way that I could have dosed 600 monkey biscuits a week by myself for this project.

Thank you.

(Applause.)

DR. BIRNKRANT: We look forward to the rest of the results when they become available.

Our next speaker is **Dr. Mary Floeter** from NIH, specifically the National Institute of Neurological Disorders and Stroke. The title of her talk is "Monitoring for Peripheral

Neuropathy." We hope she can help us answer what are the best methods to use in monitoring patients, and how often should they be done?

DR. FLOETER: I think the preceding speakers have made it quite clear that peripheral neuropathy is a very concerning side effect of thalidomide treatment. The goal of monitoring is to try and detect peripheral neuropathy early on, while there is still a possibility that it might be reversible.

There are three components to monitoring for peripheral neuropathy, and I think they're all quite important. First, patients themselves need to keep track of whether they are experiencing any symptoms of neuropathy. Physicians that follow them need to perform serial neurologic examinations, and this includes, very importantly, baseline examinations. Lastly, there are adjunctive physiologic studies.

The first component, self-monitoring for symptoms, has a number of advantages. As Dr. Schaumburg pointed out, symptoms are typically the first sign of a toxic peripheral neuropathy, and this is potentially the most sensitive parameters. Patients are continually aware of their own physical state, and are essentially monitoring continuously. On the other hand, they need to know what to look for as a sign of developing neuropathy, and they need to know what to do if they should begin to experience these symptoms.

Another disadvantage is that this is a subjective sort of monitoring, and there are some patients who are stoic, other patients who may play down symptoms of neuropathy, and still others that become hypersensitive to normal sensations, and may feel that these are signs of peripheral neuropathy.

The symptoms that patients should look for are those that occur quite early on in peripheral neuropathies. As Dr. Schaumburg mentioned, those are signs that begin in the feet, since these are typically the longest nerves. Paresthesias may be described as tingling or pins and needles sensation in the toes; less frequently, loss of sensation. Some patients describe this as numbness, or the sensation that they're wearing socks.

The symptom of pain in the hands and feet was described in these studies by Fullerton early on, but seems to be much less of a common symptom in the more recent studies that have used thalidomide for dermatologic conditions. Painful muscle cramps in the toes and feet are also a sign that patients need to be aware of. Weakness is uncommon because it's a relatively late sign of peripheral neuropathy, and there have been case reports of patients who developed impotence which was attributed to neuropathy from thalidomide.

The second component of monitoring is sural neurologic exams. The advantage of this is that it's performed by a physician and not the patient, therefore it's subjective. But the patient needs to come in for a visit, and any symptoms that develop in the interim are unlikely to be picked up. The physician who examines the patient needs to spend an extra four or five minutes doing those components of the neurologic exam that may provide signs of peripheral neuropathy.

The object is not to do a complete neurologic exam, but really to focus in on those parts of the neurologic exam which become abnormal early on in peripheral neuropathy. The sensation, the strength, and the deep tendon reflexes need to be examined. As we have heard, it's primarily a large fiber neuropathy. An early sensory lost may be the loss of vibratory sensation on the great toe, or ability to detect movement of the distal joint of the toe. Loss of light touch and pin prick tends not to be an early symptom, but may be picked up as a sign of peripheral neuropathy.

In advanced peripheral neuropathy due to thalidomide, proximal weakness has been described. Early on, physicians should look for weakness in distal muscles. These are not commonly muscles, I think, that are tested, but asking patients to spread their toes would be one example of testing for distal strength. Muscle atrophy and loss of dexterity are actually fairly late signs of peripheral neuropathy.

Tendon reflexes, if they have been present to begin with, are concerning if they become lost in the course of treatment with thalidomide. Loss of ankle jerks would tend to occur before loss of other deep tendon reflexes.

Then the third component of monitoring are physiologic studies. These are like the physical examination objective, and also offer the advantage of providing a quantitative measurement that can be compared from visit to visit.

These again have the disadvantage that they only pick up abnormalities when they are performed, and they are performed intermittently. The patient needs to see a physician who is a specialist in the performance of these studies. In this country, this is typically a neurologist or a physician who specializes in physical medicine and rehabilitation, with subspecialty interests in electrodiagnostic medicine.

A lot of these studies are uncomfortable, and patients don't like to undergo them. They take time. It's not like a simple blood test or an EKG. A patient may need to put aside an hour or two for this appointment to assess physiologic studies.

Among the physiologic studies that are commonly performed in patients, some provide more information about sensory axons of the nerve. These include sensory nerve conduction studies, somatosensory evoked potentials, and quantitative sensory testing. Other components of physiologic studies are more informative about dysfunction of motor axons in mixed nerves. These include motor nerve conductions and needle electromyography.

The first time a patient is seen, this entire battery of studies may be appropriate to perform to determine if there is already an underlying peripheral neuropathy. We've heard that there are a number of factors that are unexplained about why patients develop thalidomide-induced neuropathy. It is quite possible that one risk factor may be patients who already have a peripheral neuropathy may be more susceptible to the effects of thalidomide.

In thalidomide-induced neuropathy, just combining a large number of studies, the most

common abnormalities are seen in sensory nerve conduction studies, evoked potentials. It's less common to see changes in needle EMG, which primarily involves looking at motor axons in the enervation of muscles, and motor nerve conduction studies.

Quantitative sensory testing is the modality that has really not been very well assessed for picking up thalidomide-induced neuropathy because it is a form of testing that has really become prominent only in the last decade.

Now, based on my experience with patients over the last five years coming through the EMG lab, the studies that are most uncomfortable are needle EMG. It involves sticking a needle in the muscle. The sensory nerve conduction studies and evoked potentials, which involve pasting wire onto the surface of the skin and applying electric shocks overlying the nerves are actually moderately -- well, are much better tolerated by patients, and are really not as uncomfortable. Quantitative sensory testing is essentially painless. It's a little bit boring, but that's really the only complaint that patients have.

The sensory studies are really not completely overlapping. They assess just different components of the nervous system. Sensory nerve conduction studies assess the sensory nerve action potential, or SNAPs, from the most distal portion of the nerve. So, for example, we may zap the wrist, and measure the sensory potential from the index finger.

Somatosensory evoked potentials assess the conduction from the peripheral nerve to the brain. So we may, for example, zap the wrist hundreds of times, and record the average on EEG electrodes which are placed over the scalp. So anatomically, it's assessing the full length of the sensory pathway to the brain.

Quantitative sensory testing involves applying controlled thermal or vibratory or electrical stimuli to the lens. Patients go through a set algorithm to say whether or not they perceive it. So this test involves not only the peripheral conduction, central conduction, but also the cognitive processing of the patient.

The measure that has been of the greatest interest in thalidomide neuropathy are sensory nerve action potentials. From the sensory nerve action potentials, there are two parameters that can be measured, the conduction velocity and the amplitude of the response. As our previous speakers have alluded to, the conduction velocity is more informative about the status of the myelination, rather than the number of functioning axons. This measurement, however, is quite consistent from lab to lab. Most labs get fairly similar values for conduction velocities.

Amplitude is a much better measurement of the status of the sensory axons, recording the size of the action potential through the skin of primarily the largest sensory fibers. These fibers may be the ones that are more susceptible to peripheral neuropathy. Unfortunately, this measurement is very variable. There is a wide range of variability among normal individuals, and this may reflect differences in the anatomy of the peripheral cutaneous enervation.

In addition, there is significant variability in this measurement from lab to lab. There is also variability in the same lab from testing to testing. There are a number of reasons for this variability. One relates to the technical factors of the lab. The size of the disk that we take to the surface will allow a pickup of different amounts of the peripheral nerve action potential. The number of inches between where we record and stimulate will have a large effect on the amplitude that's measured.

There are factors that are related to the patients. Patients with cold hands will have larger potentials. Because we're measuring the potential through the skin, if a patient develops peripheral edema, we may lose our ability to detect the potential, and the patient may appear to have developed a neuropathy. There are differences related to the skill level, and the compulsion of the physician who is performing the test, as well as the trial-to-trial variability that exists.

In studies that have looked at normal individuals and trial-to-trial variability, the differences in sensory nerve action potential amplitudes may be as great as 30 percent. This is in normal subjects in which there has not been any therapeutic intervention.

For this reason, most clinical neurophysiologists are really quite conservative before calling a drop in a sensory nerve action amplitude. The rule of thumb that has really been almost universally applied is that the amplitude must drop by 50 percent before it is considered to be abnormal.

Now, the suggestion has been made in 1994 by Gardner-Medwin, specifically in relationship to thalidomide-induced neuropathy, that we may be able to reduce some of this variability by creating an index which is a summation of at least three sensory nerve action potentials. We refer to this as the SNAP-3, although that was not Gardner-Medwin's terminology.

This measure was proposed based on a retrospective look at patients treated over 10 years with thalidomide who all had nerve conduction studies performed by the same neurologist, presumably Gardner-Medwin. This index of three sensory nerve action potentials was found to drop by at least 40 percent in all of the patients who developed paresthesias. That is the basis for this 40 percent drop of three SNAPs that has been suggested as a criteria for development of peripheral neuropathy.

Gardner-Medwin also noted that if patients developed even a 30 percent drop in baseline, this was suspicious, and there may be cases of patients who should be followed more closely.

Based on this retrospective view, the U.K. guidelines were formulated, as has already been referred to. Of the three components of monitoring, the decision for self-monitoring is that patients should just stop medication if paresthesias develop. Serial neurologic exams should be performed at at least monthly intervals for the first three months. There was no recommendation of how frequently they should be performed thereafter.

Two baseline studies should be done of nerve conduction studies to include at least three sensory nerve action potentials to provide an idea of how variable they would be in an individual patient. Of course, it goes without saying that to decrease variability, these studies should be performed in the same lab, and if at all possible, by the same physician.

Follow-up studies were recommended every six months or 10-gram increment in total dose. This 10-gram increment in total dose, I would like to point out, is based on their experience with patients who primarily received intermittent treatment, usually for one month or two months. Many of the patients were not on long-term, continuous treatment. Those patients that were often were on very small doses, seven milligrams to 100 milligrams per day in some cases.

I think that there are two questions that these guidelines leave still unanswered. They are really quite reasonable guidelines based on the data that is known to date, but they bring up points that really need to be addressed in future clinical studies. That is, really, what is the best way to define probable neuropathy? If patients develop symptoms alone, is that a peripheral neuropathy? The gold standard, of course, would be a nerve biopsy. Is this alone an indication that drugs should be discontinued?

What happens if a patient has no symptoms, and develops a drop in the sensory nerve action potential? In Gardner-Medwin's paper, this was described as a putative subclinical neuropathy, but given that there is so much variability in the detection of sensory nerve action potentials, I think we need to be very cautious before considering that this drop alone is a sign of peripheral neuropathy.

Then the question, I think, that really needs to be looked at in future studies is do abnormalities occur in a predictable sequence, as has been described in further toxic neuropathy? First, patients usually develop symptoms. Then the signs of a peripheral neuropathy begin to develop. At some interval which is really undetermined, there then becomes a decline in the neurophysiologic studies.

It has been suggested that in thalidomide neuropathy, that this drop in nerve conduction studies may precede the development of symptoms. This would be a highly unusual sequence of development of abnormalities in an acquired toxic neuropathy.

So I will close by saying that, as we do clinical trials to assess the efficacy of thalidomide for clinical conditions, we need also to continually look at the question of whether we can adequately monitor for development of peripheral neuropathy.

(Applause.)

DR. BIRNKRANT: Thank you very much.

We will open it up to questions. We can allot about five minutes to questions. You don't necessarily have to fill out the pink sheets. You can come up to the microphones which are in the aisles.

Are there going to be questions from the audience? Please identify yourself.

DR. SHANNON: My name is Shannon, from the Gillis W. Long Hansen's Disease Center. I direct my question to Dr. Patterson.

Have you had any data regarding unhydrolized thalidomide in monkey semen at this point? I phrase that question with the requirement for FDA recommending that males use condoms within a month after they're off thalidomide. Do you have unhydrolized thalidomide in semen?

DR. PATTERSON: No, we haven't looked at that. We have looked at just sperm motility and function, and some different mitochondrial markers. But we didn't look at if there was thalidomide present, per se.

DR. MOORE: Cynthia Moore from CDC.

I think this is more a comment. Today several times it's been mentioned that no pregnancies occurred in clinical trials or in treatment of ENL patients. I want to note that these trials had small numbers of patients in them, and there are very few female ENL patients being treated. We're looking at so small numbers, and within those small number groups even a smaller group of women who actually could get pregnant.

I feel like there has been an inference here that this drug has been safely used in women of childbearing potential. We look at the Accutane data, in which there were a little over one per 1,000 person-years of pregnancy or contraceptive failure. With these small numbers, we wouldn't necessarily expect to have seen pregnancies yet in the data that's been presented.

I don't know if you want to comment.

DR. BIRNKRANT: In the AIDS clinical trials, women of childbearing potential are allowed to enroll. It's just that it's difficult to recruit those patients into clinical trials in general. From our database, we've allowed over the years 72 HIV-infected women, the majority of whom have been of childbearing age. But as you saw from that pie chart, the majority, or approximately half, were surgically sterilized. So you do bring up a good point.

DR. MOORE: In the ENL patients, those precautions were pretty extraordinary.

DR. BIRNKRANT: Thank you.

DR. LONG: My name is Iris Long. I'm with AIDS Coalition to Unleash Power, ACT UP/New York.

I'd like to know, Dr. Birnkrant, how your pamphlet will deal with the neuropathy part of the side effects? You didn't show that. Obviously, it's a significant problem, especially with people with AIDS who have taken drugs that affect neuropathy, in addition to HIV neuropathy.

DR. BIRNKRANT: You raise a very good point. In our second printing of our brochure, we have actually elaborated upon the neurological side effects of the drug, and we do have extensive wording and warnings about the neurotoxic potential of the drug.

DR. PONCELET: Hi. I'm Ann Poncelet. I'm a neurologist from the University of California in San Francisco. I had two questions, and the first I wanted to direct to Dr. Patterson about the nerve conduction studies in the monkeys.

The one concern that I had is, you mentioned the one change was found in the F-wave studies. That usually, in humans anyway, we interpret as a problem with proximal conduction in motor nerves. In thalidomide neurotoxicity in humans, our thought is that it's an axonal sensory process that begins distally, not proximally. How accurately may this reflect the nerve problem we find in humans?

DR. PATTERSON: Yes, that's a good question. We are trying to back this up histologically. A lot of the data, especially the conduction velocities and amplitudes in our animals, I think it's similar in humans, that there is a lot of variability there, and it's just hard to make sense out of. I don't know if just the animal models -- according to Dr. Schaumburg, I'm sure he would say that they are more resistant to showing an effect of the neuropathy.

We have taken the sural nerve to look at different markers to see if we can see an effect with some more sensitive markers besides electrophysiology. We know that electrophys is not the most sensitive measurement that we have.

DR. PONCELET: The second question I had was for Dr. Floeter, with regard to the Gardner article. When I read that article, one of the questions that came up is, when they did the summation of the sensory nerve action potentials, they were looking at sural, median, and ulnar sensory nerve action potentials. I just was kind of somewhat surprised that that was a more consistent reflection of a change, since the upper extremity sensory nerve action potentials would be less likely to reflect neurotoxicity, again in thalidomide neuropathy.

What were your thoughts about that?

DR. FLOETER: Yes, I think that most of the studies before that time have really focused on the sural nerve action potential, because that's the most distal nerve that people commonly study in the feet. The index that they describe has a normalization factor for each nerve. So if the sural nerve drops by 50 percent of the three there, then it contributes -- whatever, 50 percent divided by 3 -- to the drop in the SNAPs.

We have actually wondered about the involvement of using the median nerve, since carpal tunnel syndrome is so common, and an incidental carpal tunnel syndrome may initially present with tingling in the fingers, and being mistaken for a development of a toxic neuropathy. So in the patients that we study, we have actually been trying to do four or five sensory nerves, and have been looking prospectively at combinations of different nerves to see if they are in fact more reliable.

We have also been looking in a cohort of older patients, to match one of the cohorts that is being studied by the Cancer Institute, to see if this sort of variability of 40 percent can be seen in normal subjects. Now, that's about nine months into a longitudinal study, in which the subjects are being studied every three months, but there are occasional patients who have a 40 percent change in that summation of three SNAPs or four SNAPs.

So I think that you probably come from the same school as I do, where we interpret the nerve conduction studies as a continuation of our neurologic exam. We're very skeptical if there is a change in the numbers, and the patients seem to be perfectly fine in terms of symptoms and objective signs.

DR. PONCELET: Thank you.

DR. BIRNKRANT: One last question.

DR. LARD: Sheryl Lard, FDA.

I have a question for Dr. Patterson. You mentioned in a previous marmoset study that CD26 expression changed. Did that go up or down, and what subsets were involved?

DR. PATTERSON: I believe he showed that there was a loss of CD26 on the monocytes, and I think maybe even some lymphocyte positive there were some losses. Now, I don't know what subsets there he was looking at.

DR. CRAWFORD: There may be a possibility of introducing another test. I'd like to know what the experts here think. That's PGP 9.5. It detects axons in dermal nerves. That would be quite easy to biopsy. I believe Dr. Griffin from Johns Hopkins has done quite a lot of work, not on thalidomide neuropathies, but on other neuropathies. That would be something that could be done serially without much disturbance to the patient.

DR. FLOETER: I really don't have any experience with that. I think however, though, that the technique of quantitative sensory testing, which is really quite well-tolerated by patients, is one that might be considered as a noninvasive method for future studies.

DR. BIRNKRANT: I want to thank all of the panel members.

We'll take a 10-minute break, and return around 3:20 for the next session. Thank you.

(Recess.)

DR. MILLS: I'm Jim Mills. I'm from NICHD. I do birth defects research here on NIH facility. I'd like to welcome you all back to our last session of the day. As you know, this is on pregnancy and embryopathy. I want to congratulate you on your perseverance here. I think it should be well-rewarded. As someone pointed out earlier today, this is the main event. This is the reason we're all here instead of just looking at some notes from some meeting at the FDA.

In terms of introductory remarks, I'm going to follow the advice of Mese Vanderow, who said, "Less is more." I'm going to immediately introduce our first speaker, who is **Dr. Barbara Hill,** who is a pharmacologist and toxicologist at the Center for Drug Evaluation and Research at the FDA. She is going to speak to us on characterization of embryopathy risks.

DR. HILL: Hello. I want to take this opportunity to thank the organizers for inviting me to participate in this workshop. I was asked to give a presentation on the characterization of embryopathy risks associated with thalidomide use. This next slide provides an outline of the topics that I will cover in this presentation.

The first, just to give a brief historical perspective, followed by a discussion of the teratogenic effects seen with thalidomide exposure to the fetus; then a brief discussion of the thalidomide window, which is also referred to as the sensitive period; and then conclude by discussing some proposed teratogenic mechanisms.

This first slide goes over some historical perspective. Thalidomide was introduced to the German market as Contergan in 1956 by a West German company known as Chemie Grunenthal. It was marketed in the United Kingdom and other countries after 1958 as a sleeping aid, a sedative/hypnotic. The reason why it became so popular so rapidly was because of its reported prompt action, its lack of hangover effect, and also its apparent safety. In animal studies, there was no established LD50.

Quickly a target population developed, and that was in pregnant females. The primary indications for this patient population was as a sedative sleep aid, but it also was prescribed as an antiemetic to reduce nausea associated with morning sickness.

The availability, as was previously described by Dr. Kelsey, was initially as an over-the-counter medication. It was available in non-prescription. But then, as reports came in about potential toxicities, it later was available via prescription.

There was an article published in the Washington Post on July 18, 1994, that described an occurrence on Christmas Day in 1956. There was a girl born in Stolberg, West Germany without any ears. It was later determined that the father of this little girl was an employee of Chemie Grunenthal, and had given samples of this new drug thalidomide to his pregnant wife to calm her nerves.

This German girl was the first of an estimated 5,000 to 6,000 infants reported with characteristic thalidomide-induced phocomelia, often accompanied by deformities of internal organs. That number has increased, as reported in the literature, up to 10,000 to 12,000 infants that were affected by the phocomelia.

McBride in 1961 and Lenz in 1962 were the first to document an association between the maternal thalidomide and the limb defects. This led to thalidomide being withdrawn from the world market in 1961.

This next slide goes over a brief description of the teratogenic effects associated with thalidomide exposure. Thalidomide used during pregnancy could cause phocomelia, as reported to occur in 20 to 50 percent of women that were using the drug, although I have seen reports recently that indicate that perhaps the incidence rate could be as high as 90 percent. The startling effect is that this could occur after a single 100 milligram per day dose of thalidomide.

The characteristic effect seen is stunted, flipper-shaped arms and legs, missing fingers, absence of the proximal portion of the limb, hands or feet attached to the body by a single, small, irregularly shaped bone, and in some cases entire absence of limbs.

The sensitive period for thalidomide exposure is commonly identified as occurring from day 34 to 50 after the last menstrual period. Exposure prior to day 35 results in the earliest thalidomide anomaly, which is ear defects. Exposure in the early part of the window results in a higher number of arm deformities. Exposure in the later part of the window results in a higher number of leg deformities. It was established in the literature that there was a good temporal correlation with the thalidomide-induced deformities and the appearance of the limb buds.

However, the effects of exposure after day 50 have not been well characterized for thalidomide. It has been suggested that perhaps exposure in the later portion may be responsible for some developmental psychological effects. There has been a report in the literature to suggest that thalidomide exposure may be related to the occurrence of autism as well, but that has not been well characterized at this point. Much more research is needed in that area.

In the next two slides, I have listed what I refer to as the thalidomide embryopathy table. A version of this was shown in Dr. Birnkrant's presentation. This just shows the type of malformation that is seen after the days of post-menstruation.

I just wanted to highlight that, once again, the earliest effect is effect on the ear. Then you see an effect on the thumb. Then later effects, the first internal organ system that seems to be affected is the cardiovascular system. As was mentioned earlier, it's important to understand that not only phocomelia effects are seen with thalidomide exposure. There are effects, distinct effects, on internal organs.

Later exposure results in effects on the arms, as well as hip dysplasia. There is also malformations of the eyes seen, pylorus stenosis. Then in later exposures you see effects on the duodenum, then also malformations of the respiratory tract and urogenital tract, and effects on the gallbladder. Then the later effects for the phocomelia portion is effects on the legs. Then the last effect that was seen was the stenosis of the rectum.

On this next slide, I'd like to go into some background for discussion of the proposed teratogenicity mechanisms. First, from a research perspective, I wanted to provide you with information on the relative order of species sensitivity to thalidomide teratogenicity. That is,

man is approximately equivalent to monkey in this effect. Monkey is much more sensitive than the rabbit, which is much, much, much more sensitive than any of the rodent models that have been examined.

However, it's important to note that in the rodent models, you do not see the characteristic phocomelia, but you do see an increase in fetal resorption. So therefore, there is a thalidomide-induced effect in the rodent, just not the characteristic effect that we see in humans.

To give you an idea of the difference between sensitivity of monkeys and rabbits, is that the thalidomide syndrome was produced when eight to 10 milligram per kilogram of thalidomide was administered to monkeys on days 25 to 30, and that rabbits required administration of 150 milligram per kilogram of thalidomide on days seven to nine to produce the characteristic limb defects.

The reason for the chemical and species specificity remains an intriguing pharmacologic riddle. It has been mentioned previously that we do not have an understanding of what is responsible for the teratogenic effects. Is it the parent compound, thalidomide? Is it potentially a hydroxylated product formed from cytochrome P450, or one of the many spontaneous hydrolysis products that is formed? We have no idea at this point in time.

There was a review conducted by Stephens in 1988 that listed and discussed 24 cellular or biochemical mechanisms of teratogenesis. The conclusion from this paper was that more research is required to determine the mechanism of teratogenicity for thalidomide. The author's interpretation of this results from this review that there is not enough evidence to suggest that any one of these mechanisms may be responsible for the teratogenicity. However, based on my review of the literature, I'd like to present what I consider are the three leading possibilities in the next several slides.

The first hypothesis I would like to discuss is the neural crest hypothesis that was suggested in 1973 by McCredie and McBride. In that, they said that there was a relationship between the thalidomide deformities and the nerve supply. There is critical evidence that became available that thalidomide damages the sensory peripheral nervous system. We heard a lot about that in the previous session. It was also suggested the thalidomide inhibits the production of nerve growth factor, in a similar manner that it inhibits the production of tumor necrosis factor alpha.

Simply stated, the neural crest hypothesis says that the thalidomide causes toxic insult to the embryonic neural crest during the organogenic period.

In this particular paper, they conducted an experiment, and exposed pregnant rabbits to 150 milligram per kilogram per day of thalidomide during their sensitive period, which was days seven to nine. The nerve supply to the limb buds was examined in four control and 13 treated fetuses on day 29 of gestation. Within the 13 treated fetuses, six of those were not deformed, two had moderate deformities, and five showed severe deformities.

The results from this experiment showed that there was a significant reduction in the total fascicular area, and in a number of large diameter nerve fibers in all the treated animals. There was also a significant depletion of total fiber nerves in the deformed fetuses compared with the controls.

The results from this experiment suggested that the failure of primary embryonic limb growth was due to a drug-induced reduction in the quantity of nervous tissue within the limb bud. These findings are similar to the quantitative changes described in human adult subjects with thalidomide-induced peripheral neuropathy.

The second teratogenic proposal I'd like to discuss was proposed by D'Amato in 1994. That is that thalidomide is teratogenic due to its being an inhibitor of angiogenesis. It was shown that thalidomide was an inhibitor of angiogenesis induced by basic fibroblast growth factor in the rabbit corneal micropocket assay. What these investigators did in this publication was analyzed the effects of several thalidomide analogs with varying degrees of associated teratogenicity in this particular assay. The results showed that the antiangiogenic activity correlated with the teratogenicity, but not with the sedative or the mild immunosuppressive properties of thalidomide.

The third proposed mechanism I would like to discuss is a very recent one proposed by Neubert, et al., in a 1996 publication, which looked at the downregulation of adhesion receptors after exposure to thalidomide. It has been established in the literature by this group, as well as others, that exposure to thalidomide causes a downregulation of these adhesion receptors in peripheral white blood cells. But it was not known if that would happen in the embryos. It wasn't known if in embryos there was any expression of adhesive receptors, and if there was, what the effects of thalidomide might be on that.

So this group of investigators examined the effect of EM12, which is a thalidomide derivative and is a very potent teratogen. It's much more potent than thalidomide, but it exhibits the same spectrum of phocomelic effects. They looked at the effect of EM12 on the expression of numerous adhesion receptors in the primate, in particular the marmoset embryos.

What they observed was a dramatic and statistically significant downregulation of several surface adhesion receptors, which are listed on the slide, on early limb bud cells and on cells of the heart during early organogenesis of the embryos. This is important in that they saw it on both bud cells, and in the heart, with the heart being one of the first internal organs to be affected by thalidomide exposure. This result suggests that the teratogenicity may be due to altered cell-cell or cell-extracellular matrix interactions.

I would like to discuss what was recently talked about in the popular press, which is the potential for thalidomide to be a mutagen. There was a "CBS Evening News" special on July 26, 1997 which suggested that there was a potential second-generation effect of thalidomide. They showed a girl that was born with no thumbs, and only two digits on both hands, whose father was an apparent thalidomide victim.

What I would like to bring to your attention is that this has been discussed in the literature previous to this CBS special report. The first discussion of it was in an article by McBride, who was the initial investigator to bring up this proposal. Then that was discussed further in three additional publications following that by the following investigators shortly after that, in their opinion, they didn't believe that this was due to second-generation mutagenetic effects, that since the similarities between the girl's phocomelia and the father's phocomelia were exactly the same, that argued more towards an inheritable phocomelia syndrome, instead of a second-generation effect from thalidomide.

I'd just like to close my presentation with a final thought from a publication by Castilla, et al., in 1996. In this publication, they made it aware that thalidomide is available in eight of 10 South American countries through leprosy treatment centers. Within those eight countries, Brazil has the highest prevalence of leprosy. Thalidomide is also available at some pharmacies in Brazil, not only through leprosy treatment facilities.

Thirty-four cases of thalidomide embryopathy were born after 1965. This was determined by a case-reference approach. Thirty-three were born in Brazil, and one born in Argentina. The conclusions that these authors derived from this review of this information was that there is a need to define what to look for if this approach is to be truly effective.

I think that is important, to be able to really characterize what types of effects can be attributed to the thalidomide, and what could be attributed to a potential inherited phocomelia effect. That way, we can devise a database to follow potential thalidomide-induced phocomelia, and then further down the road determine if the benefit of the use of thalidomide truly is greater than the risk associated with thalidomide-induced embryopathy.

Thank you for your attention.

(Applause.)

DR. MILLS: Thank you, Dr. Hill.

Our next speaker is **Dr. Christine Mauck,** who is a medical officer at the Center for Drug Evaluation and Research at the FDA. She will speak to us on pregnancy prevention in patients taking thalidomide.

DR. MAUCK: We've heard several speakers talk today about the risk of pregnancy, and they have said that we cannot reduce the risk of pregnancy in people taking thalidomide to zero. I agree with that. What I'm going to talk about is how far we can reduce that risk, and how feasible it is to try to detect pregnancy early enough to stop the drug and avoid fetal harm.

Let's start out by talking about who we're worried about. The obvious group is women taking thalidomide during the sensitive period. This has been defined as 21 to 36 days after conception, or 35 to 50 days after the last menstrual period in a woman who has 28-day cycles. This means that the sensitive period starts one week after a woman has missed her

period.

The group that we're not sure about is female partners of men taking thalidomide. Cindy Moore and I were just talking that this is a study that really needs to be done, whether there is thalidomide in ejaculate.

How much do we need to worry about pregnancy? The answer is we need to worry a lot. In a population of women of childbearing age without a history of infertility, in the absence of contraception, about 85 percent will become pregnant in a year.

How good are we at preventing pregnancy? Only surgical removal of the uterus, sustained abstinence, and documented menopause are 100 percent effective in preventing pregnancy. Even sterilization is not 100 percent effective. Contraception, including sterilization, can reduce the risk of pregnancy by 99.9 percent.

I want to go to the next overhead, but keep this one because I'll come back to this one. Go ahead and switch, and I'll come back to that one.

This is a table that the FDA drew up using information from the next issue of Contraceptive Technology, which is currently in press. Sponsors of contraceptive products are being asked to include this in their next version of their labeling. What it shows is the various methods of contraception, and pregnancy rates that can be expected during typical use, which includes some imperfect use, and the pregnancy rates that can be expected during perfect use. It divides contraceptives into these categories: sterilization, hormonal methods, intrauterine devices, barrier methods, herbicides, and natural methods, and no method, which gives us the 85 percent pregnancy rate.

The most effective methods are the ones in the first three groups, which give you pregnancy rates of less than 1 percent, which means they prevent pregnancy 99 percent of the time, even in typical use. You will notice that none of these have the figure of zero.

I just want to point out that the most effective specific methods -- namely, sterilization, implants, and the copper IUD -- are what have been referred to as verifiable methods, which means that the clinician can feel assured that the woman is actually using this method. This is something that I'll come back to in just a second.

Can you go back to that other overhead? We are down to this level. Doubling up, or using more than one method, can increase the efficacy of contraceptives if methods that aren't that effective to begin with are being used. There isn't a lot of improvement in some of these very effective methods, so doubling up wouldn't really help much.

As we heard earlier, thalidomide doesn't appear to reduce the contraceptive efficacy of steroids, based on drug interaction studies. There is no reason to expect that thalidomide would reduce the efficacy of other methods like sterilization or IUDs. However, barriers, there may be an effect, not of thalidomide, but on the population treated with thalidomide on the efficacy of barrier methods, because those are the methods that require compliance on

the part of the user.

I think there are some competing forces at work here. I think that a properly informed thalidomide user would be very highly motivated to prevent pregnancy. But on the other hand, if the drug is used in people who may have impaired judgment at times, for one reason or another, like drug use or sedation or whatever, even their best intentions may go astray, and they may not be able to comply.

This is what has led to the recommendation for verifiable methods. I agree that that would reduce the risk of pregnancy the most, if everybody was using sterilization or implants or IUDs, but I'm uncomfortable with the idea that that has to be mandated for everyone on thalidomide, regardless of her personal circumstances.

I do think that emergency contraception should be available to everyone, which brings me to the next overhead. Emergency contraception used to be called the morning after pill. It's no longer called that because it's not just pills that work. IUDs work. It's not restricted to the morning after. Pills can be given up to three days after unprotected intercourse, and the IUD can be inserted five to seven days after unprotected intercourse, and it's still effective.

Emergency contraception should be distinguished from abortifacients, which are given after a pregnancy has been established.

The typical dose of emergency contraception that is in the form of oral contraceptives is a double dose of OCs or oral contraceptives 12 hours apart, or a placement of an IUD. The FDA has gone on record in the Federal Register in February of this year as saying that emergency contraception is safe and effective, but no sponsor has applied for and received labeling for this purpose.

Emergency contraception can be used when a woman suspects loss of her contraceptive protection. For example, when a condom breaks. It reduces the likelihood of pregnancy by 75 percent. I do feel that it should be immediately available -- in other words, given to a woman who is given thalidomide.

So we do have effective ways of reducing, although not eliminating, the risk of pregnancy, at least in theory. Now, how well do we think this will actually work?

We're going to hear from Dr. Allen Mitchell in a few minutes. He's going to talk about his experience with the Accutane pregnancy prevention program, which is an intensive program to prevent pregnancy in women taking Accutane, which is also a teratogen. I don't want to steal his thunder, but I will be presenting some of the pertinent results from his survey on Accutane users.

It was recommended to Accutane users that they use two methods. About 20 percent of them actually did, but only .6 percent were sexually active without any contraception at all. These women, I am told, were read the riot act, and we hope that they didn't continue to do that.

Only 1.4 of the non-contraceptors became pregnant, which is a low number, and I think encouraging. Then .4 percent of contraceptors became pregnant, which is also low, but this does demonstrate that pregnancies do occur, even with that type of intensive counseling.

Among the 74 live births, at least five of 36 who were examined had Accutane-compatible birth defects. It's hard to say how thalidomide users might compare with Accutane users. I think thalidomide users would probably be sicker, but I think they might have some characteristics that I've already mentioned that might make them have a little more trouble complying with contraception in some cases.

I think from this experience with Accutane, all we can conclude is that pregnancies do occur, despite everyone's best efforts. If we can't totally prevent pregnancy, can we detect it early enough to stop the drug and prevent fetal harm?

This is a difficult question, and it requires that we operate on three assumptions. The first one is that the sensitive period is restricted to 21 to 36 days after conception. The second is that it takes nine to 10 days for a serum pregnancy test to become positive. I'm going to use the figure 10 to be conservative.

The test can be negative -- and this is important -- even though conception is nine to 10 days along. So a negative pregnancy test does not rule out pregnancy. I think this gets to some of the discussion we had earlier, where we were saying that detection does not equal prevention. It does not equal prevention of pregnancy, or of drug exposure, either. I think that's a critical point to remember. Also, conception could occur right after a negative pregnancy test.

So all that negative pregnancy test tells you is that a woman is not more than 10 days pregnant, but she could be less than 10 days pregnant. If a woman is not pregnant, we will expect that menses will occur about 14 days after ovulation.

So given these assumptions, this is what I would propose. I have to point out that this is kind of a personal proposal. It's based on what CDC and FDA have recommended, but I have added some details about timing.

I would suggest that women get tested at baseline before they receive thalidomide. If that's negative, then they get 10 days of thalidomide. They would come in for a second pregnancy test 10 days later. If that's positive, the drug would be stopped. If the woman had been nine to 10 days pregnant at the time of her first test, which was negative, she would be 18 to 20 days along at the time of her second test, which was positive. This would allow her to stop the drug just before the sensitive period began at 21 days.

If her second test was negative, we could continue testing every 10 days, but since treatment for ENL, for example, could go on for 10 years, I think that's not feasible. Also, that sort of restriction would probably drive people to buyers clubs, and defeat our purposes. An alternative to testing every 10 days would be to give 28 days of therapy, and continue

retesting every 28 days.

The problem with this is that, if it's not linked to the time of expected menses, a woman could conceive on day 14, for example, come in on day 21, at which time she would be seven days pregnant, but her tests would be negative. She would be given 28 days of thalidomide. She would take it all, perhaps, which would get her to day 35, which is 14 days after the sensitive period begins.

Granted she should have noted she missed a period in there, but not everybody does. So what I would suggest is that retesting be done every 28 days at the time of expected menses. So a woman would be asked to come in two to three days after she expects her period to start. If the test is positive, obviously we'd stop the drug, and she probably wouldn't be more than 16 or 17 days along at that time. If it were negative, and her period had started and was normal, she would be given 28 days of treatment.

If it was negative and there was no period, she either is just having a late period, or she is pregnant. At that point, we could either give 10 days of treatment or no treatment, and bring her back in in 10 days and retest. We continue that pattern until she either had a positive test or her period finally started.

Doing it this way would, at the most, expose her to 18 to 20 days of drug before she stopped it. I think this is the best way I can think of to reduce the risk of fetal exposure, but it requires that patients keep their appointments, and also that the drug be filled pretty much the same day that the prescription was written, which would be quite challenging, but I think doable.

The real problem, though, with this is trying to predict when a woman is going to have her next period. Almost no woman has 28-day cycles every cycle. Almost no woman has cycles of the exact same length all the time. One thing that could be done is using ovulation detection kits at home, but those cost about five dollars a day to use, and I don't think that's economically feasible. So I think the clinician and the woman just have to get together and make their best guess at when the next period is going to occur.

For methods like Norplant and Depo that throw periods off completely, I think all we can do is test every 28 days without regard to when an expected bleeding is going to occur. Fortunately, those are a couple of our most effective methods.

It's critical that all unused medication be returned. Male thalidomide users should use condoms even if they are vasectomized, until we know if there is thalidomide in the ejaculate. The reason for this, and I know this is far-fetched, but I thought of this, and then someone else brought it up to me, so I'm not the only one who thought of this.

If a male thalidomide user who is vasectomized has intercourse with someone, and deposits perhaps thalidomide in her reproductive tract along with ejaculate, and then it's absorbed into her system, she won't get pregnant from him unless his vasectomy fails. But if she went

and had sex with someone else, she could possibly get pregnant from them. So, like I said, I know this is far-fetched, but I think raising this possibility is part of properly informing men until we know if there is thalidomide in ejaculate.

So, what if we have done all of this, and we've still be unable to avoid fetal exposure? What are the possible outcomes of a pregnancy? They are the same as in any other pregnancy -- delivery, spontaneous abortion, or induced abortion.

If delivery is elected, what's the likelihood of fetal abnormality? I've seen lots of figure. The figure I've seen the most is 50 percent. I've seen it as low as 10 percent. I've seen one figure of 100 percent, if thalidomide is taken in the sensitive period. This compares to a rate of about 3 to 5 percent of birth defects in the general population.

How likely is spontaneous abortion? About 10 to 15 percent of recognized pregnancies spontaneously abort. By recognized, I mean the woman has either had a positive test or she has missed her period. The effect on thalidomide on spontaneous abortion rates isn't known. There may be an effect, but I haven't seen figures that give us an idea how big that is. Just by way of comparison, 16 percent of pregnant Accutane users spontaneously aborted.

The third possibility is the one that is the most sensitive, and that is induced abortion. I've been asked if approval of thalidomide would increase abortion rates, and I think we need to look at some background figures to put that in perspective. Three percent of women of childbearing age in this country have an abortion each year. It's estimated that 43 percent of women will have one by the time they're aged 45. About 25 percent of all pregnancies end in induced abortion in the United States.

The rate is likely to be much higher in thalidomide users, as you can see, but the conceptions should be much fewer. By way of comparison, 72 percent of pregnant Accutane users chose abortion.

I've been asked, is it possible that a woman could undergo frequent ultrasound and try to determine if there's a defect present, and base her decision whether or not to abort on that? It is true that limb defects are visible on ultrasound in the first trimester, which is the time when abortion is safest and easiest to perform. But other defects, like cardiac defects, may not be detectable at all in the prenatal period. So I don't think that fetal monitoring and using ultrasound is of any particular helpfulness in trying to decide what a woman should do if she's in this situation.

The bottom line to all of this is that there will be pregnancies conceived during thalidomide use if the drug is approved. This is going to be due to failure to comply with contraception, failure of the contraception itself, or the drug falling into the hands of women who are not aware of the risks. Some of these pregnancies will be carried to term, and I think there will be infants born with thalidomide-related defects.

I'm not the first person to say this today, but I will say it. We cannot reduce this risk to zero.

If the drug is approved, I think that education of both patients and clinicians and everyone involved in the line of drug supply will be very, very important to minimize the number of affected fetuses.

Thank you.

(Applause.)

DR. MILLS: Thank you.

Our next speaker is **Dr. Robert Miller**, who is scientist emeritus at the National Cancer Institute. He will be speaking with us on how environmental effects on child health are recognized.

DR. MILLER: Thank you, Jim.

May I have the first slide, please?

This is an MRI of a grownup fetus, a woman who was exposed in utero in Hiroshima to the atomic bomb. The fetus received 1.76 gray or 176 rad in the 12th to 13th week of gestation.

That was recently found, but the story began, as almost all stories of birth defects in the human due to teratogens have begun, with clusters that have led to the recognition of almost all known human carcinogens and teratogens. These observations are usually made by alert clinicians, but they may be made by anyone at all who is observant. In China, an alert peasant pointed out that the chickens had esophageal cancer in the same area where the people did, for example.

It's not enough to show that there is a cluster and that the people were in utero at a time when radiation was given, because the drug company or the radiology profession will say that it was due to the underlying disease in the woman for which the x-ray was given, or that there was some other drug given that was the real cause. So you have to have aids to establishing causality.

These are the six main ones. Is there a dose-response relationship? Can the findings be replicated by others? Are there similar effects in animals or in lab studies? Are there alternative explanations -- cigarette smoking, for example, in studies of lung cancer? Is the finding biologically plausible? Does the affect disappear when the cause is removed?

I'll give some examples of how these observations have been used in the establishment of causality, first with regard to radiation.

May I have the next slide, please?

Here is the history, briefly summarized. In the 1920s, there were individual case reports of small head size and mental retardation in children whose mothers received therapeutic high-

dose radiation early in pregnancy. That's the way it begins with case reports, individual collections.

In 1929, at the University of Pennsylvania, a mail survey was made of obstetric experience, and a total of about 30 cases with small head size and mental retardation were discovered. This was done by a professor at my medical school. He presented it to us 52 years ago, and I've been a witness to what's happened ever since, not stimulated by him, but just by the natural course of events.

In 1938, there was animal experimentation. In 1952, a prospective study could be made at the Atomic Bomb Casualty Commission because the cohort of fetuses had been exposed to the atomic bomb, and could be followed over time to see how many of them developed whatever disease, cancer or small head size and mental retardation.

The next slide shows the clinics where the studies were done. Actually, that's a pediatric clinic. The quonset huts were really very attractive architecturally, without meaning to be.

Toward the end of these studies -- next slide -- we had a medical student on elective with us for one month. She was a statistician before she went to medical school. It is Dr. Deborah Murke, who is now at the Child Health Institute.

She made this graph. It shows the dose at the bottom in rad, and along the side the gestational age in weeks. The bottom one is zero to seven. There are no cases. The blue dots mean severe mental retardation. At eight to 15 weeks, there is a cluster, and there is some overflow into 16 to 25 weeks. The blue dots to your left are from a larger population, and really don't represent an increase. The two Xs mean that mental retardation is explained -- it was due to Down's syndrome -- so those don't count. Then you begin at 61 rad, which appears to be the lowest dose that can induce severe mental retardation.

The next slide illustrates that we're able to find small head size without mental retardation because the brain was affected, but not enough to cause severe impairment of intelligence. At the bottom, you see the doses in rad, and there's a wonderful dose-response relationship. This is small head circumference, Hiroshima children exposed in utero before the 18th week of gestation.

So we go next to the history of diethylstilbestrol-induced cancer of the cervix. Believe it or not, I'm still talking about teratogenesis. In 1970, the pathology of seven cases was studied at Mass General Hospital. An interesting thing happened. The gynecologists were impressed by this number, but they didn't know what to do with it. One of them was taking an elevator with an epidemiologist who said, "You should do a case-control study," so they did. The epidemiologist joined the group. There were eight cases then, versus 32 controls.

Even before they got to the question, two of the mothers said, "I think it was DES." It proved to be. It was confirmed at the New York State Tumor Registry, but not in Connecticut. I'll explain why a little later.

In 1973, a prospective study at the Mayo Clinic showed the risk to daughters of women who had taken DES was about -- actually I think it should be 1.3 by 22 years of age, and the risk eventually was close to one in 1,000. Hundreds of cases have now been described.

The child to your left is a normal newborn, and to your right is a child with PCB poisoning. This was in Southern Japan, Kyushu Island. It's a big island. The child with PCB poisoning shows what the Japanese call Coca-Cola colored skin until the Coca-Cola Company notified that that was an infringement of their patent, and they had better cut it out. So now they're called cola-colored babies, a generic term.

They have a small phedate, and the color clears with time. With successive pregnancy, the color diminishes. The PCBs are stored in the mother's body, and effect each pregnancy for awhile. There are other abnormalities which I won't go into, except for one is a natal tooth. Some of the children were born with teeth.

Replication. How do you replicate this? Well, unfortunately it happened. The Japanese exported some of the same equipment. It was a heat transfer system that used PCBs to transfer the heat out of cooking oil as it was manufactured. They sent this to Taiwan where the same thing happened. The children and adults developed chloracne, green acne, 1,000 or 2,000 cases in Japan. There were children who were affected in utero, nine in Japan, and I don't remember how many in Taiwan.

The next slide, another Japanese observation. This is Minamata disease, congenital. At first it was missed, but then a psychiatrist, Dr. Herada, found a number of patients. Actually, there were 40.

Here he has pieced together two of the photographs he took to show how many there were of these children who were affected when a factory dumped its waste into the bay, and the waste contained methylmercury, which was ingested by the fish, and the fish were eaten by cats. Then the birds ate the fish, and the people especially, the fishermen, ate the fish, because they ate the worst of their catch and sold the best of it. Unfortunately, the children were severely affected.

The next slide is a newspaper headline about kepone, not far from here, Hopewell, Virginia. Here neurological disease developed 16 months after kepone manufacture was started in Hopewell. One patient went to a Taiwanese-born internist in Hopewell, Virginia, and the internist did something that was disallowed. He got a blood specimen and sent it to CDC without permission of -- actually, it was Renata Kimbro. She was away. The technician said in error, "You can send it." He did, and they found kepone, the explanation for the neurological disorder. Here the alert clinician was this internist in a relatively small city.

The next slide is an even more spectacular discovery. Male workers who were making -- I have to think -- DBCP, dibromochlorpropane, wanted to become fathers, and a number of them were sterile, were unable to reproduce. So they complained to the factory doctors, who said, "You'll outgrow it." So the men took their own semen specimens to a laboratory, and

the laboratory refused to give them the results. But eventually, the laboratory gave it to Dr. Whorton, who had connections both with management and labor at the factory. He confirmed that the men had no sperm. So this was an alert observation by the workers.

The next slide shows a disorder that would be missed by a birth defect registry. For the birth defect registry to work, it has to be in the right place at the right time. This disease malformation is caused by methotrexate, a folic acid antagonist. This was the tenth one due to methotrexate at the time this was published. The next slide shows aminopyrine, which does something similar. These are individual cases, but when you can collect them from the literature, you can see clearly that such a strange abnormality must be due to the drug that the mother took.

Next is tetracycline-stained teeth. These were observed in 1956 in children who had cystic fibrosis and had received heavy doses of tetracycline. Tetracycline given at the end of pregnancy will do the same thing to the tooth buds not yet erupted. It will stain growing bone wherever it is, whatever bone.

This was missed. Forty or 50 cases were seen in cystic fibrosis, but no public announcement was made. It was published in an annual review of new drugs, kind of an encyclopedic book that nobody would read. Finally, the Australians, who always do these things well, did an epidemiologic study, proved it, published it in the Lancet, and after 1962, there are no new cases.

The next slide, this is warfarin sodium, the second case. The mother was given the drug during cardiac surgery. It's strange. This was 1968. It looked like it was due to the drug. No further cases were seen for seven years. Then there were five of them, three in South Africa, and two in Seattle.

The next slide is a little off the path of my talk, but I can't resist. This is Dr. Mianishi, who is an intern at Hiroshima University. He said to a 30-year-old patient, "Why do you have lung cancer when you're so young?" The patient said, "It's probably because I worked in the mustard gas factory for a year 10 years ago."

We funded him with a small contract for two years. Originally, they found 19 cases of respiratory tract cancer, as shown here, with the contract we provided. They eventually found 75 among 500 mustard gas workers due to an alert observation by an intern.

Finally, the last slide shows one phase of thalidomide not already mentioned. The dotted line indicates the amount of thalidomide sold. The solid line indicates the frequency of phocomelia in Hamburg, Germany. So this is an example of discontinuing the exposure ends the epidemic, which we hope remains ended, although we've already heard today that Brazil is staging a comeback.

Thank you.

(Applause.)

DR. MILLS: Thank you, Dr. Miller.

That reminds me of a story of two patients in the ophthalmologist's office saying, "Isn't it a coincidence that both of our children have eye problems, and we had rubella when we were pregnant?" That's actually the way that that particular teratogenic effect was identified.

Our next speaker is **Dr. Allen Mitchell,** who is the associate director of the Slone Epidemiology Unit at Boston University. As already mentioned, he is going to speak with us about the experience with Accutane.

DR. MITCHELL: Thanks, Jim. It's a pleasure to be here.

I want to mention at the outset, by way of full disclosure, that we had been approached by Celgene to discuss the possibility of a survey analogous to the Accutane survey, should thalidomide come to market. We have been talking to them seriously about that.

Let me begin. This is an assessment of the Accutane or isotretinoin pregnancy prevention program, a program that we had nothing to do with designing, but which we were asked to evaluate. My co-workers, Carla Van Bennekom and Carol Louik, were intimately involved in this.

Just a very brief history. In 1982, Accutane was introduced in the U.S. market. The label, from the outset, warned of potential teratogenicity based on animal studies. Between 1982 and 1988, the human teratogenicity of the drug was documented. Warnings were reinforced, but reports of exposed pregnancies and malformed infants continued, prompting in 1988 an FDA review.

Some important considerations at the time was that it was a known teratogenicity. It had unique efficacy for the treatment of severe recalcitrant cystic acne. It required generally a short treatment course of approximately five months, and it had a short half-life.

The alternatives considered, in sort of global terms, were, one, to remove the drug from the market; two, to restrict distribution; and three, to develop and implement the comprehensive pregnancy prevention program. Two and three are not mutually exclusive, as the last days have revealed.

The last choice was the one pursued. As a result, the pregnancy prevention program, or PPP, was introduced in the fall of 1988. It's a multi-component program aimed at female patients and their physicians. It was really an unprecedented and novel approach. What I'd like to do is briefly review some of the components of that program.

First of all, as I mentioned, it is a multi-component program that was provided to physicians in this box of materials. That box included a patient qualification check list, which was to be completed before placing a patient on Accutane; a patient information brochure; a birth control brochure; telephone information -- an 800 number, toll-free number was set up, and patients could call and receive information in any of 13 languages; and importantly, a

contraception referral program, in which the manufacturer would pay the patient for a referral to a specialist in contraception counseling, if the practitioner/prescriber did not feel sufficiently comfortable to provide that information. In addition, there was a patient informed consent, a patient self-evaluation, and a guide to consent as well.

Another aspect of the pregnancy prevention program that was unique was the development of this blister package, which I think has received a lot of discussion. This is a fold-over package. You can see the line drawing of the malformed child, a lot of red and black warnings, and the introduction of this Avoid Pregnancy symbol. Behind each of these is the capsule. In order to push out the capsule, you basically had to sort of see this symbol every time you took a dose.

Well, that's well and good, but the question was, does the pregnancy prevention program work? We saw this as a unique opportunity to assess whether a human teratogen can be used with relative safety, so we initiated a survey of Accutane use in women. This was sponsored by, and continues to be sponsored by, the manufacturer, Hoffman-La Roche. The Slone Epidemiology Unit, from the outset, had responsibility for the design and protocol, data collection, data processing, and data analysis, with guidance provided by an independent advisory committee.

The objectives, not surprisingly, were to assess compliance with the pregnancy prevention program, including the awareness of teratogenic risks, patient and physician behaviors, pregnancy rates, pregnancy outcomes, and risk factors for those pregnancies that did occur. But there were some clear limitations which need to be noted, and we have noted from the outset.

First of all, no pre/post comparison was possible. There was no pregnancy prevention program, of course, but neither was there any survey prior to its introduction. There was no definition of what success meant. The survey itself, it can be argued, is some form of intervention. Perhaps most important for consideration these couple of days is that it was based on voluntary enrollment, as were all aspects of the pregnancy prevention program, and therefore it raises questions about the representativeness of the survey population.

When we approached the issue of design, one of the first things we wanted to consider was, how might we enhance enrollment in a survey that's voluntary in nature? One of the obvious things was to provide physicians with a survey enrollment form, and that we did. That clearly was made as simple as possible consistent with informed consent and our institutional review board requirements, and we were paying the women $10 for the enrollment. We made this to be user-friendly, and in some ways to mimic a toaster rebate, something that would not be off-putting.

But we anticipated that physicians, for a variety of reasons, might not be terribly aggressive in enrolling patients, and we suggested another approach, which was to include the same form -- this is the back side of it, it's a fold-over form -- with each medication package. This is a direct-to-consumer approach, if you will. So we had at least two ways, two

opportunities, to have women enroll in the survey.

As I mentioned before, the period of Accutane treatment was estimated to be about five months. If we were to identify potential pregnancies and give ourselves two trimesters in which that might be detected, that would add another six months. So the average follow-up period was defined as 11 months.

The flow diagram identifies the three enrollment methods, the physician, the medication package, and later the toll-free telephone number. Women would enroll in the survey, and within 48 hours would be sent a check for $10. They were randomized upon enrollment to be followed by two different approaches. We can talk about this later. I don't think it's terribly relevant here. The telephone follow-up involved a contact early in the course of therapy, midway roughly in the course of therapy, and at the end of the defined follow-up period.

In contrast, the male follow-up or the postal follow-up involved a tracking contact after therapy was likely to be completed, and an equivalent interview by questionnaire at 11 months, or six months after discontinuation of therapy. So we were obtaining considerably more information from women randomized in the telephone arm, 5,000 women a year. The balance of women were randomized to be followed by the postal questionnaires.

Enrollments since 1989 through 1996 have increased. The first year reflects the lack of the medication package in the marketplace. There were delays in manufacturing this unique product. But since 1990, we have witnessed a steady increase in the enrollments, the absolute number of enrollments running from approximately 35,000 in 1990, and we're anticipating in 1997 roughly 50,000. So the cumulative number of enrollments at the present time is approximately 350,000 women. Of interest, three-quarters of these enrollments came to us via the medication package.

Based on the random sample of women whom we followed up more intensively, the average age was 26 years, is 26 years. The average education is two years past high school. The duration of acne is approximately 10 years. As you can see, the vast majority have gone through previous treatments for their acne.

In terms of their knowledge at the outset of therapy, 99 percent responded affirmatively to the question, "Did your doctor tell you the importance of avoiding pregnancy?" Ninety-eight percent reflected that they understood that Accutane may cause birth defects.

In the first two years of the survey, based on 10,000 interviews, knowledge and compliance at the onset of therapy with other aspects was not as high. Instructions from physicians, 78 percent said they were told to wait until pregnancy test results before beginning the drug; 63 percent reflected being told to wait until their next menstrual period; and 60 percent reported having any pregnancy test being done before therapy.

Based on this information, which we provided quarterly both to the manufacturer and to

FDA, the manufacturer on its own initiated a modification of the medication package. This is the back of the original package, which, while providing a lot of information, was also somewhat noisy. It could be argued -- and I'm sure Dr. Morris would have some comments about this tomorrow -- it could be argued that some of the messages might get lost in the detail.

So in the fall of 1990, the manufacturer changed the package to the four big musts, as we call it. You must have a blood test which shows you were not pregnant before starting Accutane. You must wait until the second or third day. You must use effective birth control one month before, during, and after taking Accutane. Something that we found kind of interesting for a voluntary survey, you must send in the form inside to sign up for the confidential follow-up survey.

Well, did that make any difference? If we compare the two years preceding with the two years following the change in the package with roughly equivalent numbers of interviews, we did see somewhere in the neighborhood of a 10 percent increase in compliance. Can we attribute it to the medication package? I think anyone can be the judge of that, but we did see a dichotomy, and this continues to this day between 1990 and 1991.

But let's consider some other aspects of the population. Among non-contraceptors, let's consider the sexual activity status among those ages 15 to 44. Among the non-contraceptors who reported being sexually active, there were 2 percent in the Accutane survey, among the non-contraceptors. In the U.S. population, the equivalent figure is 33 percent.

Among contraceptors, if we simply look at the proportions using the birth control pill, when you look at the age-specific rates, for each age-specific category, the rates among the Accutane survey participants were consistently, and often considerably, higher than those in the general U.S. population.

Well, what does that mean? Relative to the general population of women, disproportionately more women in this survey are not sexually active, and use effective contraceptive methods.

Some argue, well, this is a bias within the survey. Others, with their eyes open, would argue this was the objective of the pregnancy prevention program, was to minimize the population at risk.

But let's consider the outcome of great interest, the pregnancy rate. Based on 210,000 completed follow-ups for the years 1989 to 1995, we had 623 pregnancies reported, for a rate of 2.9 per 1,000 five-month courses of Accutane. That was the typical course of Accutane.

For the demographers, if you want to convert that to 1,000 woman-years, it's 7.7 per 1,000 woman-years. How does that compare to national data based on the National Center for Health Statistics? The U.S. population rate would be 109 pregnancies for that same population. So this is roughly one-fourteenth, or 7 percent, of the expected rate.

Let's just examine for a moment the characteristics of these pregnancies. Nine percent of the women were pregnant at the start of treatment. This is actually different, though we can't tell what this difference results from. This is considerably lower than that proportion that was observed in the studies by Lammer and by Dye preceding the initiation of the pregnancy prevention program. Twenty-seven percent of the pregnancies occurred among women who acknowledged not using contraception. But, as has been predicted by virtually everyone, contraceptive failure accounts for the lion's share of the pregnancies. Virtually two-thirds of the pregnancies were attributed to contraceptive failure.

The outcomes of these pregnancies, roughly two-thirds resulted in therapeutic abortions; 16 percent, spontaneous abortions; live births in roughly 11 percent. I'm not giving the distribution of the outcomes among the live-borns. This was not an etiologic study. We never expected to see anything but the predicted teratogenic effect of Accutane in this population. To date, our follow-up data suggests that that's what we're seeing, that roughly 25 to 30 percent of the live-born babies are affected.

One of the concerns, of course, is how long is this intervention likely to work, and in which direction is it likely to go, as time moves on? I must admit to being one of the skeptics who thought that this would work for short-term, but not for very long. To the extent that we can make any extrapolations, if you look at the year-by-year -- and pick any row you want, but let's take the 1,000 woman-year rates -- the rates of pregnancy have clearly declined over time. They have certainly not gone up. The inference here -- and there are anecdotal data to suggest that this is the case -- is that the pregnancy prevention program is indeed being incorporated into routine practice.

I should mention that 92 percent of the women in the survey received their medication from dermatologists, not from other kinds of physicians. As I'll mention in a moment, that's a relevant consideration. Dermatologic training programs are including training in pregnancy prevention related to Accutane.

Well, are there special characteristics to consider when evaluating the effectiveness of the Accutane program? There certainly are. In terms of the manufacturer, Accutane is distributed by Roche, a single manufacturer, which promotes the pregnancy prevention program on an ongoing basis by advertisement, mailings to physicians and health professionals, and the sales force. It sponsors a survey, and aggressively supports the survey recruitment, and acts on the feedback from the survey.

The physicians, as I mentioned, are largely from a single specialty. This is a uniquely effective drug which is a very important part of their practice. Finally, last but not least, the patient population is well-educated, higher socioeconomic status. They have a serious cosmetic condition which they view Accutane as being a treatment of last resort for, if you'll pardon me, which offers a likelihood of cure, in contrast to other anti-acne therapies, and there's a short duration of therapy.

Is the experience with Accutane applicable to other human teratogens? Well, I basically

listed the characteristics for Accutane, and I think it's the task of all of us to worry about whether this has any applicability to thalidomide.

Finally, while this experience suggests that the PPP for Accutane is effective, it's unclear whether the same program would be similarly effective for other therapeutic teratogens.

Thank you.

(Applause.)

DR. MILLS: Thank you.

Our last speaker today is **Dr. Cynthia Moore**, who is the acting deputy chief of the Birth Defects and Genetic Diseases Branch at the CDC. She is going to provide a summary and recommendations based on preventing birth defects due to thalidomide exposure and the CDC meeting.

DR. MOORE: I'm happy to have this opportunity to speak with you today and participate in this meeting as the last speaker, because in essence that gives me the final word today, and that's a situation I always like.

I also participated in the FDA meeting last week, and I gave this presentation. I wanted to point out, especially for those of you who weren't at that meeting, that, although the FDA advisory committee did vote for approval of thalidomide, saying the benefits were greater than the risks, they also voted that all the safety issues have not been adequately described.

The Centers for Disease Control and Prevention entered this arena because a major part of the Division of Birth Defects and Developmental Disabilities' mission is to improve the health of American children by preventing birth defects. To a great extent, our division owes its existence to the tragedy that was the first thalidomide epidemic, and we as well as others do not wish to see a second epidemic occur.

In March of this year, CDC sponsored a workshop in Atlanta entitled "Preventing Birth Defects Due to Thalidomide Exposure." We were fortunate to have the participation by individuals from many different areas of expertise, including our federal colleagues from the FDA, the NIH, many pharmaceutical companies, professional practice representatives, academicians, and others. The purpose of this meeting was to provide a forum devoted to the discussion of the teratogenic effects of thalidomide, and methods to limit fetal exposure to this drug, should it be approved for use. This meeting was not designed to develop a consensus on this issue, and no attempt was made to reach one, but merely to gather individual suggestions by meeting participants.

Although other adverse effects of this drug are known or suspected, the CDC meeting addressed only the teratogenic effects. I believe that we are all well aware of these birth defects. We've heard from several presenters today that we know when this drug is used by women of childbearing potential, the risk for causing serious birth defects can never be

lowered to zero.

In situations where there is indiscriminate use of the drug, or poor control surrounding its use, as in Brazil, infants with thalidomide embryopathy are being born. This is an infant born in 1994 to a Brazilian mother who received thalidomide for treatment for leprosy. He has the typical malformations associated with thalidomide exposure.

I'd like to comment, kind of in response to Dr. Hill's presentation, that one of the problems that was pointed out in Dr. Castilla's report of these Brazilian infants was that we had typically characterized the limb deficiencies as phocomelia, even though other authors had described the preaxial or radial ray defects. In the small group that Dr. Castilla reported -- and this is one of those babies -- the incidence of preaxial defects was about half of the infants, which I think were 11 children.

This presents a difficulty in surveillance systems because, although phocomelia has very few causes, especially bilateral phocomelia, there are many causes for bilateral radial agenesis.

So who is at risk in the United States if thalidomide is approved for use by the FDA for ENL? Is it individuals with ENL? We've been told that there are currently five patients at the Hansen's Disease Center in Carville, Louisiana, who are receiving thalidomide for treatment of ENL. Four of these patients are male. The numbers of individuals with ENL in the other parts of the United States also appears to be small.

The risk for individuals who have been buying thalidomide through buyers clubs may be low, since I understand most of these individuals are male. At least in Atlanta this is true, where we were recently told that the membership was 91 percent male.

The CDC meeting participants considered, not only the teratogenic risks for individuals with ENL, but also the risks that this approval will bring to a population of patients with other disorders for which treatment with thalidomide has given beneficial results, and those who may receive it through indiscriminate use. We did not have an opportunity to discuss risks that will occur if this drug is ever used as a drug of abuse.

There isn't time to present every one of the dozens of suggestions we heard at the March meeting. Our staff considered all of them, and extracted those which we thought would be most effective and practical in preventing fetal exposure.

In the form of draft recommendations, these suggestions have gone out for comment to meeting participants and the members of the Thalidomide Interagency Working Group. They are now under revision by CDC staff. I'd like to highlight some of these suggestions this afternoon.

We noted that virtually all of the suggestions to prevent birth defects centered around the concepts of limiting the use of the drug, educating health care providers and patients about the use of the drug, and monitoring those who are using the drug.

These concepts were summarized by CDC staff into these five proposed recommendations focused mainly on women of childbearing potential. They are as follows. Patients should be suitable candidates for thalidomide. They should be educated and counseled about the teratogenicity, and about contraception. The drug should be packaged and dispensed in a manner to minimize both inappropriate and inadvertent use. Prescribers and dispensers should be well educated about thalidomide and its use. Patients should be monitored during use to reduce the risk for fetal exposure.

When considering if a woman of childbearing potential is a suitable candidate for thalidomide therapy, we thought these four points were very important. The most difficult issue has been the first point listed, for it seems that most would agree with the other points, that a prospective patient should not be pregnant at the initiation of therapy; should have access to and be a capable and effective user of birth control; and should understand the risks associated with using this drug.

However, when to use the drug is the question. It was also suggested at the meeting that the drug should have not only been proven to be effective for the condition, but because of the severe risk, other options, hopefully nonteratogenic, should have been tried first, if they are available.

Since approval of a drug for a specific use must be based in part on its effectiveness, it was suggested by some meeting participants that the common practice of off-label use of drugs be prohibited for thalidomide, to prevent the indiscriminate use for disorders for which thalidomide has not been found to be effective in rigorous trials. Again, the suggestion to prohibit off-label use is controversial, but it would limit exposure, at least until other indications are approved.

Patients should of course be counseled about the teratogenicity. In all patient education activities, the concepts of appropriate and pretested messages with post-educational knowledge assessment are included. Several meeting participants stressed the need for inclusion of photographs of affected infants. The line drawing of an infant with Accutane embryopathy that's included in the Roche pregnancy prevention program was thought to be inadequate.

Also, avoiding possible fetal exposure caused by sharing pills, or taking leftover pills, necessitates counseling all patients about the teratogenicity and the importance of not keeping unused pills.

The choice of an effective contraceptive approach, particularly for individuals with chronic illness, can be challenging, according to our OB/GYN colleagues. For example, we were given, as one example, that IUDs are probably not a good idea in women with HIV infection. It was suggested that this practice of prescribing contraceptives be limited to those providers who have expertise in this area.

Although consistent and proper use of contraception is a goal, unprotected intercourse could

occur under a number of circumstances. This topic also elicited many comments from our meeting participants, since we proposed that emergency contraception be discussed and prescribed. At the very least, as one of our participants suggested, female patients of childbearing potential who have unprotected sexual intercourse should stop taking thalidomide immediately, and not resume until they are evaluated and found not to be pregnant.

This same suggestion would apply to women who are uncertain about the effectiveness of their contraception at any point in time. The last approach would necessitate that we have reliable data on the elimination of thalidomide from the body, however.

Packaging suggestions included labels that state, "Causes severe birth defects," and the word "thalidomide." How recognizable the word "thalidomide" is to individuals in their 20s and 30s, who may be patients or even health care providers, is not known to us, although some preliminary data from the FDA indicates that at least 50 percent of individuals do not recognize the name.

Other ideas, such as blister packs, and use of a tested symbol to denote no use in pregnancy were also discussed during the meeting.

Although we've received both positive and negative feedback about these suggestions on dispensing, the last two stimulated the most discussion, mainly pertaining to the idea that the pharmacist would also be a gatekeeper for thalidomide, and in some ways serve as the ultimate control over who receives the drug. This is not an idea without precedent. For at least one drug, Clozaril, dispensing cannot be done unless the pharmacist is presented documentation of requisite laboratory results.

The most notable point under this heading is the suggested concept that prescribers and dispensers should do more than just register to obtain the privilege. Education and knowledge assessment should be connected to this privilege, a privilege which also could be revoked. The development of specific practice guidelines by professional groups was also suggested.

Monitoring suggestions pertaining to follow-up of the female patient while on therapy by her health care provider, and referral for specialized counseling in the event of exposed pregnancy, were also suggested. In addition, a more global monitoring of all women of childbearing potential through the establishment of a prospective, consolidated, and multi-company registry was suggested.

This registry would follow all women of childbearing potential on thalidomide for fetal exposure and outcome of exposed pregnancies. The registry would provide information to determine the magnitude, and hopefully the source, of prevention failures.

As an aside, it was encouraging to learn at the FDA meeting last Friday that Celgene will include the patient's diagnosis in their proposed registry, and would be able to monitor this

data to limit inappropriate or trivial use of thalidomide.

That's the last slide, so I can have the lights up.

I've given a brief overview of the suggestions from the CDC meeting, "Preventing Birth Defects Due to Thalidomide Exposure." As an encompassing summary, we were told that the most rigorous pregnancy prevention program yet established, the Roche pregnancy prevention program for women on Accutane, was a good starting point, but was not rigorous enough for a teratogen as potent as thalidomide.

Evaluation of this program has shown that some women received Accutane without a pregnancy test. Pregnancies did occur during therapy, and effective pregnancies were aborted, or went on to live birth.

Unfortunately, even with a stronger program for thalidomide, some affected infants will be born.

I'd like to thank all the participants of our March meeting, and those who gave us feedback on those draft recommendations. Our Birth Defects Branch at CDC is eager to further explore suggestions from our meeting, and work with all parties to develop a prevention program that hopefully will assist women who receive thalidomide, their partners, and their health care providers in preventing these serious, but preventable, birth defects.

The desire for a healthy baby is nearly universal. In my clinical experience, that desire is intensified in women who battle a chronic disease during pregnancy. Regardless of how long it takes, I believe we owe all women our best efforts to try to make this desire a reality.

Thank you.

(Applause.)

DR. MILLS: I'd like to thank all of our excellent speakers for what were uniformly well thought out and well presented talks.

I'll invite you all to come to the microphones for questions, and while you're flocking down to the microphones, I was asked by Steve to mention that we start at 8:00 tomorrow. That's 8:00 a.m., not 8:30, so be prepared.

I'll open it up for any of your comments or questions to the speakers.

DR. LONG: My name is Iris Long from ACT UP/New York.

I would like to know how available is the data on pregnancy with respect to Accutane to patients and their doctors, with respect to, shouldn't this be updated? Information like this is very sort of shocking, when you see that there are so many pregnancies occurring, and that decisions concerning abortions will have to occur, and some live births with these defects

are unavoidable.

DR. MITCHELL: I assume that question is something I should respond to. I had a little trouble hearing, but if I understood the question correctly, how much feedback is provided to physicians and patients?

DR. LONG: Well, yes, with the actual data concerning like the 623 people who became pregnant, and so forth? I mean, just because you're taking the registry, how does the public get that data, and their doctors, and the pharmacists, and so forth? Because that data should be available, I think, to the public.

DR. MITCHELL: The principle mechanism for relatively rapid feedback is a series of newsletters that are sent to prescribers. Those are prescribers identified as being anyone who is a practicing dermatologist, and the list of prescribers that the manufacturer has of non-dermatologists.

DR. LONG: (Inaudible.)

DR. MITCHELL: Yes, well, that's done through the usual route of medical publications, but it might be interesting to talk to you later about other suggestions you might have.

DR. MILLS: Could we get the microphones turned up? There is some kind of machinery behind us that makes it difficult for the people up here to hear the questions. Thank you.

PARTICIPANT: Hello. I just wanted to make one comment on things like the registries of birth defect. I think Dr. Miller mentioned this, too. You have to have the right kind of birth defect to be in the registry, and this is certainly true of the Brazil situation.

I had the opportunity of looking at a large number of affected individuals in Sweden. There is a very significant number that just have craniofacial, and maybe thumb. Thumb is the most exquisitely sensitive throughout the whole thing, but there are many that have no other limb anomalies than just facial nerve palsies and ear anomalies and other craniofacial. So that doesn't seem to be as appreciated as I think it may be, should be.

Thank you.

PARTICIPANT: I'm reading a question for another person. "Have mothers of children with birth defects been interviewed to find out what they knew about thalidomide and birth defects, whether they had been counseled, and where they received the drug? This can be in any country, and I guess particularly Brazil." Also, the same question on Accutane.

DR. MOORE: Unfortunately, I'll have to say I don't know the answer to that question for thalidomide. I think that the infants that were born in Brazil were in more rural areas, and I don't know what kind of health care information they were given before they took the drug, or if they were interviewed afterwards.

PARTICIPANT: Thank you.

DR. MITCHELL: With respect to Accutane, the vast majority of the pregnancies we identified occurred in women who -- about two-thirds of them were on contraception, had been informed, and so forth. I mean, they were not unaware of the risks.

DR. FOST: Norm Fost. Question for Dr. Mauck.

We've all said that zero risk is not a sensible goal, and that therefore there is some number of severely affected infants that would be an acceptable tradeoff, but I'm wondering if you've thought at all about what would be an unacceptable number? That is, if there were, let's say, some disturbingly high -- I'm not asking for an actual number. None of us can come up with that.

But suppose there were hundreds or thousands down the road when there were more indications, a large number of children born with full phocomelia. Is there some point at which you would say, "This is unacceptable," and some more intrusive regulatory scheme is possible? Or would you say that the guidelines that you recommended are about as far as we should go, regardless of how it turns out?

DR. MAUCK: It's hard for me to respond. It's almost as if you're asking me a question for the agency. My guess is that if the level is high enough to cause alarm, there would be some sort of regulatory action, but don't hold me to that.

I think the thing we need to consider, too, that I didn't say and probably should have, is that if we approve this drug, there will be birth defects caused by approved use of this drug. But there is this drug in this country now that's been available through buyers clubs, and the risk per patient of an affected pregnancy is much lower, I think, if the drug is obtained through regulated means versus through a buyers club.

So in a way, I think regulation will decrease the likelihood, and will be a good thing, provided that it doesn't increase the number of users so much that it actually overwhelms the reduced risk per patient.

MS. SAPHIR: I had a question. My name is Ann Saphir. I'm from the Journal of the National Cancer Institute.

I had a question about off-label use. That's kind of confusing to me. I don't understand if the thalidomide is approved for use with ENL, will it be then available to physicians to prescribe for all sorts of things for which it is indicated, and how do you control that?

DR. MAUCK: It's legal for a physician to prescribe an approved medication for a non-approved use. That's the way emergency contraception is used now. At the advisory committee meeting, it was discussed whether off-label use could be limited, and I think there wasn't a clear answer. It's something that the agency has to look into.

DR. COHEN: Peter Cohen, National Institute on Drug Abuse.

Just to get at that question, there is at least one example of a class of medications whose off-label use has been controlled by statute, and that's methadone. Because of concern that methadone would be used off-label for the treatment of addiction, a political decision was made to regulate it. So any drug that is to be used for the treatment, long-term, of addiction falls under special regulation. So it can be done, but not unless statute is passed.

The question I had, we have an example of a known teratogen, probably milder, but certainly more used, and that's alcohol. I'm wondering if anybody has any data of the incidence of fetal alcohol syndrome from a drug that is unrelated to bring into some comparison, because I for one might -- I agree with much of what has been said. But I could have a worry about the degree of intrusiveness in terms of regulation. One can educate patients. One can demand that they read and sign an informed consent. But when the government itself steps in, and says, "You must have pregnancy tests, you must use contraception," I think there's a worry about crossing over the line. It's a balancing. It's a risk/benefit. But I'd be interested in hearing some feedback regarding fetal alcohol syndrome as an almost societal disease.

DR. MILLS: May I answer that one? I think there are a number of points there. One is that the rate of fetal alcohol syndrome varies tremendously depending on the survey and the population. But to take one rate, one per 1,000 births, you can see that it's very, very much less a risk in terms of the number of people exposed versus the number who had bad outcomes than thalidomide is.

The second point is that this is a historical question as much as a medical question, that, were someone to put alcohol on the market today as something that had to be approved by the FDA, I suspect there would be any number of challenges put in the way of approving it. So it's not really a comparable situation, much as cigarettes are not a comparable situation, in terms of the health effects, and the fact that they were approved or not approved, but got on the market long before these ways of avoiding problems were instituted legally by the FDA.

So I think that it's not really quite a comparable situation, in terms of alcohol versus thalidomide.

PARTICIPANT: I have a two-part question. How long after the last dose is taken does it take the body to fully clear thalidomide? Is it possible for someone who has been on a thalidomide therapy then to later decide that they want to get pregnant?

DR. HILL: I can partially address the first part of your question, although I'll have to have you repeat the second part. For clearance of thalidomide from the body, there have been no formal distribution studies per se on that.

However, we discussed this during the advisory committee last week. The pharmacokinetic,

of the 623 had malformations.

DR. LONG: So that would be 11 percent, approximately 10 percent, or 60, and then a third of those?

DR. MITCHELL: Right, yes.

DR. LONG: Okay.

DR. MITCHELL: That's the expected rate with Accutane. I mean, there was no reason to believe that in the survey it would be higher or lower.

DR. LONG: What are the effects of Accutane on the fetus?

DR. MITCHELL: They are primarily neural crest effects -- ears, craniofacial, central nervous system, major categories.

PARTICIPANT: I'd just like to make a comment to the Accutane. I don't know if it's a really good drug to compare to thalidomide because most people who might be taking thalidomide might be really much more sick than people taking the Accutane. So I don't know if it's a good drug to compare it to, to see how many women are really going to get pregnant.

DR. MILLS: I'd like to thank all of our speakers again, and to thank the audience for your sustained interest. We will see you all tomorrow.

(Whereupon, at 5:03 p.m., the meeting was recessed, to reconvene at 8:00 a.m. on Wednesday, September 10, 1997.)

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