U.S. Food and Drug Administration

THALIDOMIDE: POTENTIAL BENEFITS AND RISKS

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TRANSCRIPT

THALIDOMIDE: POTENTIAL BENEFITS AND RISKS

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P R O C E E D I N G S (8:14 a.m.)

DR. GROFT: Good morning, everyone. I see you were able to make it through what for Washington this summer is an unusual event, a day of rain. So despite the travel and everything else, the problems that go with traffic, we do appreciate the rain and need it.

My name is Steve Groft, and myself and Terry Toigo have served as co-chairs of this workshop and had the opportunity to put together the program. This morning we're ready to turn it over to risk communication, risk management. We've asked Lou Morris from the Food and Drug Administration to chair this session, be the moderator and put together the panel, which he has done an outstanding job of, so I'll just turn it over to Lou to get us started.

I'll have some information later on about the breakout sessions, and then the CME credit for those who are filling out the forms. So between the first and second session, we'll put some information up on the overhead.

Lou?

DR. MORRIS: Thank you, Steve.

Good morning, everybody. Congratulations. You made it here. If you walked, you were fine. If you had to drive, you were lucky.

This morning we're going to talk about risk management from a number of perspectives. First, we will be talking about it from a theoretical perspective in which we'll talk about both perception and behavioral influences. We'll then talk about some issues in informed consent and consumer perspectives, and then, lastly, we'll hear from Bruce Williams regarding Celgene's plans for a risk management program for their thalidomide product. The way I'd like to structure the session is, first, I'm going to introduce everybody in the panel, then we'll each take our turn at the podium, and then, finally, we'll have a question and answer period.

So let me start by introducing myself. My name is Lou Morris. I work in the Division of Drug Marketing, Advertising, and Communications at FDA, where we work on regulatory issues and patient information issue, and I also am scholar in residence at the American University Center for Marketing Policy Research.

On my right is Dr. Martin Fishbein, who for the last five years has been at the Centers for Disease Control, where he's worked on behavioral initiatives regarding HIV and AIDS policy. He's currently moving to the Annenberg Center, where he'll be an active member of a new public policy unit.

On his right is Dr. Gail Povar. Dr. Povar is clinical professor of medicine at George Washington University, where she not only teaches new and innovative courses -- she mentioned she's teaching an Internet course this year -- but she actually sees patients. She's one of those few people who have multiple perspectives not only from a broad public policy and ethical sense, but also from a sense of patients' perspective.

On her right is Mark Senak, who is with the AIDS Project in Los Angeles. He's the director of public policy there. Mark has a long career in AIDS activism. He's been in the Gay Men's Health Crisis Center and the AIDS Action Council.

Then on his right is Bruce Williams, who is the vice president for marketing and sales at Celgene. Mark actually moved Celgene from a research to a commercial corporation, and he's primarily responsible for developing there the thalidomide distribution and communications program. We'll be very interested in hearing from him.

So with that, I'm going to start off, set my own timer. Can I have the first slide?

Thalidomide has special meaning for lots of people, and for someone who has worked at FDA, this is one piece of the meaning for thalidomide that I think FDA staff has. In the library in the Center for Drugs, there's a picture of Dr. Frances Kelsey receiving an award from President Kennedy. That picture, I think every time we go into the library, communicates to people at FDA in a very special way.

I know critics of FDA frequently think that we see thalidomide as the reason why we keep drugs off the market. At least for me, that's never been my interpretation of this. It does remind us that we have a very important job and that what we do has huge implications for individual patients and for the country as a whole. I think that's the way we have seen thalidomide historically, and I think that's the way we see thalidomide today. This is symbolic for us and it's symbolic because it means an awful lot about defining who we are and what we do. So the things we do and say about thalidomide I think have important implications at a national level and on a personal level for the people who work at FDA.

So with that aside, if we can turn that slide off, I'll move to the high tech stuff. We can try talking about risk communication and thalidomide. What I would like to do is present more of kind of a general theory and then some specific data that we've collected on thalidomide and risk communication.

First, from a marketing perspective, I think it's clear that we can characterize products in three different ways, and we as consumers characterize products in these ways. First, we can characterize a product in terms of its

physical properties. We're taking a capsule of medicine, but it's more. It has more meaning to us than just that.

It also has a functional property. Whatever this drug is, this thalidomide is, it has certain benefits that we anticipate, and it also has certain risks that we need to be aware of. For some products, products that have very high meaning, high involvement products, not only do we take in and think about what it is that people tell us, but we also elaborate on those meanings for these kinds of high involvement products and we integrate this information.

There's still a third level of meaning by which we can characterize products, and that is that products have symbolic meaning. They mean an awful lot to us. For me, as that previous slide showed, thalidomide has a special meaning. I think that if you ask people, at least of my age cohort, what it means, they're going to talk about what they see. They have a very, very vivid understanding and a recall of certain pictures that they saw. If you speak to anyone, they say yes, and they'll see these pictures.

How people use products depends upon several things. It depends upon, first, how they perceive them. That first part, that perception, depends upon their beliefs about the product itself and their personal use of the product. In my presentation, I'm going to focus on this.

But it also depends on beliefs about other things. For example, beliefs about what other people think. It also depends on situational factors. Dr. Fishbein will give us a much broader perspective on the behavioral outcomes related to people's use of different products.

Let's now turn to the people's perceptions of risk. One of the things we know from research is that knowledge is not simply something that's transferred. It's actually constructed. When people process information they only retain small bits and pieces. What they retain from a message, their takeaway is going to be fairly limited. One of the things we do know is that very vivid images are more likely to be transferred to people's memory.

When they then have to act on those behaviors, that information is integrated with their current context. So meaning changes. Memory is very creative because we're only retrieving bits and pieces and then we're integrating it with our current situation. There's a lot of differences in terms of how people behave depending upon how familiar they are with the product. If it's a product that we're very, very familiar with, we're going to have a very standard way of seeing it. If we take an aspirin every day, we know what that aspirin means to us, we know what it does, we know when to take it, how to take it, and we know what to expect from it.

However, if we take a new product, a product that we've never taken before -- a new drug, for example -- how we behave towards that product is going to be very variable because a lot will depend on the contextual situation. So, for example, if we get a headache after we take this unfamiliar product, we may say that new product did it. If we get a headache after taking an aspirin, we'll say, well, the aspirin wasn't strong enough, for example. We know what to expect in one case. In the other case, we don't know what to expect.

People build mental models of products. They also have situational inputs. What is retrieved when knowledge is put to use is a very important issue. One of the things that we've been concerned about in the risk communication package for thalidomide is what's going to happen at the point in time when an individual is faced with a sexual encounter. How will that patient behave? Part of that's going to be dependent upon what they retrieve in memory at that point in time and if those memories are what we're trying to build in the risk communication package.

The reason I put up these data, one of the things we want to know is what do people already know about a product. We're lucky enough that a couple of weeks ago we started collecting data from another study.

The PowerPoint is not on. Help!

(Laughter.)

DR. MORRIS: Let me go on to talk about what it is and I can describe it. We collected some data from a small

sample. This is an ongoing study and we literally just last week compiled the data that we had so far. In this study, we asked a very simple question. We gave people certain words. We just asked them to define them, what does this word mean. We collected these data from males and females and what I would show you with numbers, if we had them, is that there's an incredible age cohort effect if you look at these data, and I can turn this around and you can all see it.

(Laughter.)

DR. MORRIS: That if you're over age 45, over 50 percent of the people, about two-thirds of the people, can correctly define at least partially what the word "thalidomide" means. If you're under 45, it's a total reversal. There it is. It's not real clear, but we separated out for genders. It's percent correct, partially correct, incorrect, or don't know.

If you look at the age groupings, if you look at the 45 split, about two-thirds of people either get it wrong or don't know if you're under 45. If you're over 45, two-thirds get it at least partially correct. It's a VANOVA, a visual analysis of variance here. You don't even need to do the statistics. It's an incredible cohort effect. We separated out for males and females, and we didn't find any difference in genders, but we do find this enormous cohort effect in terms of age.

I think my explanation for it is, again, if you ask people over 45 about thalidomide, they just see these very vivid images. They retrieve it. Under 45, they just don't have those memories.

So from a risk perception standpoint, one of the things I think we need to think about is how do we build this risk profile. We can think of this in three successive levels of building. For a lot of products what we do is simply put out a simple warning label. That warning label has a signal word, it tells people what they should do, and what negative outcomes should occur. I think if you look at just about any consumer product --over-the-counter drugs, ladders, lawn mowers, anything like that -- you're going to see this kind of warning message. That's the minimal thing we can do. It tells people, "Pay attention to me. Here's what's going to happen to you unless you take the following preventive action."

At the next level, I think what we need to do is build very, very vivid memorable inputs. I was very pleased that the advisory committee said we need to make sure there is a picture or a video. There needs to be something that people retrieve. Another thing about these age cohorts, one of the things that my understanding is from my reading, is that if you look at the way people learn in Generation Y, it is very visual. I think that matches well. So I think that's an important issue.

At the highest level, I think what we need is a very persuasive argument. We did some research a few years ago on pregnant women's use of alcohol. What we found, to our surprise, was that women who continued to drink during pregnancy were the ones who were more educated, not less educated. In our analysis what we found was that those women believed that they could control the risks by simply moderating the amount of alcohol they consumed. When we gave them risk messages, they counterargued them. They said, well, that doesn't happen, I can control the risks.

Our sense is that for people who are very involved in an issue, they may believe that they can control the risk themselves. What we have to do is persuade them, we have to counterargue their other examples and say, no, it really is important, for example, that you use two forms of birth control. One form is not enough. We may have to think about those kinds of messages.

In terms of our concerns, there are many. One of the things is we're dealing with a very heterogeneous audience. It's heterogeneous in terms of literacy, it's heterogeneous in terms of existing knowledge, it's heterogenous in any number of factors. We're dealing with a single system. How well can we segment, how well can we target, and how well can we communicate?

The second concern that I have is that we're dealing with a long-term behavior and that things learned under one state of emotions, normal, rational emotions, those behaviors may not be engaged in when people are in a

different emotional state. Our learning doesn't generalize necessarily to those different states, and people may have conflicting motivations. I think Dr. Fishbein will talk more and more about how we have to understand all the relevant beliefs, not just the ones that we see, but the ones that consumers see as well.

I think with that, I'll leave this, and I'll ask Dr. Fishbein to continue our trek through thalidomide. Thank you.

(Applause.)

DR. FISHBEIN: Good morning. I'd like to begin by thanking Steve Groft and the other organizers for inviting me to participate in this very important workshop, and, maybe more importantly, for recognizing the role of the behavioral and communication sciences in addressing what's clearly a very delicate and perplexing issue.

I think what we just heard Lou talk about is kind of a traditional way of looking at the product and information about the product and how this can impact on people's behavior, but I think the bottom line, unfortunately or fortunately, is that risk management in the context that we're dealing with it is really a question of behavioral change and it's a behavioral problem. We're asking people to change their behavior.

Yesterday, we heard quite a bit about what needs to be done or recommendations. Many panelists argued forcefully for the importance of education, but one of the things I'm going to try to show you today is that educating potential thalidomide users or the general public about the dangers of taking thalidomide during pregnancy, or simply telling them that what they must do in order to prevent pregnancy, is really unlikely to lead to behavioral change.

I was asked to kind of provide an overview of how communications can effect behavior and behavioral change. It's really more of an overview of what do we know about factors that influence behavior. What I want to do is to briefly go over some lessons I think we've learned from behavioral science theory and research. Let me just go through a series of five lessons that I think are important.

I think the first thing that we've learned is that we can change behaviors. We can change behaviors that many people felt were difficult, if not impossible, to change. As many of you may know, for the last five years I've been working in AIDS prevention and we've had to deal with some pretty difficult behaviors there, both sexual behavior and drug-taking behavior. There's now I think an abundant amount of evidence that well-designed, theoretically-based interventions or messages, or a combination of interventions and messages can, in fact, produce significant behavior change.

There was a recent OMAR conference, a consensus development conference, on the effectiveness of behavioral interventions to produce behavior change in AIDS prevention that basically concluded that the evidence was now there that we can, in fact, produce behavior change. I think that's important to recognize, that even difficult behaviors can be changed if we know what we're doing.

The second lesson that we've learned is that information in and of itself can, in fact, produce behavior change. We've been told many times that information in and of itself was insufficient. What the behavioral sciences has to offer in this arena is really an understanding of the kinds of information that's necessary to produce behavior change.

As I mentioned earlier, knowledge about a disease and how it's spread, or knowledge about a drug and its potential dangers, in and of itself is insufficient to produce behavior change. Simply telling somebody that they must use condoms all the time if they're a male, or that they should use a minimum of at least two contraceptive techniques if they're a female, isn't enough to produce behavior change. Again, what the behavioral sciences and what the behavioral science theory has to offer is an understanding of the kinds of information that are necessary to provide to the public or to a person in order to get them to change their behavior.

The third lesson that we've learned is that the most effective interventions will be those directed at specific behaviors, not at behavioral categories or goals. What I mean by that, let me use a simple example. If I try to convince people that they should lose weight, weight loss isn't a behavior, it's an outcome of performing a

behavior. There are many different factors that are going to influence whether or not a person loses weight. Two people who follow exactly the same regime may wind up one of them losing a lot of weight, and the other not, because of metabolic factors. So simply trying to get somebody to increase their intentions to lose weight is no guarantee that they'll lose it.

In the same way, preventing pregnancy is not a behavior. It's the outcome of a number of behaviors. So trying to convince people that they should prevent pregnancy isn't necessarily going to lead to some positive outcome.

Well, if we're not going to try to get people to lose weight, what should we get them to do? Most people say you could have them diet or exercise. But dieting and exercising aren't behaviors either. They're categories of behavior. What I mean by dieting isn't necessarily what you mean by dieting, and what I mean by exercise isn't necessarily what you mean by exercise, so when we tell people that they should diet or exercise, we're not really giving them a very clear message.

So "practice contraception" doesn't give you a very clear message. We're going to need to say something more specific. The more we get down to particular behaviors -- always use a condom every time you have vaginal intercourse with your spouse or with some other person -- then we may start having some impact on behavior.

Intentions to perform specific behaviors will tend to influence the likelihood that those behaviors will be performed. Intentions to reach goals or to engage in behavioral categories may or may not have any impact on specific behaviors. So, again, one of the lessons that we've really learned is that when we're developing interventions or messages, we've got to identify a particular behavior or set of behaviors that we want changed, and then worry about what kinds of information do we have to provide in order to produce that behavioral change.

The next lesson we've learned, and perhaps the most important one, is despite the fact that behavior is very complex, and all of us can think of lots and lots and lots of variables that may influence behavior, there's a general consensus that's starting to be reached, at least in the behavioral sciences, that there really are only a limited number of variables that need to be considered in attempts to influence or maintain behaviors. Let me just try to briefly and quickly go through what those variables are.

As I mentioned before, one of the things that we've found out is probably the best predictor of what people are going to do in the future is what they've done in the past, but we can't change past behavior.

The next best single predictor, and sometimes it's even better than past behavior, are people's intentions or commitment to engage in a behavior. If someone commits or really says it's very likely that I'm going to do this, the chances are pretty good that they will in fact do it. It's not a perfect predictor, but it's there.

But in order to perform a behavior you have to have necessary skills. You have to have the ability to actually carry it out. One of the things in this new area that many of you will be getting into is that if in fact you're recommending to men that they should consistently and correctly use condoms all the time, there is an ability factor.

People don't always use condoms correctly. In fact, some 75 percent of condom users have used condoms incorrectly at least once, and by incorrectly, it has to do with when they put it on, when they take it off, how they put it on, whether they remember to leave a reservoir at the tip. There is a whole set of abilities related to proper condom use, as opposed to consistent condom use. All too often we neglect the skills.

Another factor that we need to take into account is, is there anything out there in the environment that's actually preventing this behavior from occurring? Are there environmental constraints? I draw on AIDS issues because that's where I've been working for the last five years, but clearly, if condoms aren't available, you can't use them. It doesn't matter how strong your intentions are and how well you know about how to put them on. If they're not out there, if you don't have access to certain services, facilities, and skills, you can't carry out intentions that involve the utilization of those skills.

These are three important variables. The other three are more psychosocial, I suppose, and they have to do with attitudes. These are attitudes towards performing a behavior. Lou is talking about the attitudes or perceptions toward the product itself, but these have to do with attitudes towards using the product.

In terms of risk management, it's attitudes towards carrying out or conducting the behavior that you want people to engage in. So the feeling that it's good or bad to always use condoms every time I have vaginal sex with my main partner, or to always use two contraceptive methods when I'm engaging in vaginal sex.

The norms have to do with perceptions about what others think one should or shouldn't do. One of the factors that is going to influence the likelihood that I engage in a behavior is my perception of what others expect me to do as well as my perception of what others are doing. I'll come back to this.

Then the final variable that seems to be very important in influencing behavior and behavior change is the notion of self-agency or self-efficacy. People are unlikely to engage in behaviors that they don't believe they really can do. So it's a perception that I have the necessary skills and abilities. Unlike the skills and abilities at the top, which really have to do with whether you know what to do, this has to do with your perception. If you don't perceive that you're capable of carrying out a certain behavior, you're very unlikely to try to carry out that behavior. If you try to do something and it doesn't succeed, you're very likely to just give up. On the other hand, if you believe you can do something, even if you fail the first time, you may continue to persist.

Let me try to make some sense. I've also talked about the fact that attitudes, this feeling that performing this behavior is good or bad, are based on underlying behavior or beliefs. That is, my beliefs that if I perform this behavior, certain outcomes will occur. The more I believe good outcomes will occur, the less I believe bad outcomes will occur, the more I think performing this behavior is a good thing.

For norms, it's beliefs about what specific others think I should or shouldn't do, or what specific others are doing. Self-efficacy has to do with my perception of barriers to carrying out a behavior.

Let me try to just summarize this and talk about a general model of behavior and behavior change. What the model is suggesting is that there really are three variables that are critical in determining whether or not a person will perform some specific behavior: skills, the intention or commitment to do it, and environmental constraints. What this is really saying is given that a person has the intention to perform some behavior, they are likely to perform it as long as they have the skills available and there are no environmental constraints.

Clearly, what this suggests is that the kinds of messages or interventions that are going to be necessary to produce behavior change -- to get women to always use contraceptives, to get men to always use condoms -- are going to be very different if they haven't yet formed an intention to do this, if they haven't made a commitment to engage in this behavior, than if they've made the commitment but either don't have the skills or there's something out there preventing them from doing it. What this is really saying is we need very different interventions, and probably very different messages, depending upon where people are in terms of their commitment to engage in some course of action.

If they haven't made a commitment, then the likelihood of forming or making this commitment is going to depend on one of three factors: their attitudes, their perception of the norms, and their self-efficacy, which I described. One of the things that is important to recognize is that the relative importance of these three factors will vary as a function of both the behavior you're considering and the population you're considering. That is, for a given behavior, attitudes may be more important than norms, while for some other behavior self-efficacy may be what really influences intention.

So we need to figure out which of these is the predominating factor. For the same behavior, it may be attitudinally influenced in one population, but normatively influenced in another. So again, we need to do our homework. You just don't put out a message and expect it to have an effect on behavior change. What we need to do is figure out whether the behavior we want, in fact, people intend to do it or not. If they don't intend to do it, then is their intention due to their attitudes, their norms, or their self-efficacy?

But saying I want to make somebody more favorable to performing a behavior isn't enough. We have to know where that attitude comes from, and that's talking about underlying beliefs and their valuative aspects, or normative beliefs and motivations to comply with the norms, and these efficacy beliefs about barriers. That is, is it more difficult to do it under some circumstances than others?

I'm going through this very quickly because I'm trying to give you an overview, but what I hope I'm getting across is that behavior change is complex. Designing effective behavior change messages is no easier than developing vaccines. You don't just throw together a message, just as you don't throw together a vaccine or some other drug. You need to test it, you need to evaluate it, you need to quantify it, and you need to do the research that says this is the message that's going to be effective.

As I pointed out at the beginning, if you're going to have risk management with this drug, what you're asking people to do is to change their sexual behavior. You're asking women to use at least two contraceptives, and to get pregnancy tests regularly. Which of these factors are going to be influencing? We don't know at this point in time for this particular population. Have these women formed intentions?

While the Accutane trials really suggest that pregnancy prevention programs can be highly effective, it's very different getting a women to use some form of contraception other than condoms and getting her to get her partner to use a condom or having a male always use a condom. These are very different behaviors and they're going to require very different kinds of interventions or messages to produce this.

The other point I want to make is that the other thing that we have learned is that the substantive meaning, these beliefs are very different depending upon the behavior and the population that you're dealing with. That is, my beliefs about the consequences of always using a condom every time I have sex may be very different if I'm a Catholic than if I'm a Protestant. It may be very different if I perceive that I'm at risk of transmitting a disease than if I'm not. That is, the substantive meaning of these underlying factors also change.

Let me just quickly try to summarize what I've said, and I know I'm going quickly. So what I've tried to point out is the relative importance of the eight variables as determinants of intentions and behavior depends upon both the behavior and the population being studied, and that the substantive meaning of these variables -- that is, the beliefs underlying the variables -- also depends upon both the population and the behavior being studied.

I see the warning light, so I'm going to try to move ahead.

What we need to do is to pay more attention to the fact that we are in a behavior change game. The more we understand the factors influencing intentions and behavior, the more likely it is that we're going to be able to design effective interventions.

Let me just back up and show you one thing, because one thing I didn't talk about was perceived risk. In all the discussion of the variables that influence behavior, I never talked about perceived risk. The reason for that is it's not that perceived risk isn't important. It's back here with these other individual difference variables.

As I pointed out, people from different cultures, different communities, different religions, and different age groups are going to have different beliefs about consequences, are going to have different beliefs about who is important or not important to them. They may perceive different barriers. People with different personality traits may have different things.

People who perceive they're at risk for something may also have different behavioral beliefs, but it is at this level, not at this level that we can intervene. So what we need to do is develop interventions that are effective.

I've just been told to stop, so I will do that. Thank you for your attention.

(Applause.)

DR. POVAR: I'm going to have a change of focus and a change of lighting, because I don't have any slides, so

you can wake up a little bit. As I often am early in the morning, darkened rooms are dangerous.

I want to, first of all, forewarn you that I'm not going to be talking exclusively about ethical issues as they regard the risk of pregnancy with thalidomide. There are a broader set of issues that we need to be concerned about. So that while I will touch on that, from an ethical perspective I think it's worth reviewing the general problems and not limiting ourselves to that discussion.

I want to thank the organizers, particularly Steve Groft and Lou Morris, for inviting me to be here this morning. But I'm not going to thank Lou for his data on cohort gaps, because I'm about to make it very clear, if any of you had any question, exactly which cohort I belong in age-wise.

When I was first asked to give this talk, I shuddered. There are few drugs for my generation that are associated with the cover of Life magazine, that carry the pharmacologic, political, and emotional baggage attached to thalidomide. Because of all that baggage, my initial intuition was surely there are enormous ethical issues that must attach to thalidomide use that are different from other drugs. I was mistaken.

When one sets the history aside, when one sets aside the Life magazine cover of a drug that was widely used as a sedative in pregnant women and resulted in a generation marked by an epidemic of phocomelia and amelia, one finds that one is simply dealing with an agent that, like many other pharmacologic agents, purchases it promise at a price. There are potentially great benefits, substantial risks, and it is up to physician and patient to weigh these carefully in the clinical setting.

Clearly, everything we've heard for the last day, and that you will hear today, indicated that thalidomide has undergone sort of a pharmacotherapeutic rehabilitation since Kelsey refused to allow it to be used in the United States decades ago. The teratogenicity remains undeniable. But thalidomide's attraction, as this conference demonstrates, lies in its capacity and its potential to be an effective, and with relatively few side effects, drug for conditions that are immune-mediated, from aphthous stomatitis in HIV-infected people to graft-versus-host disease, and in people for whom other treatments have thus far been sorely missing the mark. For these disorders, thalidomide may spare the patient exposure to other more immediately toxic agents.

Under such circumstances, it would appear that there is a strong ethical justification to approve and, indeed, to promote the appropriate use of the drug. To use a teratogen for insomnia is quite different from making it available for the treatment of profoundly disabling or life-threatening disorders, and we should not forget that. If one of the primary ethical obligations of medicine and of our medical-industrial complex is to do good, there's always the parenthesis "accepting appropriate risk." But we still have to do good, and we ought not to forget that.

Within those contexts, within the context of disabling or life-threatening conditions for which alternative therapies are also a problem, thalidomide poses no more and no less of a challenge to the practitioner than any drug with substantial promise and toxicity. In every instance, I and my colleagues are obliged to abide by the tenets of medical ethics to do good, to avoid unreasonable or trivially assumed harm, to respect the patient's values and choices, and to encourage and facilitate appropriate and careful use of a drug. Whether we're talking about the use of NSAIDs for tennis elbow, or thalidomide for severely deforming dermatologic conditions, doing good and avoiding harm entails recommending the treatment indicated on the basis of ample research for which the toxicity profile is proportionate and acceptable to the patient.

Now, doing good does involve due care in the application of the drug relative to its risks. It's been pointed out any number of times that a physician and a clinician should not offer to a patient a drug whose risks far outweigh the implications of the disease for which the drug is being used. That's considered irresponsible, by and large.

Thus, the patient who is in good health and has reoccurring aphthous stomatitis -- and for those of us in primary care practice, we see HIV-infected patients with horrible aphthous stomatitis, but we also see lots of other people who are unpleasantly and annoyingly affected by recurring outbreaks of this problem. Nevertheless, while these patients might, strictly speaking, benefit from thalidomide -- and indeed I have had dermatologists

say to me, why don't you try her on thalidomide? -- there are serious questions to be asked about whether such a drug ought to be offered to that patient population, particularly if other palliative measures have not been tried. It's not clear, for instance, whether one should substitute or offer thalidomide in lieu of an oral wash that tastes bitter, but is otherwise effective.

There is always the risk, furthermore, that once a drug has been approved, and the FDA is painfully aware of this and physicians have used this necessarily, that it's use will extend beyond the so-called approved indications, to first quasi-approved indications to what amounts to experimentation, and that it will be used too casually.

I don't think I need to remind too many people here that therapeutic misadventures early in the release of Prozac nearly sank that drug, because its purported safety led practitioners to give people a six-month supply, send them out the door, and say see you later. Drugs are dangerous. All drugs are dangerous. You know that. I know that.

My profession, in its requirement to do good and avoid harm, cannot send people out the door with these drugs and say see you later. If we're going to work on things like beliefs and behaviors, we need to see that patient frequently.

The best analogy I can give you is that in smoking cessation behavior, the literature clearly states that someone who is in regular contact with a person, not merely a nicotine-containing patch or spray or whatever, has a higher probability of quitting and staying quit.

The same thing is true with these drugs. If we want people to use them responsibly, we can't prescribe them and send them out the door. We have to see them regularly. I will leave it to you to decide whether our current health care system either supports that for those who have no insurance or facilitates for those who are in managed care. So we can't send a patient out the door either without information or even with information without behavioral reinforcement and regular monitoring.

Those are fairly, I think, self-evident points. What worries me to some extent, because of the exciting potential of thalidomide, is that it may tempt clinicians and patients who are desperate to go well beyond well-documented indications into what might be called experimental practice, and I use the word "practice" here advisedly.

In that context, the ethical requirements of both informed consent and appropriate monitoring go way up. Medical practice, which I do six half-days a week, is in theory and in reality always a series of N of 1 experiments. David Sackett has some very elegant literature on that. But for the most part, those N of 1 experiments bear close enough characteristics to previous N of 1 experiments that one can engage in what Faden and Beauchamp have called "presumed informed consent." There's a relatively limited need for a lot of monitoring, a lot of interaction.

The familiar aspirin or the familiar ibuprofen might be a good example if we're treating tennis elbow. On the other hand, if I have read in a journal that I get about thalidomide's tremendous efficacy in a small series or case report in disease A or condition A, and I, because I'm an astute student of the problem, recognize a pathophysiologic or a mechanistic relationship between condition A and the condition that my patient has, which is condition B, and my patient isn't doing terribly well on something else, I might be very tempted -- and my patient may push me if they're on the Net or in a user's group that says, hey, my doctor gave me thalidomide and it works -- to in a sense take that notion of an N of 1 experiment and make it a very real one.

Once you go beyond the sort of colloquial notion of the practice of medicine and enter into this perhaps legitimate, but absolutely clearly experimental situation, the obligations go way up for the clinicians, in terms of informed consent. You now have to be clear with the patient that this is an experimental use, unequivocally. That means that if there is an outcome that is unfortunate or disabling, either for the patient or for a fetus, the implications morally go up considerably as well, because you've now not taken a known risk in the face of a known benefit. You are now engaging in experimentation.

You're not only engaging the patient in experimentation, but, if she or her spouse or her lover is not terribly reliable, are engaging an uninformed and uninformable third party in the experiment, and that third party may suffer horrific consequences. So as soon as we start with this practice model, we up the ante considerably.

Clearly, I've alluded now to the problem that concerned the previous two speakers, and that is the effect on the potential fetus. Because of the grisly past of thalidomide, some would suggest that this drug not be offered to fertile women at all, and that has clearly been suggested.

These concerns, obviously, are not unique. There is a paper that is abstracted in the program that references Accutane and, clearly, accutane is being used for a condition that while profoundly important emotionally and sometimes disabling or deforming for patients, cystic acne, it is widely used for people with routine acne vulgaris, and it's used in the population at highest risk for getting pregnant. So there's really nothing new under the sun here. The general rules of informed consent apply.

Furthermore, the patients who will be receiving thalidomide, if they are appropriately selected, are patients who will otherwise also have to take drugs that have congenital side effects, whether they are prednisone or the antimetabolites. These are patients whose fecundity in general, not necessarily specifically, but across a wide variety of illnesses, is significantly reduced, or whose pregnancies would be jeopardized in any event. So there's arguably a higher level of justification for using thalidomide by a long degree of margin than there is for Accutane.

Some physicians will be unwilling to prescribe thalidomide to women who cannot, in a sense, come in once a month for a pregnancy test, or who do not show the scars of tubal ligation. There is a long tradition supporting the right of a physician to withdraw from treatment in a case where he feels that the risks are being unreasonably assumed and to refer to another clinician. But at the risk of repeating myself, I would simply reiterate the necessity of balancing risk and benefit, both as one formulates a therapeutic recommendation and as one discusses these options and monitors the use of the drug with patients.

I guess I'm an optimist in a perverse sort of way, because I believe that the thalidomide will, because of its history, force the sort of conversations about risks and benefit and the kind of monitoring that in reality ought to occur whenever a medication is prescribed to a patient. It would be unfortunate if, because of its misuse in the past, thalidomide were deemed too much of an ethical risk to use in the present.

The responsibility for using it wisely falls I think with the medical profession. Cognizant of its toxicities, we should be cautious in extending its use beyond populations with fairly desperate illness and for whom experimental models exist and provide reasonable evidence that the benefits outweigh the risks.

Beyond that, physicians, just as they will have to work with smokers to get them to quit and stay off cigarettes, or alcoholics and help them to stop drinking, will need to work closely with patients on thalidomide to ensure that a child does not suffer the consequences of careless or inappropriate use.

Thank you.

(Applause.)

MR. SENAK: Good morning. I'm not a doctor, so I always want to start out by telling people that. The last time I had a speaking engagement for NIH was several years ago, actually, and it was done in Memphis, and the day before I left a woman called me up and she said, "Hello, Mr. Senak. I have you down as a speaker tomorrow and there are these initials behind your name and I don't know what they mean." I said, "Oh, that's J.D. It's for juris doctor." She said, "What?" I said, "Juris doctor." She said, "Jewish doctor?" And I said, "No, but you just made my mother the happiest woman in America."

(Laughter.)

MR. SENAK: That being said, in discussing my topic today, patients' rights versus physicians' responsibilities,

I have a two-fold difficulty. The first, as I said, I'm not a medical doctor, and the second is that I also refrain from being a medical patient as much as possible, being a dream come true for my HMO. Also, patients' rights and a physicians' responsibilities are not written into a Bill of Rights or a code of ethics which can be easily referenced. They're an evolving body of thought enunciated from time to time by academics and sometimes jurists.

But in discussing the topic today, I'm going to focus less on traditional lines of ethical thought than I am on the environment in which we are reintroducing thalidomide therapy. I want to begin by painting a thumbnail sketch of that environment and some of the pressures that I think that are involved in the environment, and without repeating the well-known troubled history of thalidomide, it's important for us to acknowledge where we are before we decide where it is that we're going to be going. I think there are three primary areas of concern regarding the environment in which we're reintroducing thalidomide.

The first characteristic of this environment is that physicians and patients have a different set of issues in health care decisionmaking. As I considered the dilemma posed by thalidomide therapy in putting this talk together, I recalled a saying from the Talmud, "I was afraid of a dog until I saw a lion." I picked that quote because I believe it aptly characterizes the essence of the dilemma faced by both doctors and patients in dealing with the administration of a dangerous, yet effective and perhaps desperately needed, treatment such as thalidomide. The only difference for the two principals, the doctor and the patient, is that they're each fearing different dogs and different lions.

Because of the dangerous side effects to unborn and even unconceived children, thalidomide represents a specter about which any patient would be normally terribly frightened. But faced with a catastrophic condition --leprosy, esophageal ulcers, loss of vital body mass due to wasting syndrome -- the fear of thalidomide may pale next to the dire situation being faced by the patient.

For the physician, he or she may have always harbored a dread of having a patient for whom nothing can be done, but when faced with the last resort as dangerous as thalidomide, that dread must be weighed against the fear of harm to the unborn children, of the patient, and even a fear of liability as a consequence of that harm.

In effect, the mixture of different dogs and different lions may put the medically needy patient at odds with the cautious and legitimately concerned physician. That's the first of three points regarding the environment. While the ultimate objective of the patient's health is common to the physician and patient, the perspectives and motivation of the physician and patient are very different. That may go a long way to state the obvious, but it begs the question, ultimately whose perspective is going to prevail?

The second point on the environment and the reemergence of thalidomide therapy is that this is occurring at a historical time when the dynamic of the doctor-patient relationship is in a state of flux. It is being changed by opposing forces, forces which are actually opposed to one another and which serve to take the traditional notion of the doctor-patient relationship and turn it into something else entirely, as a coal to diamond.

What do I mean by the opposing forces? I refer primarily to the turbulent migration into managed care, which significantly changes the rules of the relationship, restricting the choices of both the doctor and the patient. During the 1950s and 1960s, most people who were provided with health insurance through their employer group did so under indemnity plans. These plans made the insured a free agent who could go to any physician that he or she desired, or any number of physicians, and make his decisions based on professional reputation and personal rapport.

Health care and access to treatments were based on the acceptance of the physician's recommendation, and it was a physician's duty to discuss options and make a recommendation. Generally speaking, medical consumers of that time were more ingenuous than today, and hence more inclined to accept that recommendation without question. But if a question did arise in a patient's mind, then a second opinion could be sought.

Today, however, under some managed care practices, we have gag rules which do not necessarily allow the exploration of all options, restricted pharmacy formularies in which some drugs or families of drugs are not

carried, timed allotments for physician-patient encounters, and ceilings on the amount of dollars allocated to the prescriptive care or procedures for a patient, and the restriction of second opinions on varying procedures.

A case on point. One patient came to me last year to complain that she had been diagnosed with breast cancer by her doctor in an HMO who recommended a complete mastectomy. She requested a second opinion and was advised that she would have to go outside of the system, and would have to pay for that opinion out of pocket, which she did. The second opinion informed her she needed only a lumpectomy. When she opted for that procedure, she was informed by the HMO that they would not honor that second opinion and she would have to pay out of pocket for the lumpectomy, which she did. How is off-label use of thalidomide therapy going to fit into this environment?

A second force bearing down on the nature of the physician-patient relationship comes from the advent of the HIV epidemic itself. As a force of social change, one of the effects of the epidemic is the spawning of a new generation of patient, the activist patient. As we have seen, people with HIV are more activist about their condition than any other disease-specific group. In fact, HIV advocates have set an example for other disease groups, most particularly breast cancer. The effects of this advocacy should not be underestimated in determining the motivation of a patient, or the determination of a patient in getting a therapy like thalidomide when faced with a difficult medical condition.

For example, when protease inhibitors were in clinical trial, pressure on the Food and Drug Administration resulted in the approval of these drugs faster than any other government on earth. This is but one example of the history-making impact of the kind of patient advocacy brought about by HIV. It is without doubt that patients in general, and people with HIV in particular, are becoming more assertive about their desire for their own autonomy in the pursuit of their own treatment options. This is in direct conflict with what is occurring in the managed care environment.

When viewed together, one sees that the relationship between the doctor and the patient is under a great deal of pressure diametrically by the two forces and the self-awareness and self-advocacy mindset of a growing number of the patient population, as well as the uncertainty of the physician of his legal responsibilities, thereby enhancing perhaps a tendency to err on the side of caution. Given this set of circumstances, it would seem difficult to map out a set of rights and responsibilities by which all could seem satisfied for a drug like thalidomide.

The third issue of the environment, however, which is of concern in the administration of thalidomide therapy is the population of people with AIDS itself and the administration of thalidomide for HIV conditions. We're in a new era of HIV treatment. A paradigm shifted in December of 1995, when we went from the treatment of AIDS to the treatment of HIV for the first time. With that era came a whole set of new complications for the patient. Being on combination therapy and taking prophylaxes to guard against opportunistic infections can result in a patient taking as many as 28 pills a day.

We have to understand what synergistic effect thalidomide will have with prophylaxes for opportunistic infections and with protease inhibitors. In addition to that, we're going to introduce two methods of birth control to make a walking pharmacy of a woman who is on thalidomide therapy, ingesting protease inhibitors, ingesting birth control, and ingesting all of the opportunistic infection prophylaxes that she may have to take in the course of a given day.

We're also talking about a regimen of therapy and combination therapy that isn't you can take a pill when you feel like taking it. Some of it must be taken on an empty stomach, some of it must be taken on a full stomach, some of it must be refrigerated. It's a very complicated regimen of therapy that even the most competent patient is challenged by.

In addition, the women affected by HIV are predominantly women of color. In doing a survey of our own clientele, and we have 6,350 clients at AIDS Project Los Angeles, we asked our clients a number of questions about their quality of life and their socioeconomic indicators. What we found is that women, and in particular women with children, had the least amount of personal resources at their disposal in response to the epidemic,

meaning they had the least amount of formal education, they had the least amount of income, they had the least amount of insurance. The socioeconomic challenges for these women are significant.

In addition, for women with children, and in particular who have children with HIV, the HIV treatment of their children occurs generally at different medical points than their own HIV care, meaning that they're going to take their child to their child's appointments and forego their own.

What I'm trying to point out is that there is a significant amount of chaos involved in the life of any person with AIDS. For many people who are on the socioeconomic fringe, there is already a given amount of chaos going on in their lives that makes the normal administration of any HIV therapy extremely challenging. Introducing a drug like thalidomide is going to add to that challenge significantly.

Which leads me to a dilemma because I believe that any attempt to issue guidelines in the administration of a drug like thalidomide are going to fall short, but at the same time, I come from a historical perspective that says any drug that is approved should be used by a patient for a condition that he or she needs it for. I believe that the ability to seek treatment for the drug should not be delineated differently based on economic status, race, or even, in the case of thalidomide therapy, by gender, particularly if the treatment is one of last resort.

I also have a fear that guidelines that have been discussed, such as informed consent and administration of birth control advice, leaves the physician in a spot where the discharge of the physician's responsibility occurs when a signed informed consent slip goes into a file. My trepidation is that, in these more elaborate efforts, guidelines will result in the feeling that this duty has been discharged when the signed piece of paper is obtained and that quality assurance reviews will demonstrate physician compliance with guidelines, but that in fact those guidelines will not, given the chaos that is in the lives of these people, significantly address the issues which are at hand and will in fact result in some of the tragedies we seek to avoid.

I think that the circumstance involves us to go outside the medical box, because thalidomide has implications which also go outside the medical box. Thalidomide therapy is not going to occur in a medical or clinical vacuum. If we're going to administer this kind of therapy, particularly for people with HIV, it means that there must be funding efforts to support community-based organizations in the provision of social services for people who wonder where their next meal is coming from, who wonder where their next ride to their doctor appointment is coming from, who wonder if they're going to be able to keep their housing next month. The idea of their drug therapies, or the idea of their birth control, is not on the top 10 issues of their list. No matter how many visits to the doctor's office they make, it's never going to get there.

What is happening in today's environment, particularly with an impoverished population, is that the social services provided by community-based organizations are in partnership with the medical care a person is getting, because a doctor cannot write a prescription for an apartment, and a doctor cannot write a prescription for food, and as long as those things are true for the significantly socioeconomically challenged population, this type of therapy will only invite more chaos into their lives.

The situation is not unlike the protease inhibitor therapy we face today. In giving people therapies that are so complicated in terms of their regimen, without the social support that they're going to need to be able to stabilize them to the point where we can get those therapies administered successfully, we invite the creation of drug-resistant strains of HIV when people are prescribed, for instance, medications that need to be refrigerated, and in fact they don't have a refrigerator, or they're living in a home environment where the people in the house don't know that they have HIV. How are they going to use two methods of birth control and introduce that into their family life when in fact no one in their family may know they have HIV, much less that they're taking combination therapy or protease inhibitors?

In conclusion, the need and responsibility of mindful and effective birth control and consequences to a fetus must be thoroughly explained to a patient, but if the patient is not competent to the task for whatever reason, she must be supported by other means which reduce the impediment to compliance that she is experiencing. This will not happen by getting women to sign pieces of paper. It will happen when the physician practice goes beyond the practice of medicine to a model of care that looks at the whole person and assesses any

impediments to compliance.

Unfortunately, this runs counterintuitive to what we know of today's environment. The chances of that seem remote, though one would hope that managed care systems would see the benefit of involving more time to support the patient in compliance, rather than take the chance of having to care for a child injured by thalidomide therapy.

But without such an approach, elaborate guidelines mandating birth control will de facto ultimately be not successful and will not create an environment in which the physician will be truly liable to fulfill his or her ethical responsibility, nor will the patient's right to autonomy and decisionmaking capability be respected, in spite of the fact that this is a growing trend.

There will always be cycles of dogs and lions, times when our biggest fears are dwarfed by the advent of a new and bigger and more dangerous one. One thing I've learned in 15 years of HIV work is that meaningful advance only comes when we look in the face of these forced fears and Hell loses its power in that way. We must look to the dangers of thalidomide therapy and face them and, in its compassionate and responsible administration, end suffering.

Thank you.

(Applause.)

MR. WILLIAMS: Good morning. I'm Bruce Williams from Celgene Corporation.

Last week, as you all heard yesterday, our company presented its NDA for the use of thalidomide in the treatment of ENL before an FDA advisory committee. Under normal circumstances for a pharmaceutical company, reaching that milestone would be a very important and very exciting event. However, when we're talking about thalidomide, as I think we've heard over the last couple of days, very little represents normal circumstances. While in fact we are pleased to have had the opportunity to go before the advisory committee, we do so with a great sense of responsibility and concern and recognition that this drug needs to be handled very specially.

It's history is undeniable, and yet the potential benefit, as we've heard in part over the last couple of days so far and will hear more this afternoon, could be very large for patients in desperate need. A lot of the issues that were raised already on this panel this morning are issues that we have been wrestling with for all the time that we've been developing the drug.

What I'd like to do today is share with you the proposal that Celgene has made to the Food and Drug Administration for a distribution and education system that we think will go a very long way and, in fact, will represent a new model potentially for the distribution in a commercial setting of drugs with great benefit, but significant risks.

In developing this proposal, we had a number of key objectives. First and foremost should be no surprise, it's what we've all talked about significantly during the last couple of days, is to limit the risk of fetal exposure to this drug and, therefore, any birth defects that might occur, and to do that by supporting appropriate use. We concur with the recommendations that the appropriate role for this drug is in serious debilitating and/or life-threatening conditions where current therapy is inadequate or unavailable.

It's important that we are able to provide positive evidence of universal compliance with the program. We've all seen Dr. Mitchell's presentation on the Accutane program, and while I think at the time that was a significant step forward, there is no way in that program to know what true level of compliance is occurring with the program.

Very importantly, to facilitate appropriate access. Yesterday, this was mentioned by a number of folks, including Dr. Woodcock in her opening statements. We know that if the program is made extraordinarily

restrictive, it can be extraordinarily effective in a vacuum at minimizing the risk of fetal exposure. We've seen that, for example, in the experience of the U.S. Public Health Service IND that's been providing the drug to Hansen's disease patients for over 20 years. On the other hand, if the program is made so restrictive that, in fact, it limits access to patients who desperately need the drug, those patients will find other means of gaining access to the drug.

It shouldn't be a surprise that when we started in this endeavor we looked to see what else was in the marketplace that might serve as a model. We accepted that we were unlikely to find any single model that carried all of the elements that would likely be necessary for this drug, but we did find two that in part covered many of the elements that might be required.

Accutane, we heard about yesterday. Comprehensive educational program, counseling, and good contraception, informed consent, a package with integrated product warnings, and a surveillance system, albeit voluntary. Many elements that clearly with either change or updating or enhancement would likely be relevant to what needed to be done for thalidomide.

We also heard about the Novartis program for Clozaril, a drug used to treat schizophrenia and introduced in an era where existing anti-schizophrenia drugs were not particularly effective for many patients. In addition, they carried their own baggage of side effects. However, in a small proportion of patients who take this drug, a granular cytosis can develop in a very short period of time.

The system was designed so that only pharmacists who agreed to dispense the drug only one week at a time and only after seeing this week's blood count were allowed to purchase the drug and dispense the drug. Our understanding is that the system has, in fact, been working quite well. While pharmacists will complain that it's an extra layer of administrative burden for themselves, they recognize the need, they recognize the importance, and they recognize their obligations as members of the health care team to participate in the management of that risk.

Looking at these two models, extending and adding additional elements, we believe that we've created a unique system, a system that truly can manage the known and serious risks of thalidomide therapy while making it available to those patients who need it. Elements will include education, both at the professional physician, the pharmacy level, and at the patient level. We've been working closely with the Thalidomide Victims' Association of Canada, whose CEO spoke so eloquently yesterday, to include them in many of the major elements that will be part of this educational package.

We will be providing support for the contraceptive counseling that will have to accompany this drug when women are prescribed the drug. If the prescriber either does not feel competent or for whatever reason is unwilling to provide that counseling on their own, we will provide an opportunity for that prescriber to refer the patient to a competent OB/GYN who, in fact, can then provide the counseling.

Accepting that informed consent by itself is not enough, we do believe that informed consent is a very, very important element. Patients need to make informed choices, and patients need to understand their responsibility in managing the risk factors for the health care decisions that are made. One way to help ensure that patients in fact do understand and do accept that responsibility is through a formal informed consent process. The informed consent form would be in a multipart form where the patient would be able to keep a copy, the physician, one copy would go back to the folks managing the registry, and another copy would be for the pharmacy.

In speaking of the registry, patients in signing the informed consent will be agreeing to participate in the registry. I'll talk more about the registry in the future. This is something we struggled with significantly, along with a number of folks that we've consulted with because of obvious concerns on patient confidentiality.

We knew we couldn't develop this program in a vacuum. We knew we couldn't simply lift the Roche program and the Sandoz program and somehow glue them together. We conscientiously spent much of the last year talking to physicians who might prescribe the drug, pharmacists who might have to dispense the drug, and

patients who might take the drug, both male and female patients and in a variety of disease states, including, as was just discussed, people living with AIDS, both men and women, including women from minority and various color groups.

This was important because we had to know that women understood the message that was being developed, that they understood their responsibilities, that they accepted their responsibilities, and that the materials we were preparing would be able to communicate that well. Pharmacy was important because they were going to play a critical role and it was important that that role could work within pharmacy practice. The same also with physicians.

I think one thing that we saw universally in speaking with all three of these groups is that there is a healthy respect for this drug once people understand what the risks of this drug might be. In our research, no one expressed a disregard for those risks and in fact spontaneously offered up that this is a drug that would not be used unless it really were in fact a last resort drug, in the sense of other drugs not being adequate for the condition.

Other input came from public health officials, meetings like this, the CDC meeting in March, discussions with the Food and Drug Administration, discussions with people in academic/public health and others, patient advocacy groups, including groups such as the National Organization for Rare Diseases, significant numbers of folks involved in AIDS advocacy, and others. Women's health organizations, we knew that this issue was particularly sensitive to the women's health movement. Of course, as I indicated earlier, the thalidomide victims themselves. Their perspective is unique and must be heard and factored in.

Let's move to the program and its major elements and how it would work, at least at the big picture level. In the physician's office, the first point of contact, the physician and patient will have made a decision that, because of the nature of the patient's condition, alternative therapies and their relative risks and benefits, and the patient's willingness to consider a therapy such as this, that this is something that they are now going to seriously discuss.

Counseling would occur, with facilitation from materials that Celgene is preparing, to discuss risks and benefits associated with the use of this drug to ensure that the patient understands not only these risks and benefits, but their responsibility and their need to actively participate in the management of these risks. That would ultimately lead to an informed consent discussion and a signing by both parties of an informed consent document which would include, as I mentioned earlier, agreement to participate in the registry survey.

When all of this is done, a prescription could be written for no more than four weeks' worth of therapy, and that prescription could not be automatically refilled. This is all patients. We believe that it is important for both men and women to understand the full risk profile of this drug and the full responsibility for all patients, men and women, to avoid fetal exposure.

I'll say that again. Fetal exposure. This is not a pregnancy prevention program. It is a fetal exposure prevention program. That's critical and it's a very important distinction. Male patients need to know that they cannot allow their drug to be in a position where someone for whom it was not prescribed might take it, for example.

Female patients, in addition, would receive contraceptive counseling, as I mentioned earlier. Initially, they would have to have a negative pregnancy test before therapy could be initiated, and there would be a recommended or a required pregnancy testing regimen that would be included in the final labelling. I can talk about, and it's already been talked about, what some of those regimens might look like. We, and the agency, and other officials need to ultimately finalize what that recommendation should be.

Lastly, women would be asked to delay initiation of therapy, of course, until they got that negative pregnancy test result back, but also until both the initiation of effective contraception and their next menstrual period.

The prescription is now ready to go to the pharmacy. We've made the decision, as was recommended in part by Bill Zellmer from the pharmacy community, that pharmacies who agree to participate fully in the program and

register and certify their agreement to the program will be able to purchase the drug. However, the distribution will be established such that a pharmacy that has not agreed will not be able to purchase the drug. If they get a prescription showing up and try to purchase the drug, they will be told they cannot purchase it until they are fully in compliance with the program and have signed all the documentation and acknowledged that they understand the program.

Pharmacies in registering are agreeing only to dispense four weeks or less of therapy at any one time in the original package. The original package will be not unlike the Accutane package, a blister pack in a carded system with very, very clear and coherent warnings, including photographs of an affected infant. This is something we have been doing for over two years in our compassionate use program for AIDS wasting. We do not believe that line drawings are sufficient. I believe the thalidomide victims would agree with us.

The initial dispense will occur only with informed consent presented, and subsequent dispenses will occur only with a new prescription. Pharmacists will register the patient into a tracking system and will register each subsequent dispense. That registration will allow us to then confirm back to the survey, the registry.

I am just about done. I know I'm running a bit over.

The survey will be managed by independent investigators at the Slone Epidemiology Unit at Boston University. One might ask, why did we choose them? As we heard yesterday, the Slone Epidemiology Unit has had a lot of experience with the Roche program and the survey there, and has been able to provide very, very important input and guidance into our thinking. We believe they are already well up the learning curve. All patients will participate and all patient data will be confidential to the investigators at the epidemiology unit. Female patients will complete the survey monthly on monthly visits, and male patients at least once every three months when they are in the office.

The registry will track compliance with the program, which to us is as important as tracking any possible fetal exposures that may be reported. It is important because it provides us with constant feedback on the level of compliance with the program, what's working, what's not, are there pockets of areas where compliance is better or worse than others, can we learn from that, and can we enhance the program.

I think I'll close here by again summarizing. We've really struggled with this issue. It is one that no one can move forward on without treating very seriously. We believe we've created a new program, and we are confident that with vigilance on our part, on prescribers' part, on pharmacists' part, and very importantly, patients' part, that this program can in fact allow the drug to be made available to those patients who really do need the benefit while at the same time adequately ensuring the public health safety.

Thank you.

(Applause.)

DR. MORRIS: Thank you, Bruce. I'd like to thank all the other members of the panel.

I know we're running quite a bit late, but I do want to give you all an opportunity to ask some questions, and also give members of the panel an opportunity to perhaps ask each other questions. So with that, why don't we start with the first question.

PARTICIPANT: I have a question for Bruce Williams. First, I must compliment you on the excellent program that you are proposing, but I wonder if this is going to pose a real problem. There have been questions raised before regarding off-label use. The Food and Drug Act is an act which applies to pharmaceutical companies. It licenses a drug for interstate shipment for the approved use. The fiction in a sense, the legal fiction for off-label use, has always been the company doesn't know that it is being used off-label, doesn't advertise it, doesn't recommend it.

Let's make the assumption that those rules don't change, and I know there are potent forces to change them, and

also assume that the drug is licensed for a very rare condition in the United States. Thousands of pills are going to be manufactured, released into interstate commerce, and there is going to be feedback with this excellent program. Clearly, the company will know that the drug is being used off-label and will know that it is being shipped in interstate commerce for non-approved uses. I just wonder how this is going to be handled from a legal perspective.

MR. WILLIAMS: I can't speak to all of the implications that your question raises. However, I can say that we've consciously designed the program to capture any and all use that may occur with the agent, because we fear greatly, as do many of the rest of the folks in this room, the continued distribution of the drug through unlabeled channels.

In the registry that Allen Mitchell and his colleagues are developing, there will be a requirement that the indication for which the drug is being used be disclosed. Now, that data is going back to the Slone Epidemiology Unit and not to the company, but when the Slone Epidemiology Unit reports out what's going on with this drug, both of us, the Food and Drug Administration and we, all would expect in academic publications that will be known data. There's no question about that.

Again, I think you're accurate in saying that the licensing of the drug licenses it for labeling for a specific indication. The manufacturer has an obligation to promote the drug only for that indication. We fully intend to comply with that.

However, yes, to the extent that unlabeled uses are occurring, we and hopefully everyone else will be aware of that. I think that's important because it provides an opportunity for people to monitor that in a way that can't be with existing drugs, and therefore make intelligent decisions whether or not interventions are in fact needed.

DR. MOORE: This is a question for Mr. Williams. Cindy Moore from CDC.

I think we've seen an evolution in the language surrounding thalidomide from babies "may" be born with birth defects to babies "will" be born, and we heard this over and over yesterday. I think this evolution is a good thing, but I also have a concern that perhaps now, when we see that first baby who is born with thalidomide embryopathy, we'll say, well, we expected that this would happen, we knew it would happen when we approved the drug, instead of being shocked or outraged that it happened.

I wonder what your thoughts are on when we should get shocked and outraged? How many babies are too much? When is the risk too great?

DR. MORRIS: That's an easy one, Bruce. Just put a number up.

MR. WILLIAMS: Yes, I'm not going to be satisfied -- we are striving for zero risk. We acknowledge, as has been said here, that zero risk in any endeavor is an admirable goal, but is hard to even define what that means.

DR. MOORE: Unrealistic.

MR. WILLIAMS: So from my perspective, any baby is unacceptable, and we are going to have to all be vigilant to do everything we can. I think if our focus is on zero risk -- I shouldn't say zero risk. If our focus is on we're trying to avoid any exposure, we have a much higher likelihood of, in fact, having an effective program than if we sit back and casually say, well, you know, it's inevitable. We are not willing at this point to say it is inevitable for that reason.

DR. MOORE: Thank you.

MS. VAUGHN: Hello. This is for Mr. Williams. Brenda Vaughn.

I have two questions. One, I'd like to know if there is a patient who refuses to sign up for the registry and they have a life-threatening disorder, how would that be handled? And the other question I had is, how will this

change how ENL patients now receive their thalidomide?

DR. MORRIS: Can you repeat the second part?

MS. VAUGHN: How will this program now change how ENL patients receive their thalidomide?

MR. WILLIAMS: Two parts. The program is designed to require informed consent and registry participation. Under some circumstances, if a patient refuses to participate and there's an open protocol that might capture that patient, the patient could conceivably go into the protocol.

But we've really wrestled with this and we believe that in serious situations such as this, access is important, but so is some level of control, and it is important to provide a level of balance. Confidentiality will be ensured in the registry, but beyond that, I think patients have to make decisions whether or not they really want to be treated with this therapy, and if they do, here's what it's going to take to do it, or whether or not they wish to try something else.

As for ENL, I expect there will likely be some transition period during which some ENL patients may continue to get it through the existing system, but over time those patients will transition onto this system. I don't expect it to take very long.

DR. ERICKSON: Hi. Dave Erickson from the Centers for Disease Control.

We've heard comments this morning and yesterday as well that there's a great need for this drug for people with severe and life-threatening diseases. I'm just wondering how to realize the desire expressed by Mr. Williams to reserve this drug for severe and life-threatening diseases.

Dr. Povar pointed out this morning that at least the use of Accutane doesn't seem to be limited to severe acne. In the qualification checklist that Roche uses in their program, the first thing that a physician is supposed to answer is does the patient have severe disfiguring nodular acne. Then it goes on to say that if no, she must not receive Accutane. Yet, it seems to be widely acknowledge that it is used for much less severe forms of acne, regularly used. Certainly a large fraction, and maybe even a majority of the use, is for less than the most severe forms.

I'm just wondering what sorts of mechanisms, short of statutory limitations, there might be put in place to limit the use of thalidomide to situations where we do have a life-threatening or extremely severe situation?

DR. POVAR: I think the problem, particularly facing Accutane, is the word "severe." Severe is a subjective concept. Acne encompasses, as the dermatologists in the audience will acknowledge, a huge range of not only expression as a disease or as a condition, but a huge range of people with that condition. The severity is measured not only in terms of whether it's acne conglobata or a severe cystic formation, but severity in terms of the patient's tolerance of whatever level they have.

And so a physician might -- and I'm not providing cover here. I'm just saying it is understandable that a physician and a patient might believe that they are being truthful in checking off that this is being used for severe acne when in their eyes it is, and yet anther observer would look at that and say this is disingenuous behavior.

My hope is that we can articulate very specific diagnoses that do not lend themselves to quite so much subjective latitude with respect to the use of thalidomide. That is to say, if we talk about HIV wasting syndrome, that has a specific conditional description, it doesn't include severe or not severe, and it is or it isn't to a much greater extent. The same thing is true of aphthous ulceration in the context of an HIV-infected patient.

Where I am concerned is if we slide from aphthous ulceration in HIV-related conditions to aphthous ulceration, which then encompasses a huge population of patients for whom I personally would feel that we would then get

into exactly the same difficulty as we currently have with Accutane and acne, and where I would be very loathe to see that kind of use supported, either by the medical profession or promoted by the pharmaceutical industry.

DR. ERICKSON: But what mechanisms do people have in mind for seeing that this happens?

DR. POVAR: Well, you could limit its use at least to specific indications. Now, what the legal implications of that would be, or what the teeth would be to enforce that, I think is always a problem that faces the FDA and I suspect would work itself out, unfortunately, for the first time in a tort context.

DR. MORRIS: Let me suggest one other possibility of something down the road. I know Mark mentioned the MCOs as an issue. I know, for example, with the smoking cessation treatments, they created their own policies about when those treatments would be applied, under what conditions. There is a whole distribution channel here. FDA's authority may be limited in certain ways. We don't know what those limits are frequently, but managed care organizations, in addition to perhaps being a barrier, maybe can also be a facilitator in terms of risk management.

MR. WILLIAMS: In fact, we've gotten significant indication that many managed care organizations would expect to play that role, and have expressed in some respects relief that we're putting a system like this in place because they are concerned, as anyone else would be, about indiscriminate use of this drug.

MR. ROEHR: I'm Bob Roehr with the Bay Area Reporter.

For Mr. Williams, on an annual basis, approximately how many patients do you expect to be on this drug, and could you give a sense of the breakdown of what percentage of use you expect to be off-label?

MR. WILLIAMS: You know, at this time, that's very difficult because as additional research is completed and published, that could change significantly. We expect initially this is going to be a rarely used medication in the sense that the existing disease states for which the evidence is either before the FDA or already beginning to come out in the published literature have small numbers of patients. We've talked about ENL over the last week and a half or so, varying numbers, but generally in the mid-100s in terms of existing patients with ENL, as opposed to new patients, have been cited in this country.

In addition, those familiar with aphthous ulceration in AIDS patients recognize that while it is a severely debilitating condition, it is not at any one point in time affecting a large percentage of people living with AIDS.

MR. ROEHR: But what numbers are you projecting for your first year?

MR. WILLIAMS: At this point, I am not in a position to share that, but I can tell you they're going to be quite small.

DR. MORRIS: I'd like, because we're running so late, to limit the questions to people already waiting at the mike.

DR. MOORE: I have a comment -- this is Cindy Moore again from CDC -- to follow up Dr. Erickson's question. It seems to me that we may have already started down that slippery slope because the advisory committee recommended the approval of thalidomide for the cutaneous manifestations known as ENL and not the systemic life-threatening manifestations.

But my question was actually for Mr. Senak. You were talking about the difficulties of using this drug or multiple drug regimens in individuals with HIV. One group you did not address are individuals who also are addicted to illicit drugs. Could you make some comments on how you think that's going to --

MR. SENAK: Well, this sounds glib, but it's really not meant to be. I just have a personal theory that people who take illicit drugs, one thing they know how to do is take drugs. We often assume that they don't because they take drugs.

I actually recently wrote an article about doctors who are reluctant to prescribe protease inhibitors to this population, because they feel that they will not necessarily be compliant. I don't have a rock-solid answer to say they can be or they can't be. This is going to sound like a researcher now, but I think it is something that merits some study, though in terms of what the prescription drug-taking habits of an illicit drug-using population might be. We might be surprised to find out they're very organized about it.

DR. MOORE: And use of contraception?

MR. SENAK: I'm sorry?

DR. MOORE: And use of contraception?

MR. SENAK: I think that there are studies with respect to that, and I think they would show not such a good track record.

DR. MOORE: Thank you.

MS. RATSKOFF: Ellyce Ratskoff. I have a two-part question for Mr. Williams.

One, will the informed consent specifically detail that this drug has only been approved for ENL and that other uses of this drug are off-label, et cetera?

And could you detail the indemnification program that you would intend to provide to pharmacies and pharmacists that agree to participate in your program, knowing that patients who are coming to them may not, in fact, be using it for label uses, and the reimbursement issues that arise from that if in fact the drug is being prescribed off-label? Will the federal government knowingly pay for this under Medicare or Medicaid or other participating programs?

MR. WILLIAMS: Could you repeat the first part of the question?

MS. RATSKOFF: Are you going to in the informed consent specifically tell that, and also inform the patients that this drug, if used for conditions other than ENL, may not be reimbursed by their provider and that it would be their responsibility to pay for this drug themselves?

MR. WILLIAMS: Yes. A couple of points on that. First, the finalization of the language in the informed consent is still subject to significant discussions with the FDA, and I think that's one of the areas where there's going to be a lot of discussion. One way or the other, we would not object to that if that was the outcome of those discussions.

As for payment, which I think is also a very important question, there are a variety of ways in which drugs are paid for in this country. Some of us have private insurance, some of us pay for it ourselves, and some of us are through government programs. Many of the programs are not today capable of distinguishing between an on-label and an off-label use in terms of the payment decision. Some are. It really depends on the payment scheme.

We do believe that in the event a patient is being prescribed the drug by a knowledgeable, informed physician and that patient's financial circumstances are such that either because of inadequate insurance, no insurance, or some form of denial of payment that patient is going to be denied access to the drug because of financial circumstances, that we will in fact be announcing at a later date a patient assistance program to find another means for that patient to obtain the therapy. I'm not prepared to talk about the details of that, but we won't believe that the simple lack of an ability to pay for the therapy by itself should stand as a barrier to use.

MS. RATSKOFF: Are you prepared, in exchange for participation in the program, for offering an indemnification program for pharmacists and participating pharmacies who are dispensing this drug under these very rigid conditions in the event that there are malpractice claims against the pharmacist and the pharmacy?

MR. WILLIAMS: At this point, I'm not prepared to address that, but it is a very important question.

MR. LINDIN: Also for Mr. Williams. My name is Keith Lindin.

In continuation of that discussion with regards to access, do you anticipate that the protocols that you're putting in place at the pharmacy are going to inhibit pharmacies from picking up your drug or from wanting to deal with it, and could in fact prevent access to it because of HMO enrollment or other managed care factors?

MR. WILLIAMS: We certainly hope not. We look at the Clozaril experience and while, again, only pharmacies who agree to participate can buy the drug, we've not heard since the original program was modified -- the original program was highly restrictive -- we've not heard about access issues associated with that. We've designed the program to try to minimize the impact of any access issues as it relates to pharmacy availability.

DR. MORRIS: I'd like to thank you all.

We'll now take a brief break.

(Recess.)

DR. GINSBERG: Welcome back. We are now going to start the session on perspectives on present and future needs relating to thalidomide and its uses.

I'd like to first introduce the panel. I'm Ann Ginsberg from the National Institute of Allergy and Infectious Diseases, where I direct the tuberculosis, leprosy, and other mycobacterial diseases research program.

I'm pleased to be able to present the panel to you today. On my immediate right is Dr. Gilla Kaplan, an associate professor at the Rockefeller University in New York, and an expert in the human cellular immune response to mycobacterial diseases, especially tuberculosis and leprosy. She is one of the leading investigators into the immunomodulatory effects of thalidomide in human clinical trials.

To her right is Peter Andrulis, the president and CEO of Andrulis Pharmaceuticals Corporation.

Following Peter is Frank Woodside, a defense attorney at Dinsmore -- I'm sorry, they've switched positions on me. Thomas Bleakley is next, who is a plaintiff attorney at Bleakley & McKeen. He has 25 years of trial practice, including several thalidomide cases, the first DES case in the United States, Oraflex, Celacaine, oral contraceptives, et cetera. He has co-chaired the Birth Defect Litigation Group of the American Trial Lawyers Association.

To his right is Frank Woodside, a defense lawyer at Dinsmore & Shohl. Mr. Woodside defends manufacturers of medical devices and drugs in birth defect law suits.

Together, they will present a variety of perspectives on thalidomide and its present and future needs, starting with the research perspective by Dr. Gilla Kaplan.

DR. KAPLAN: This is a kind of interesting situation for me to be presenting quite a large body of research in a few minutes and focusing predominantly on what we have not yet done. In order to avoid that, I would like to go back into the issue of where, for us at least, this whole story started and discuss with you a little bit the rationale for us getting involved in the research of the immunomodulatory effects of thalidomide, and in involving studies in a number of diseases where we think thalidomide could provide an important immunomodulatory role.

For scientists, and this is a slide I've borrowed from a prominent colleague of mine, our role, our message, is that science is organized knowledge, and our responsibility is at least predominantly to acquiring that knowledge and hopefully acquiring it in an organized fashion.

The history of my involvement with thalidomide originates from the fact that for the last 17 years or so, I have been studying the regulation of the immunology of the immune response of the host infected with M. lepri, the immune response in those individuals who have leprosy. As many of those of us who are in the field know, leprosy is really a very complicated disease and, more so than many other diseases, it is a personal crisis management treatment of individual patients because, as patients are treated with antilepromatous drugs and their skin lesions are healed, the physician is faced repeatedly with the complications of leprosy, ENL, and reversal reactions. In effect, those are the questions, the problems, the issues in leprosy.

Now, there might be a bit of a feeling in this audience that this is not a severe disease, and that ENL in leprosy is not a severe disease. I'd like to emphasize that the first episode of ENL is the beginning of a potentially very long sequence of inflammatory flares which leads to continuous and developing complications which would ultimately result in deformities, loss of digits, blindness, et cetera. That is not to say that all patients with leprosy develop ENL, but from my experience, especially in South America, the Philippines, and other countries, this is the bread and butter of the most complicated aspect of patient management in leprosy, and the physicians involved in this obviously would concur.

What we were interested in was why patients develop ENL. Why do patients who basically are relatively nonresponsive immunologically or anergic to M. lepri antigens develop these acute flares, which ultimately result in destruction of the nerves, loss of digits, and all the other complications?

We set out to use thalidomide, the drug of choice in ENL, in those countries where ENL is very common. We used thalidomide as a tool to ask what causes ENL. What we found was, and this is quite a few years back, that patients in ENL have increased levels of TNF alpha, tumor necrosis factor alpha, one of the hormones of the immune response in their serum. I'll get back to discussing this molecule in a minute.

When they are treated with thalidomide, as the symptoms disappear, the levels of this inflammatory cytokine, this hormone of immunity, are reduced concomitantly with clinical improvement. This was a very exciting observation, and I'd like to explain to you why we thought it was exciting or what the implications of this observation were.

Tumor necrosis factor alpha, or TNF alpha, is a normal component of the host immune response to infection, to autoimmune disorders, to parasitic disorders, and even to tumors. The molecule is required as a component of the protective immune response, and is generated by the host to combat and to overcome the infection.

However, the same molecule, whether at higher concentrations, whether because it's produced chronically in the high doses, or because of the site of its production, is associated with the signs and symptoms, the toxicities, the pathology of diseases which involve activation of the immune response, and those really are very many of the diseases we deal with.

TNF alpha is associated with fevers, weight loss, muscle weakness, night sweats, tissue necrosis, and so on. As I said, these -- the tissue damage, the muscle weakness, the weight loss -- these are signs and symptoms, the pathological manifestations, of disease. Here we had a drug that appeared to reduce the production of TNF alpha while eliminating these symptoms.

The question we had asked at that point was, why do leprosy patients have TNF alpha in their circulation? What we could show was if you take the blood of leprosy patients and stimulate them with various components of the organism, Mycobacterium lepri, the organism that causes the disease, blood cells would make large amounts of TNF alpha and release them into the environment; i.e., the tissues or the blood in which the exposure occurred. I would like to just point out that this is a property of the components of many infectious agents, including the components of Gram-negative organisms, the components of other mycobacteria, such as M. tuberculosis, M. bervis, and so on.

So the ability of biological components of infectious agents to induce TNF alpha for production is relatively universal, pretty universal. Again, that flagged a lot of interest in the potential implications of this observation.

One of the other things we've done recently is we've asked, well, if thalidomide affects the outcome in ENL patients or in leprosy patients by reducing TNF alpha production, how does it compare with other known or potential drugs that could be used in this clinical situation? Prednisone or other steroids have been used as immune suppressive drugs in ENL patients, especially where thalidomide has not been available. The drug is an immune suppressive in that it blocks the production of many cytokines, the majority of cytokines. Those are the molecules, the hormones of immunity, which drive the entire cascade. So they are nonselective compared to thalidomide.

What we asked was, what effect does prednisone have compared to thalidomide? Then one of the other drugs we looked at was another known TNF alpha inhibitor, pentoxifylline, which had been shown in vitro at least to be very efficient at inhibiting TNF alpha production, had been used clinically, and had no history of any teratogenic activity. We were investigating the effect of these three drugs as potential drug treatment of ENL on cytokine production.

As you can see, pentoxifylline, although very efficient at inhibiting TNF alpha production in vitro, appeared in our hands not to affect cytokine production in ENL patients, while thalidomide and prednisone, the two commonly used drugs in the management of ENL, shared this ability to reduce the levels of cytokine production in the patients.

We also looked at the clinical efficacy of these three drugs. What we're looking at here is this is thalidomide, and we're using a disease index defined as the severity of disease and the elimination of symptoms. You can see that as you treat the patients with thalidomide, the symptoms disappear completely in many of these patients by 21 days, although if the drug is discontinued, in some patients ENL will flare up again. This is low doses, regular, normal doses of pentoxifylline, 1,200 mg per day. This is 2,400 mg per day of pentoxifylline and prednisone, and as you can see, pentoxifylline did appear to eliminate some of the symptoms of the disease at very high doses, twice the routinely used dose, but is not as efficient as thalidomide.

So the concept of TNF alpha inhibition or cytokine inhibition for the management of ENL appears to be applicable to other potential therapeutic interventions, including thalidomide. That's an issue I'd like to come back to at the end of my talk.

The next step was to ask, well, is this a universal observation? Does thalidomide inhibit TNF alpha production in other settings, not only in the blood or in the circulation, but in the cells of leprosy patients with ENL? We have looked at the effects of thalidomide on TNF alpha production in monocytes obtained from normal donors, and we have actually been able to show that this is a universal effect that, yes, thalidomide can reduce TNF alpha production when monocytes are stimulated by contact or exposure to bacterial components such as LPS, M. lepri, M. tuberculosis, and so on.

At this point, we had already established that thalidomide inhibits TNF alpha production by monocytes. The inhibition in vitro is selective, and other molecules produced as part of the immune response, other cytokines necessary for the mediation of protective immunity, were not affected. This is an important issue because the selectivity of the drug means that you can use it in a more focused way.

We found that thalidomide reduces the half-life of the TNF alpha messenger RNA. That was the first attempt to start looking at the mechanism of action, and this is being pursued further. Finally, that thalidomide reduces the activation of NF kappa B. All of these observations suggested that thalidomide could be used in other diseases, too.

This brings me to a slide that I am not going to go through with you, only to demonstrate what is the general concept in modulation of immunity of changing of the immune response of the host in order to improve outcome. This is a schematic representation, a very simplified schematic representation, of what we think happens in a patient infected with leprosy or tuberculosis, the cells and cytokines, or the cells and soluble mediators, that are involved in the host response which ultimately when successful would contain the infection and limit the severity of disease.

There are two components to this slide. There is the protective cellular immune response and the generation of a number of inflammatory mediators and cytokines that activate the cells that participate, and there is immunopathology here at the end.

This scenario could be applied to pretty much every infectious disease, every autoimmune disorder, and many other complications which involve activation of immunity. The question that we are faced with as scientists is, which cells and which cytokines play exactly what role in each disease, and if we understand how this network is regulated in various diseases, does TNF alpha or other molecules affected by thalidomide, can the modulation or the reduction in the production of these molecules affect outcome not only in leprosy and tuberculosis, but in other diseases, too?

I have a list here of some of the potential indications. I think this is where the responsibility of scientific investigation and further studies lies. Obviously, TNF or other molecules are involved in all of these diseases. The responsibility we are facing is to characterize the contribution of the various components of immunity to each one of these situations, and identify the potential effects that thalidomide and other immunomodulatory drugs would have on outcome in these diseases.

Once we understand the mechanism that regulates the disease in each one of these cases, we specifically test thalidomide and other molecules for their effects in each one of these diseases separately. What I'm saying is we need a rational approach to understanding the regulation of immunity and understanding the potential for modulation of immunity in each one of these diseases.

Our group has concentrated on HIV, leprosy, and tuberculosis, but as you can see, there's a diverse list of diseases or clinical situations which have been potential candidates for immune intervention. Ideally, what we would be looking for is a drug that is better than thalidomide; i.e., a bit more active, less toxic, nonteratogenic, that can be targeted for each one of these diseases so that we can rationally modulate immune response of the host and modify outcome, improve survival, reduce toxicities, et cetera.

Thank you very much.

(Applause.)

DR. GINSBERG: Thank you, Gilla.

Dr. Andrulis?

DR. ANDRULIS: Thank you, Dr. Ginsberg, fellow panelists, conference participants. I'd also like to thank the organizers of this conference for inviting me to provide the industry perspective. I think they'll be pleased to know that I will help them catch up on their schedule because I will easily finish in less than 15 minutes.

Much of what I would have said is similar to what has been expressed so eloquently by others. This is so because of our similarity of purpose, treating women while preventing damage to the fetus if she is pregnant. In order to provide you some context for my remarks, perhaps I should tell you a little bit about Andrulis Pharmaceuticals Corporation.

APC was the first domestic firm to manufacture thalidomide, the first to commence clinical trials, and the first to report on a clinical trial. APC also provided the thalidomide to investigators who discovered its antiinflammatory, antiangiogenic properties, and who affirmed that it did not increase metabolism of oral contraceptives.

APC was founded as a division of Andrulis Research Corporation in 1971, and spun off in 1991. Prior to its experience with thalidomide, Andrulis manufactured 15 kilograms of clinical grade cisplatinum on five National Cancer Institute contracts for NCI-sponsored Phase III clinical trials against ovarian cancer. Bristol-Myers used the data from these trials to obtain market approval from FDA.

In 1987, APC was issued a three-year contract by the Hansen's Disease Center to manufacture clinical grade thalidomide for the treatment of erythema nodosum leprosum. Over 50 kilograms of 99.5-plus percent pure drug was delivered and used. Thalidomide clinical trial planning commenced in 1989 with the submission of the drug master file, inspection by FDA, and planned orphan drug designation submissions. The first pilot clinical trial against Crohn's disease was begun in 1991.

In 1992, working with the Division of AIDS of the National Institute of Allergy and Infectious Diseases and an AIDS Clinical Trials Group principal investigator, planning began for a trial against recurrent aphthous ulcers in HIV-positive patients, a theretofore untreatable and incurable condition that severely degraded the quality of life. The trial commenced in 1994 as a multicenter, randomized, double blind, placebo-controlled Phase II/III clinical trial against both oral and esophageal aphthous ulcers in HIV-positive patients. The trial was sponsored by the Division of AIDS of NIAID.

Study interim analysis in October of 1995 showed that 61 percent of treated patients had complete healing of all of their ulcers versus 5 percent of placebo patients, and 91 percent of treated patients had partial or complete healing of all of their ulcers as compared to 18 percent of placebo patients.

This data was affirmed in a paper in the May 22nd issue of the New England Journal of Medicine, where an update showed that 55 percent of treated patients had complete healing of all of their ulcers versus 7 percent of placebo patients, and 90 percent of treated patients had a partial or complete healing of all of their ulcers versus 25 percent of placebo patients. No grade III or grade IV toxicities were seen, but significantly, and contrary to expectation, both viral load and TNF alpha levels in the blood stream increased. More on this trial will be reported by the ACTG principal investigator later today.

Finally, from 1993 to 1997 to the present, pilot trials were started against three AIDS-related conditions -- Kaposi's sarcoma, prurigo nodularis, a severe dermatological condition, and immunodeficiency in AIDS patients. Pilot trials were also started against multiple sclerosis with thalidomide against glioblastoma and a combination chemotherapy regime. Dr. Toby Maurer, the prurigo nodularis principal investigator, will be discussing some aspects of the use of thalidomide against prurigo nodularis later today.

With that as background, let me share some thoughts on thalidomide with you from an industry perspective. One of the things that occurs, first of all, is that there are some differences between thalidomide and Accutane. Thalidomide will be used on a very sick patient population, for one, while in all but the most seriously ill patients Accutane will not.

Because of its unique potency and prospective mechanisms of action, thalidomide is, and probably will continue to be, an essential drug, not a discretionary drug, let alone a "me too" drug. It is to be used, and it must only be used, to treat people who are otherwise untreatable. This could serve as an additional checkpoint in the process of control and reporting and monitoring, that a physician or provider certify that he or she has tried all other reasonable therapies, and in his or her professional judgment, thalidomide is the only realistic option remaining.

The dilemma that this gives rise to is how to maximize the availability of thalidomide to patients for whom nothing else works while inhibiting its routine availability, so as to ensure a pregnant woman can protect her fetus. Thalidomide must, therefore, be safe and effective not only clinically, and not only in the regulatory sense, but safe and effective for everyday use. This is a significant challenge, as other speakers have well noted. If we do not accomplish this, we will never be able to treat the patient while ensuring the safety of the fetus under the optimum set of circumstances.

To add to this mix of variables, the political pendulum is swinging from a paradigm of government as protector and as agent of its citizens to one of less regulation and more consumer and independent citizen decisionmaking. If there are fewer government resources to provide comprehensive knowledge and regulatory balancing of risk and reward as they pertain to thalidomide, the patient's ability to make a fully informed and objective use decision can only be adversely affected. When cost-effectiveness constraints and time constraint pressures on providers are added, risk to the patient can only increase further.

The result of all of this will increase the chance of accidents and, therefore, increase the threat of litigation. Such a series of events would be nothing short of catastrophic, not only to the victim, but to all others then benefitting from thalidomide and all who might benefit from it. Investment and development initiatives would be chilled or halted, probably irrevocably.

Because of this ominous scenario, some question and future issues come to mind that we believe need to be considered and that may not have been raised yet or considered in the depth they deserve. First, how do we ensure no gaps exist in education, counseling, monitoring, tracking, and reporting of all drug and by all parties who control, possess, or use drug? Should there be audits? If so, what should be their scope and limit? Should there be informed audits or surprise audits, and by whom, government, industry, patient representatives?

What scenarios can we expect if FDA has to pull the drug for any reason? What of patients who need it? What are their rights under such circumstances? What are the risks to them? What is the risk of return of illegal thalidomide now with a greater market-driven incentive than before?

Third, what are the relative interests of the pregnant woman needing thalidomide and the fetus? Have we identified and do we understand all the permissible perturbations of that relationship of woman and fetus, the mandatory perturbations that we are obligated the perform, and the impermissible perturbations? Many considerations in this area were eloquently presented by Kathleen Kinslaw of the Center for Ethics in Public Policy at Emory University at the CDC-sponsored birth defects prevention meeting in Atlanta, and by Norman Fost yesterday, but more still needs to be done.

A constant vigilance is necessary to anticipate and respond to real-life scenarios that could confound our best protective procedures. For example, what is the responsibility of the pharmaceutical firm, the government, providers, and the like to a female patient off thalidomide, but whose autoimmune condition suddenly flares up, where nothing else works, where the flare is life-threatening, and she has just entered her third trimester of pregnancy?

These same questions need be asked if she's in her second trimester of pregnancy and, once again, when she is in her first. What if the flare is something less than life-threatening? What if it "only" severely erodes her quality of life? What if thalidomide is simply the optimum treatment?

In conclusion, the interest of industry is intimately intertwined with the interest of others in the safe development and use of thalidomide. We can only protect the pregnant woman and the potential for this drug if we constantly review how safeguards work out in the real world.

Finally, I would like to thank those who have shared their insights and experiences that I have found so useful and enlightening in this presentation today: Paul Freiman, former chairman and CEO of Syntex Corporation, and former chairman and CEO of the Pharmaceutical Manufacturers Association; Jess Stribling, former special assistant to the commissioner of the Food and Drug Administration; and Dr. Mark Novich, former deputy commissioner of the FDA.

Thank you.

(Applause.)

DR. GINSBERG: Thomas Bleakley?

MR. BLEAKLEY: Thank you, Dr. Ginsberg. I'd also like to express my gratitude at having the opportunity to speak before this group.

By 1959, thalidomide was being marketed as a safe sedative in 48 countries, and doctors had already reported 12 cases of limb defects in children born in West Germany. By 1962, 10,000 to 12,000 such children had been born. About half of these children died as infants.

In the aftermath, the manufacturers of these drugs abroad resisted the imposition of liability for nearly a decade, and the compensation scheme that was devised basically counted the number of limbs that were missing and a child was awarded money, a mere pittance I might add, based on that scheme.

Since that time, things in America have changed and we are a more complex culture. What has changed most is the expectation of justice. Individuals throughout our country have developed a growing appetite for human rights, epitomizing the great American dream, "justice for all."

So here we are now more than 30 years later since this tragedy. We are faced with the terrible reality that this drug will be marketed. We are told that children will be harmed and that the implication is that this expectation is acceptable in a benefit versus risk analysis.

I view my function here, as an attorney representing injured victims, to develop three points. First, to serve as a reminder of the past. The adage is those who ignore the past are bound to repeat it. The second is to provide you with some information as to what the law can or cannot do for these injured children and, I might add as well after listening to the presentations yesterday and this morning, those suffering from peripheral neuropathies as well. Finally, I view my role to ask the hard question of just how many children will need to be harmed by this drug before the risks of the drug are deemed to outweigh the benefits.

The question thus becomes, what can the legal system do for the victims of thalidomide? I would like to give just kind of a brief dissertation on the function of our tort system of justice. Basically, it serves five fundamental purposes. First, it compensates victims. Second, it deters misconduct that may cause injury, and punishes wrongdoers that inflict injury. Third, it prevents death and injury by removing dangerous products and practices from the marketplace, and thus spurs safety innovations. Fourth, it forces public disclosure of information on dangerous practices and defective products. Finally, it is responsive to the health and safety rights of the public in a world of expanding technology.

Because this emphasis at this forum has been about injury prevention, I'd like to comment more specifically on that aspect of tort litigation as being a preventer of injury. Tort law prevents injury by placing manufacturers and service providers on notice with strong incentives to take precautions against foreseeable harm. It often forces immediate, specific action to protect against the danger identified in a case by means of recall and corrections of the product, removal of the product from the market, or redesign.

This generally unknown, as well as unappreciated effect, of tort law was documented by the Conference Board in 1987 in a report entitled, "Product Liability: The Corporate Response." After surveying risk managers of 232 United States companies with annual revenues of at least $100 million, the board concluded, "Where product liability has had a notable impact, where it has most significantly affected management decisionmaking has been in the quality of the products themselves. Managers say products have become safer, manufacturing procedures have been improved, and labels and use instructions have become more explicit."

That report establishes a direct connection between products liability and public safety. Almost one-third of the manufacturers surveyed have said that products liability has led them to improve the safety design of their products.

The preventative rule of the civil justice system has also been demonstrated by the Rand Institute for Civil Justice, which is partially funded by the insurance industry. It has found that of all of the various external social pressures influencing product design decisions, product liability seems to be the most fundamental. Changes in the drug product labeling of many products have occurred as a result of the tort litigation system. Products have been removed from the marketplace. The plaintiff's personal injury bar has been personally responsible, in my judgment, for saving countless thousands of human lives, and I cite Dalkon Shield and DES just as a basic primer on the topic of that issue.

Tort law expands human rights and basic values as society grows, new hazards emerge, and technologies change, such as in the instant situation. Some of the most majestic statements ever made are found in the case law of product liability litigation, statements by Justices Cardoza, Learned Hand, and Holmes, and others. They

articulate the proper ethical standards of behavior in a civilized society. These principles are not found on MTV, or on the editorial pages of our newspapers, or in academia. They are found in the decision of judges and juries who witness the conflict between seller and buyer, between doctor and patient, between manufacturer and user.

The courts articulate the proper duties of the defendant, the obligation to warn or to invest in safety protection. Without tort law, Ralph Nader reminds us, society loses a principal reservoir of experience and balance. It loses a fountainhead of civilized values that emerges out of the equality enforced in the courtroom between the powerful and the powerless, the perpetrators and victims.

With that background, I would like to just briefly discuss the legal setting for the new thalidomiders. There have been some conflicts that have emerged in society in the last 10 to 15 years that have seriously eroded the constitutional rights of persons who are injured by the health care system. Tort reform and various case decisions emanating from our Supreme Court, as well as our federal judiciary, have seriously compromised the rights and abilities of people to gain the compensation which is essentially guaranteed to them by the Seventh Amendment of the United States Constitution.

For example, Dr. Barbara Hill, in her presentation yesterday, as fine as it was, presented three competing, alternating explanations for the etiology of the teratogenic effects of thalidomide. I would submit that given recent case law, in the federal system in particular, that it would not be unlikely for a judge to dismiss a case in which it was contended that thalidomide had caused limb defects because the expert witness was not able to give a cohesive explanation as to how the damage had occurred.

The case law is replete over the last four years since the holding of Daubert v. Merrell Dow, a United States Supreme Court decision, stating in effect that it is necessary to demonstrate by admissible scientific evidence the basis for an expert's opinion. Since that time, federal judges and a host of state judges have followed, have played amateur scientists, and have not heeded the spirit nor the intent of the Supreme Court in rendering that decision.

In tort reform, in my abstract I cited my home state, Michigan, as an example. Many states have enacted legislation which seriously restrict the rights of persons to bring personal injury law suits. This would certainly be no exception in the instant situation. In Michigan, as of April 1, 1994, if the FDA has approved a drug, that means that the drug is safe, period. No lawsuit can be brought unless it can be demonstrated that FDA approval had been procured by fraud, and that the FDA would not have approved the drug without evidence of the fraud.

The limitations, in my experience as a litigator against the drug industry and against members of the medical professions, imposed legally upon the rights of plaintiffs are also found in the drug distribution schemes that are set forth.

I'm personally involved in a law suit involving death as a result of Clozaril. The situation, very simply, and I think it's important to relate it in as much detail as I can, is a young man was in a hospital manifesting signs and symptoms of one of the black box warning problems associated with Clozaril, and he was prescribed Clozaril by a new psychiatrist over the phone without ever having seen the patient, and he died two days later. So I'm citing this as an example of what I would call the trickle-down theory.

We're in a room full of fine physicians and scientists, caring, loving, and open-minded human beings who are willing to say, yes, this is a major risk and we're trying our darnedest irrespective of our perspective to deal with this. But the trickle-down theory is when this gets out into the marketplace, with the physician who has only partly paid attention to the dangers, or simply ignores them, or feels that all of these proclamations that are being made are only relevant to protecting the manufacturer from liability. Probably the most frequent statement I hear in that regard from physicians is, well, even aspirin wouldn't be approved today if it were offered to the FDA on a new drug application basis.

So this trickle-down theory of mine is something that I think needs to be taken with a certain degree of seriousness. The impact of noncompliance by literally everyone in the distribution chain is a high likelihood,

not an isolated instance. I think, from what we've seen with the figures, that the degree of noncompliance is a significant percentage of users, which has the net effect of exposing people to the serious risk of harm.

I want to conclude my comments by asking the question once again. Just how many children will need to be harmed to make the determination that the risk of marketing this drug outweigh the benefits?

Thank you.

(Applause.)

DR. GINSBERG: Thank you.

Our final presentation, a second legal perspective, will be provided by Frank Woodside.

DR. WOODSIDE: My name is Frank Woodside. I'm a defense lawyer. I practice in Cincinnati, Ohio. I got called by David Banks, who I had not met, and he asked me if I would appear on this program. I readily agreed. I spend most of my life fighting with Mr. Bleakley in birth defect litigation involving bendectin. Mr. Banks asked me if I would present this from both the defendant's and the plaintiff's standpoint. I told him it was virtually impossible for me psychologically to ever think like a plaintiff's lawyer. I have purported to say things from Mr. Bleakley on occasion to get him in trouble, but anyway I got him to do this because we do fight, because he has handled thalidomide litigation for plaintiffs.

I appreciate the opportunity to be here, and I thank those who organized it for inviting me. I made some notes -- and see, this is going to be real difficult for me because I walk all over the damn place. Is this being recorded? Peter, is it? All right, then I have to exercise some modicum of decorum.

Let me tell you what I was going to do. I was going to talk a little bit about the tort system. I was going to make the comment that no matter how exemplary the conduct of the manufacturers is, no matter how good a job of warning the physicians and the pharmacists do, there will be children born with birth defects as a result of thalidomide. It's a fact. There will be.

And there will be law suits, and I was going to talk about those, and actually I was planning to do it, but I have to respond to a couple of things Mr. Bleakley said, because we did agree that I got to go second, even though I'm on the schedule first, because defense lawyers always go second. It just seems fair.

(Laughter.)

DR. WOODSIDE: He talks about the tort system, and he goes though and he identified five benefits, ramifications, or whatever. Generally, I agree, but I have to pick on him on the first one. He says the legal system exists to compensate victims.

Now, I want you to know that when defense lawyers handle lawsuits, I've never, in the last 20 years, had the opportunity to defend a case filed by a plaintiff or a person. I only handle cases where they're filed by victims. Bear in mind, people are not always victims.

It is, in fact, the case in the American system of justice that individuals can be harmed by drugs, they can be harmed by automobiles, but the manufacturer or the pharmacist or the physician doesn't necessarily owe them compensation. You're only owed compensation if under a given theory of liability you are entitled to recover, and I'll go through those. So the system does not exist to compensate victims. It exists to determine whether there are theories of liability under which the plaintiff is entitled to recover. Sometimes the answer is yes, and sometimes the answer is no.

In this day and age -- that is, the 1990s -- the plaintiff's bar in the United States is pushing this concept that the plaintiffs of the United States are denied their constitutional right under the Seventh Amendment to a jury trial. Their position is very simple. The way lawsuits ought to be handled is we file the lawsuit, we put on our case,

the defendant puts on its case, the judge doesn't do squat, we let the jury decide.

The problem is in many instances, particularly in instances involving birth defects -- and I must tell you, I have a medical degree, I'm licensed, I am a very compassionate person, I represent Children's Hospital in Cincinnati, and I have two children. My oldest son actually -- when your child gets presented at neonatology grand rounds, you don't know whether that's good or bad. It's good because he's there to be presented. Anyway, I'm a compassionate person and I'm compassionate about many of the children who are born with birth defects.

But you don't get the automatic right to have a jury determine you're entitled to money because the jury is going to be sympathetic. I've tried lawsuits all around the country. I've never walked into a courtroom anywhere where somebody said, "You know, I really feel sorry for the drug company." It doesn't happen. They never say, "I feel sorry for the United States government." That doesn't happen either. It's just a fact of life. They are sympathetic to the children, and they ought to be. I'm sympathetic to them, but I don't want juries deciding cases without good, qualified, scientific evidence that forms a basis for opinions, so that the jury can decide a case based on science, not on sympathy.

In addition, if you look around, you can find an expert that says anything. I'll be fair here. By the way, I'm not getting paid for this. This is a disclosure of sorts, and when I'm not getting paid, I don't necessarily feel compelled to be particularly -- well, I generally tell the truth, but I overstate a little, all right?

You can find an expert that says anything, but I will tell you, just so we're clear, defense lawyers are sometimes just as bad as plaintiff's lawyers. It is sometimes really hard to find an expert that says something if you're a defendant. So it's not just the plaintiff's bar, but you can find an expert that says anything, and that's particularly true in product liability litigation involving birth defects.

Now, let me go back to what I was going to talk about for a minute. Generally speaking -- this is true, but it's an oversimplification -- generally speaking, in lawsuits, product liability cases and malpractice cases, there are only a limited number of theories of liability. Please understand that in a case you can have fraud, misrepresentation, lots of things like that. I'm just trying to simplify this in my 15 minutes. Generally speaking, manufacturers, for instance, are alleged to be liable two different ways. One is negligence, and two is on a strict liability theory.

If you look at theories like negligence, breach of warranty, and misrepresentation, things which crop up in lawsuits, those are fault-based. In other words, the manufacturer had to do something wrong or, as my 18- and 20-year-old sons would say, they had to screw up. That's what negligence is. It's more appropriately articulated as a deviation from accepted standards or things of that sort. It means you had to screw up. You are at fault.

On the other hand, going back to the mid-1950s, there is a different theory, which is known as strict liability. What strict liability means is that the product was defective and, because of its defect, it was unreasonably dangerous. There can be three types of defect. There can be a manufacturing defect -- in other words, in the process something happened in the car, the drug, or whatever and it didn't come out right; there can be a design defect; and there can be a failure to warn.

Let me explain something very important. With strict liability, generally speaking, and the law varies from state to state, there is no fault. In other words, the company can have performed admirably, but for some reason the product is defective. It causes problems. So lots of times my clients will say, but we didn't do anything wrong, how can we be liable? You don't have to have done anything wrong. Under the negligence theory you do, but not under strict liability. There's something wrong with the product. So if the plaintiff can show in part that there's something wrong with the product, so that it is unreasonably dangerous because of the fact that it is defective, then they may be entitled to recover if they can show it caused damages, and I'll get to that in just a minute.

But if you look at strict liability, it's important to understand that for products which are unreasonably dangerous, or unavoidably unsafe, I should say, they can be stripped of their defectiveness, so to speak, under what's known as Comment K to Section 402 of the Restatement of Torts.

Now, I will tell you that I'm not one who can ever cite statutes or code provisions or things like that, but any lawyer who claims that he or she is a product liability lawyer knows about 402(a). Section 402(a) is a section of the Restatement of Torts, actually a second, and it's actually in the process of being revised, which sets for what strict liability is. When you get done reading it, there are a whole bunch of comments. Comment K is the one that talks about unavoidably unsafe products.

While the law varies from state to state, in most places pharmaceutical products are unavoidably unsafe. If you properly warn, then you are in a situation where you can take advantage of the defense in Comment K, and a product which would be defective and thus unreasonably dangerous without it no longer is defective or unreasonably dangerous. So that you have to warn, and if the product is properly prepared and accompanied by the proper warnings, it's not defective and it's not unreasonably dangerous.

Now, in the situation that exists right now, and based upon what I've learned yesterday and today, it seems to me that the manufacturers are in the following position. They are doing their best to warn, to give advice, to develop programs. We have physicians' selection and education and accreditation programs suggested, we have patient selection, verification, and monitoring programs, we have pregnancy prevention programs, et cetera.

It seems to me that if you look at it from the standpoint of the theories under which a drug company might be liable, that it would be difficult to demonstrate that they have been negligent. I'm sure that the plaintiff's bar could come up with some theories or witnesses that would take the opposite position that they will have done a good job. In addition, it is probably the case that the product is not defective because there are adequate warnings and the product is thus not unreasonably dangerous.

What everybody talks about here in this seminar, in this program, in this workshop really doesn't have to do with legal liability. The point is suppose there's no legal liability. Throw that out. We aren't considering that. We're talking about whether the product should be on the market. That is a different consideration.

My point is, as I look at the tort system and the law that exists today, and looking in particular at what's happened with the Accutane situation where Roche -- I'm not a Roche lawyer -- where Roche has been very successful in defending its cases, that the companies who have made presentations here today are going beyond what Roche did and are in a situation where they are probably going to be able to readily defend themselves.

Now, I do have to make a comment or two about other potential defendants. It is not unusual in lawsuits for the physicians to be named as defendants and sometimes the pharmacists. Mr. Zellmer takes the position which I'm not certain he wants to take. I don't know him. I don't know if he's a real pharmacist. I'm not picking on him, I just don't know, but I would suggest to him that if he's going to get in this program, he better go find himself a big malpractice policy because the pharmacists, if they're going to go out and take on this additional responsibility which they're not currently obligated to take under the law, they better be careful.

Now, the pharmacists can say we should do that because it's good for the patients. I agree. I agree with that completely. I'm not saying he should duck the responsibility, but I'm telling you, if you look at the law in most states, that which is proposed for the pharmacists is going far beyond which they're currently obligated to do, and they better make sure that their interests are protected. Now, it's also in the best interest of the patients, and it's in the best interest of preventing pregnancies for the pharmacists to do what he's talked about, but there's potential liability.

The physicians, generally speaking, the law in this country is that it is the obligation of the manufacturers to warn the physicians, who thus serve as a learned intermediary. So generally speaking, if the manufacturers warn the pharmacists, they don't have an obligation to warn the patients. However, when the manufacturers determine that they are going to make certain that information gets communicated to the patients, they've basically volunteered and assumed an additional responsibility, which in this instance seems to be appropriate, but they have to make sure that they're correct, adequate, the information that's communicated to the patients is readily understandable, et cetera.

I've got one minute and 16 seconds and I have to talk about one other thing. There are going to be lawsuits.

Maybe a small number. Hopefully, a small number of children born with birth defects that result from thalidomide. But I will tell you, in some of the lawsuits that will be filed, there will be a question as to whether the birth defect is a result of thalidomide or not.

In other words, just because a child is born with a birth defect, and just because that mom ingested thalidomide, that doesn't mean there's a cause and effect relationship. They are going to have to show that the birth defects are the type that could be caused by thalidomide.

I note when we talked yesterday, somebody made a presentation and talked about inheritable phocomelia. So it is not necessarily the case that any child that's got phocomelia and whose mom ingested thalidomide is going to have a slam dunk case. So there will be in these cases significant causation issues, in my opinion, although not in every case.

Let me sum up in 12 seconds. There will be lawsuits. I predict a small number. I think the manufacturers and the pharmacists and the physicians are in a good position to defend themselves. Just because there has been exposure does not mean there is causation. Just because there is a causal connection does not mean that there is liability or the obligation to pay. The rights and obligations of the parties have to be analyzed in accord with the rules of law.

It's important, I think, for you all, and everybody who is involved in this decision, to make the decisions based upon the scientific evidence as presented, and one should not take into consideration whether there will or will not be lawsuits. That's something to be dealt with outside of the processes that exist here.

Thank you.

(Applause.)

DR. GINSBERG: Thank you.

The panelists will now entertain questions for 10 or 15 minutes.

DR. LAWRENCE FOX: I'm Lawrence Fox from the Division of AIDS, NIAID.

This is directed at our attorneys to respond to. I recall reading of a case historically, during the peak of the incidents of phocomelia secondary to thalidomide, of a mother who was awarded damages when a child was born with what in retrospect is clearly loss of a limb due to amniotic band constriction, who had not taken thalidomide, but who was presumed to have somehow had to have taken thalidomide because a baby was born without a limb.

Do you know if this is true, first of all? And if so, do you think we'll see cases like this again?

DR. WOODSIDE: I don't know that that's true. I've never heard of that before, but let me make a comment that may be instructive. There is a case -- it's got nothing to do with birth defects -- there is a paternity case that was filed against Charlie Chaplin. It is a reported case from 50 years ago in which it was conclusively demonstrated to the court and jury, based upon blood grouping, that he was not the father. Nevertheless, the court determined that ABO blood grouping wasn't reasonable and, therefore, did not permit the evidence in.

The point I want to make is sometimes cases get decided wrongly, or sometimes the scientific evidence which is admitted is ultimately determined to be erroneous, or sometimes the scientific conclusions which are drawn are ultimately determined to be erroneous.

It could be that somebody could say, well, it's phocomelia, therefore it had to be thalidomide even though there was no ingestion. I think under the current standards, if someone could not demonstrate ingestion of thalidomide, and if phocomelia could be caused by something else, then there probably would be no recovery and, indeed, the case would probably be disposed of preliminarily by motion for summary judgment.

DR. MOORE: Hi. Cindy Moore from CDC.

I had a question about a statement you made, Dr. Woodside. You said that the manufacturers were responsible for educating the physician or warning the physician about the safety issues for the drug. Since there could be different safety issues in different patient populations who use the drug, is this duty to warn limited to the indication for which this manufacturer is marketing the drug or for any safety issues?

DR. WOODSIDE: I think I understand your question, but it got to be long and so I might have gotten lost.

DR. MOORE: Sorry.

DR. WOODSIDE: Normally speaking, in most states, the manufacturers are obligated only to give the warnings to the prescribing physician. There is a certain limited body of law which says that if the manufacturers volunteer to do that which they are not required to do, then they have to do so properly and completely. So that if you go beyond that obligation, you have to be thorough, complete, do so in a manner which the patients would understand, et cetera.

I'm not sure that answers your question because I got lost in the middle of it.

DR. MOORE: Sorry. I'll just clarify a little bit. There are several proposed indications for this drug. The safety issues may be different in patients with leprosy versus patients with HIV. A manufacturer who has approval to manufacture the drug for an indication for use in leprosy, would they also have a duty to warn about other possible uses, safety issues in other groups of patients?

DR. WOODSIDE: I don't believe they would, but it's an unclear area of law.

DR. MOORE: Thank you.

MR. ROEHR: Bob Roehr with the Bay Area Reporter.

I guess sort of a broader question there. How does liability change between labelled approved usage and off-label usage? Is there a difference in liability?

MR. BLEAKLEY: Yes, I would say that the difference is very clear in potential liability. What Frank has said is correct, if the manufacturer has adequately warned physicians about approved uses and indications, essentially they're off the hook, if that would be the correct term.

But if a physician chooses to use a drug for an off-label use, he or she does so at his own peril. As was heard earlier this morning, this is really in effect an experimental use, and that would be the nature of the claim against the physician. That is, using the drug for unapproved use where the benefit versus risk were not well appreciated or well understood that the benefits were clearly outweighed by the risks.

DR. WOODSIDE: It's important to understand that with regard to off-label use the public sometimes thinks this sounds terrible. I will tell you, off-label use is extremely prevalent. For instance -- and this is not an overstatement, this is accurate -- over half of the uses of chemotherapeutic agents by oncologists are off-label use. So it's very frequent, common, accepted. I believe the FDA has said it cannot regulate the practice of medicine, but it's a decision made by the physicians and they generally are the ones who would have the liability, if any, for that. But the mere fact that something is used off-label is appropriate.

MR. BLEAKLEY: I just want to add one additional thing with respect to my comments on off-label use. It would still be incumbent upon a plaintiff in a given situation to present an expert witness from that particular specialty that would say that the use of the drug for that unapproved indication did not meet acceptable standards of practice. That is generally defined as what a physician of ordinary learning, training, and experience does.

MR. ROEHR: I suppose a cynic could look at the recently recommended application and say that the company went forward with a request for approval knowing that a substantial amount of use would be off-label, perhaps a majority, and that this could be one way for them to limit their liability.

DR. WOODSIDE: A cynic could say that, but there is some law out there -- I can't give it to you chapter and verse now -- there is some law out there which suggests that if the company knows how its products are being used and things like that, they have some obligations to investigate, take steps to make sure it is being done properly. I can't be as specific about that as I would like.

But the companies are not likely to do that. That's not to say that they wouldn't know that there may be some off-label use, but if there was off-label use that they knew was improper -- in other words, it was being used for something which it was contraindicated -- I believe that they would face potential liability. So they're not big on that.

MR. BLEAKLEY: In fact, there was a case in Chicago that's recently been upheld by the Illinois Supreme Court, Proctor v. Upjohn, where Depomedrol was injected into the conjunctival region of the eye and there was a lost eye. It was a mega-multimillion dollar verdict eventually reduced to a more proportionate amount, but the theory was that Upjohn knew about the off-label use and tacitly encouraged it by remaining silent about warning against the use in that indication.

PARTICIPANT: Several concepts have come up during the course of the meeting the last couple of days and I want to see if I can put some of them together. The first is that it's very clear that thalidomide is a very effective hypnotic sedative drug. The second is that it's going to be widely used in AIDS patients. Third is that AIDS patients, or a significant portion of these, are drug abusers and partners of drug abusers.

Given the fact that this is a sedative hypnotic, and the drug-abusing population has a long track record with sedative hypnotics, it seems reasonable to conclude that there will be a black market developed for this drug as a sedative hypnotic on the street. I wonder what comments you might have about the perspective for either product liability or physician or pharmacist liability in that light.

MR. BLEAKLEY: Well, my perspective is -- and I had a little note made yesterday about the one doctor that mentioned that the patient asked, "Can I get more of this? I've never slept better in my life" -- I think that is more than a theoretical possibility. I think that from my perspective, and Frank has been very eloquent in waxing on the defense perspective, from my perspective, I do think that these manufacturers share some responsibility to prevent this from happening at the outset. There's no question but I think it's an unwise thing to do to even consider approval of this drug, so anything I have to say is in the context of that, but I do think that there would be an ample basis for the imposition of liability if drugs are diverted from the drug distribution scheme into illicit sources, and damage and suing, of course.

DR. LONG: My name is Iris Long. I'm an AIDS treatment activist.

I'm concerned that the mechanism of action of the drug is not widely understood. You may understand that you're saying tumor necrosis factor goes down in leprosy, but what happens in AIDS? The information on the AIDS clinical trial did not show that type of effect. There needs to be much more research. Patients really should be titrated if there were a way to measure the TNF and know what effect the drug is having, rather than just saying take the drug, it does help here.

Yes, I agree that it does help in these AIDS patients with aphthous ulcers, but I think there needs to be much more work. I don't think it's really a good idea to promote the TNF alpha mechanism when it's really not known in all these cases where the drug may be used.

Could I have a comment from Dr. Kaplan?

DR. KAPLAN: Well, first of all, I think the fact that the mechanism of action is not known probably applies to the majority of drugs that we've been using for many, many years. The primary indication for licensing a drug

or putting it on the market for many years was whether it worked or didn't work clinically, whether it gave clinical effects. The concept of mechanism of action is a relatively new one. In many cases, the mechanism of action of a drug was actually established after the drug was quite widely used, so that was sort of a secondary component of research associated with drug development and the use of drug in clinical settings.

On the other hand, I do agree with you that we need to know a lot more about, one, in which diseases will thalidomide and other drugs like thalidomide work, and two, why will they work, and the question of why do they work is an important one because that will enable us to exclude situations where we know in advance that they won't work. So the mechanism of action will actually facilitate a more efficient review evaluation of a whole range of diseases where potentially immunomodulation could work.

But there are issues here that these are mixed issues, and I don't think the FDA would ever require that the mechanism of action is known before a drug is licensed. It is just in the interest of rational drug development that we know the mechanism of action.

DR. MAURER: I'm Dr. Toby Maurer from the University of California, San Francisco, Department of Dermatology.

Birth defects are one thing, but there are other serious side effects of thalidomide, such as peripheral neuropathies, many of which are irreversible. Are we who use thalidomide therefore obligated to measure these each and every time as carefully as possible, and how would it be looked upon from the legal perspective if these weren't measured, or perhaps as current day knowledge we don't really know how to measure these very carefully. How is that looked upon legally?

DR. WOODSIDE: You're talking about measuring what?

DR. MAURER: Peripheral neuropathies, the development of peripheral neuropathies.

DR. WOODSIDE: One of the speakers yesterday mentioned it, it really is hard to hear up here. It's much more difficult than you would expect.

I'm not sure I know the answer to that question, but let me address a little bit different question. One thing that bothers me is, based upon my perspective, and Tom's, too, we tend to think about the birth defect issue here. Lots of people do. I perceive that happens here.

If I were the manufacturers, I would be worried about being in the following situation. Wait a minute, you worried and have all this literature and all this consent and everything that's got to do with birth defects, but peripheral neuropathies are really a bad problem and you gave them an eighth of an inch of space in the back. Did you fail to warn the doctors? The drug companies may have to be concerned about that.

Now, at the same time, there probably are a very limited number of physicians who are going to be prescribing thalidomide and, hopefully, they would know about the peripheral neuropathies because the drug companies may have told them, they may have gone to meetings, read literature, et cetera. In which case, it ends up being the responsibility of the physician, not the drug companies, to be on his or her toes in monitoring this. So the answer to your question is, you do have some potential liability there if you're not very diligent.

MS. WINCKLER: I'm Susan Winckler with the American Pharmaceutical Association. As a real pharmacist, as is Mr. Zellmer, I just wanted to take the opportunity to respond to Dr. Woodside and say that I think, particularly in this discussion, we should acknowledge that pharmacists are emerging into this role of patient education and taking more responsibility, and acknowledge the liability that goes with that. So I think as we discuss this and think about the distribution systems that were presented earlier today, to look at the pharmacists not only as a gatekeeper in allowing access to the actual product, but also as an important piece of patient education with the physician.

MR. BLEAKLEY: And what I'd like to do is I'd like to comment both on your comment as well as Dr.

Woodside's, because I tend to quite frankly agree with Dr. Woodside.

DR. WOODSIDE: I'm now getting worried.

(Laughter.)

MR. BLEAKLEY: Well, one thing we should agree on, right? Case law throughout the United States really, in effect, protects and insulates pharmacies. As an example, and I did a review and gave a talk on this before a national organization, all the pharmacist has to do is fill a prescription as written. It can be completely out of line, it can be for the wrong drug, it can be for the wrong dose, and the pharmacist in the United States does not bear any liability for the filling of that prescription.

So I, like you, and I know Frank would agree, we would appreciate having pharmacists take more of an active role, but when push comes to shove within the legal system, they hide behind this facade of case law that really insulates them from any type of professional responsibility for the harm that they cause.

DR. WOODSIDE: Let me expand upon that. I think it's admirable that the pharmacists want to be more active. I think it's admirable for a couple of reasons. Notwithstanding what a lot of the physicians think, the pharmacists really know a lot, and so it's nice for the pharmacists to be able to have some input. Second of all, because the pharmacists frequently see the patients, and if they have the opportunity to give additional information, then the patients are better off. So it's like an additional gatekeeper.

What happens in product liability litigation, and I'm telling you this from 26 years of experience, I represent a manufacturer's medical device, a pharmacy gets sued and the first thing it does is the general counsel for the pharmacy or the pharmacist or the company writes the manufacturer and says we didn't do shit, indemnify us and hold us harmless. We don't do anything.

Excuse me, Peter. I apologize. I was not supposed to say that, but that's what they say. They say we don't do anything. Now, that's just not the way it ought to be.

MS. WINCKLER: And I would acknowledge that it is changing to the point where pharmacy practice acts at the state level are changing to require the pharmacists to complete that patient education and monitoring role. So acknowledging the current state of case law, and then I think predicting we will see a change in that.

DR. WOODSIDE: I think that is right.

MR. BLEAKLEY: Right, and at least a dozen states where those laws are active now have specifically said it doesn't matter. All the pharmacist has to do is fill the prescription as written.

PARTICIPANT: There have been some questions raised as to street use of thalidomide and at least one hypothetical case was presented where the actual manufacturer's drug was not what did or did not do the harmful act.

I'm reminded, and this is a question to the two attorneys, as you well know, one of the defenses in the original DES case was maybe the DES did it, but somebody else made it, even though they were clear across the country. It was the same time, but it wasn't our DES. You can't prove we did it, therefore.

The courts carved out for that time a novel concept of proportional damages, that if you made half of the DES, well, you can't be proven to have made it, but you can't prove you didn't make it. Unless you can really prove you didn't make it, you're going to share 50 percent of the damages.

We've heard from the company of very meticulous record keeping so that they will have a pretty good accounting of what of their pills got into whose hands. Is there anything more that you would suggest, so that if something does come up in the future the company itself, if they did not make or distribute the specific thalidomide, will not be involved?

DR. WOODSIDE: Let me make two comments. One, I think if the companies are able to do that which we've heard about, they've done about as much as they could. The only reason I say about that is because maybe there's something else. I don't know what it would be.

But let me address the street use of drugs. You really can't compare it to the DES situation, because in the DES situation you had physicians who prescribed DES, et cetera. I have been involved in the defense of cases, mostly bendectin cases, in which a mother borrowed her sister's bendectin, or something like that. In all the time I've been doing drug litigation, I've never had to defend a case where there was street use. Frankly, there may be cases where that's come up. I don't know of any. The manufacturer's liability only goes so far. I would say that they have been very thorough and diligent and professional in what they contemplate doing.

MR. BLEAKLEY: I would concur in that. I would think that the DES experience was really a one-time, fairly unique situation that was really caused by the delay in time between the onset of recognizing that there was a problem -- there were some 20 years that passed -- and the identification of specific manufacturers of the injury-producing drug was really an impossibility.

DR. GINSBERG: We're running quite late, so I'm going to ask that these two questions, and Dr. Kaplan has a question, be the final questions of the session.

PARTICIPANT: I was curious, you mentioned the idea of inherently dangerous medicines and devices, like firearms and automobiles and airplanes and thalidomide, and somebody else invoked the Nader corollaries to tort, which is where you've got to protect everybody from anything they might do to themselves. What I want to know is where does reckless indifference to the well-being of the unborn fetus come in? Where does that idea come in? I direct that to either one of you, but it does seem to me to be a vital part of this equation.

DR. WOODSIDE: If you talk about something like reckless indifference, or willful and wanton conduct, generally those words in the law come in in the area of punitive damages. In order to have a punitive damages claim, you first generally have to show a negligence claim or, depending on what state, sometimes a liability claim.

In this particular situation, I recognize the plaintiff's lawyers may well disagree with me, the manufacturers and the physicians and the pharmacists are clearly not showing reckless indifference. They're acknowledging that there is an issue, they're going to great measures to prevent pregnancies, so I don't see this as being a punitive damages situation.

MR. BLEAKLEY: I would agree with Dr. Woodside on that, and perhaps I could contrast, just for reference sake, what the company that was attempting to get thalidomide approved in the United States did back in the early 1960s. They distributed the drug to some 2,000 physicians under the guise of clinical trials when, in fact, it was an advanced promotion awaiting Dr. Kelsey's approval, which never came. So there were 2,000, principally OB-GYN, doctors throughout the United States that were prescribing Kevadon to their patients.

PARTICIPANT: (Inaudible.)

MR. BLEAKLEY: His comment was he was referring to the doting parent who takes the medication and causes the damage to the child. I think my comment on that is I don't know of a parent on earth that would knowingly inflict such a damage on a child. Generally speaking, there would have to be a reason for that, such as ignorance. It's the ignorance that would have to be built into the compliance-noncompliance factor by the drug distribution scheme. That would be my point.

DR. LEE: I'm Dr. William Lee. I'm with the Angiogenesis Foundation. I'm a practicing physician as well.

I would like to raise an issue that I think makes thalidomide unique among drugs in development. This relates to off-label use. The current topic is of thalidomide as an agent for AIDS. For example, aphthous ulcers and other applications, and we have heard about one mechanism against tumor necrosis factor alpha. Yet, concurrently, there is a great deal of emerging information that thalidomide may also be an effective

antiangiogenic agent for diseases in addition to AIDS, in addition to Kaposi's sarcoma, and at the hematology/oncology session which is to follow, there is going to be some discussion about glioblastoma, prostate cancer, and breast cancer.

That the FDA will approve thalidomide for a labelled use, presumably for the AIDS application, is what is being considered, but there is a lot of publicity that physicians receive and patients receive regarding thalidomide as an antiangiogenic. Our organization receives calls from both patients and physicians requesting information about where clinical trials are being done for thalidomide to treat cancer, for example, and if thalidomide is approved for an AIDS application, it is very likely that physicians will begin to use it to treat their oncology patients.

So, actually for Mr. Andrulis, and to the attorneys, if appropriate, it would be interesting for me to hear and for our organization to know, but I think also for the general public, at least for thalidomide, when you have multiple mechanisms, multiple targets and two very promising areas of science being developed concurrently, how can we actually properly educate physicians and control the off-label use in order to protect patients?

DR. WOODSIDE: Off-label use is at the peril of those who prescribe it for that, so that unless there are clinical trials of some sort going on -- I'm not sure what you're asking, but if the folks at Boston or other places are planning on using thalidomide for its potential use to prevent angiogenesis in developing tumors and there are some problems, they have a much different liability picture than the physicians who would use it for leprosy and other things that we've been talking about.

It's a completely different ballgame and it would probably take me an hour to go through it in detail, but it's a different ballgame and potential liability is large. By the way, it also may well be the only method to save somebody or give it a shot, in which case we'd be talking about informed consent and things like that. I'll be happy to talk to you about it for a minute afterwards.

MR. BLEAKLEY: In my background, I spent seven years with a pharmaceutical company that had one of the first beta blockers that was approved, and the initial approval was for pheochromocytoma. We all knew and understood that it was being widely used for hypertension and for migraine and whatever, and in fact that has resulted in substantial basis for liability against physicians for off-label use.

DR. GINSBERG: Thank you all very much for a very stimulating session.

(Applause.)

DR. GINSBERG: Before you all leave, Dr. Groft has an announcement.

DR. GROFT: Let me just go over a few logistics for the breakout sessions that we're looking at. I would ask the chairs to convene the groups, their breakout sessions, and then make a determination of whether they want to go to lunch and then come back, or however you want to do it. We'll leave it up to the discretion of the chairs and the presenters, not knowing what their schedules are and there are so many people involved. So if you'll do that.

What we're going to do then, we will reconvene here at 2:30. We will have an open public session at 2:30. There is one person who has requested time to make a presentation, and we'll ask that person to limit their presentation to five minutes. We'll have people available then up here to respond to any other questions before we receive the comments and the summaries of the breakout sessions.

At 3:00, the chairs of the breakout sessions will reconvene and will present those summaries. Following that, Dr. Janet Woodcock from the Center for Drug Evaluation and Research will come and present the closing remarks. So that is the schedule.

If you'll hold on, I'll give you the breakout sessions. Here in this auditorium will be Section A, the pharmacology, pharmacokinetics, and teratology of thalidomide and analogues. In Conference Room C, which

is in that direction, there will be discussion of the dermatological uses. In Balcony A, which will be upstairs, the immunology/rheumatology section. In Balcony B, the hematology and oncology section. In Balcony C, up there also, will be the infectious diseases.

Thank you very much for a very interesting morning.

(Whereupon, at 11:55 a.m., the meeting was recessed for lunch and breakouts, to reconvene at 2:30 p.m.)

AFTERNOON SESSION (2:34 p.m.)

DR. GROFT: We'll begin the open public session. I just want to acknowledge first the various co-sponsors. Everyone knows that the FDA, the CDC, and the NIH were the primary sponsors, but I'd like to at least mention the various offices and centers and institutes who also served as co-sponsors, either by arranging sessions of the meeting or providing speakers and other expenses.

At NIH, the Office of Research on Women's Health in the Office of the Director; the Office of Medical Applications of Research, OMAR, the group responsible for the consensus conferences; the National Institute of Allergy and Infectious Diseases; the National Institute of Arthritis and Musculoskeletal and Skin Diseases; the National Institute of Dental Research; the National Institute of Child Health and Human Development; and the National Institute of Mental Health.

From the Food and Drug Administration, the Center for Drug Evaluation and Research, the Office of Special Health Issues, and the Office of Orphan Products Development.

Then the Centers for Disease Control, I think we probably could say Dave Erickson's and Cynthia Moore's office, pretty fair. Thank you.

I'd like to correct and also add something. As I mentioned earlier, we had an interagency working group, and in our preparation for the meeting and our review of individuals on the interagency working group we had some degrees omitted. On page 13, lucky 13, and page 14, we omitted several people's degrees. I would just like for the record to add those.

Dr. Peter Dudley is an M.D. from the National Eye Institute; Katrina Johnson from the Office of Research on Women's Health is an M.D.; Jeanne Ketley from the Division of Research Grants is a Ph.D. Then on the next page, Dorothy Sogn from the National Center for Research Resources in the General Clinical Research Centers Program has her M.D. So my apologies to those people for the oversight.

What we'd like to do this afternoon at this session, before we get into a summation and report from the various workgroups, is to have the open public session. We had one request to present comments. Dr. Iris Long from the ACT UP/New York group has requested time to make a presentation, so we will be asking her to make comments.

Then we will open the microphone for maybe 20 minutes or so for any questions from the audience to the various representatives from the three agencies sponsoring the workshop. If we can answer the questions, we'll try, and if not, somehow we'll try to get information back to you. We'll get over to that then after the one presentation.

I'd also like to mention that even though you've heard from two pharmaceutical firms involved in the development of thalidomide, the Celgene Corporation and Andrulis Pharmaceuticals, there are two other companies who are pursuing the development. One is Pediatric Pharmaceuticals, I think it is, and another is EntreMed. All four groups were invited to participate or contribute however they felt appropriate at this meeting. In order to give fairness and balance, we did extend an invitation. Two groups did elect to participate in the workshop, and we're really pleased to have them. I think at any future workshop, we would welcome the participation of all four.

One last bit of housekeeping. If any of the speakers did not pick up their slides, they are in the speaker ready room. Please don't forget them before you leave.

So, Dr. Iris Long, if you'd like to come up.

DR. LONG: My name is Iris Long. I reside in Jackson Heights, Queens. I am a Ph.D. pharmaceutical chemist. Since 1987, I've been an advocate for people living with AIDS or HIV, focusing on access to experimental treatment and approved treatments for AIDS and tuberculosis. I am a member of ACT UP/New York, and the chair of the community advisory board for the AIDS Clinical Trials Group of Mt. Sinai Medical Center. Both of these organizations are volunteer organizations. There are a number of points which I wish to make.

Given the number of possible off-label uses of thalidomide, the mechanism of action data is weak. If the drug is approved, this must be emphasized. The deficiency here must be emphasized to patients and doctors in brochures and advertisements.

Thalidomide needs to be studied with sufficient women in trials to do gender analysis and determine adverse reactions in this population. Possible racial differences needs to be studied also.

Within the thalidomide registry, the demographics of the population receiving the drug should be gathered along with the doses received by patients.

In the age of highly active antiretroviral therapy, the use of thalidomide has to be reevaluated.

In AIDS, there is differential access to AIDS treatments, such as human growth factor and thalidomide. All clinical trials of thalidomide must have sufficient numbers of women, Hispanics, and African-Americans in them.

Thank you. That's what I would like to say.

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

Are there any questions from the audience? Anything at all?

(No response.)

DR. GROFT: We may speed up if we can. I'm reluctant to move too much further ahead. How many of the chairs are here from the various workgroups? Dr. Woodcock is here, so we can move ahead with that. We won't move ahead with the closing comments until we get the reports back from the working groups. Terry keeps me straight here the last 11 months. Attention deficit disorder does have its many wonders.

We'll take a five-minute break. If you will just stay in your places, we'll try to locate the other chairs of the working groups and have them assemble here. We will get right into the report from the working groups if they're prepared to discuss it.

Phil Fox is here. Jim Pluda, do you want to come up?

Dave Banks, if you could help maybe mention to the folks outside that we're going to do this and continue with the meeting, we'll move on. It's been two long days and we'll try to conclude this early. So if you'll excuse the movement, we'll make some moves.

(Recess.)

DR. GROFT: I think we'll begin the summation. I would just like to thank all the participants. Coming here after a lot of travel, a lot of time away from home, for a 10- or 15-minute presentation is asking an awful lot, so I do appreciate it. I think we all appreciate you're taking time and informing us and imparting to us a little bit of

your knowledge that you've gained with the use of thalidomide over many years of research, so thank you.

We know there are going to be other opportunities perhaps for longer presentations that you'll be able to take advantage of, but I think these speakers really did an excellent job of encapsulating their comments and keeping them brief and really bringing us up to speed on where we were going.

Now, I would just like to get into the research aspects of where we are currently with the many potential uses of thalidomide, where we might be going, what other indications for use could be studied, and then some of the problem areas that are being encountered during the research process. So we've assembled the five groups, and I guess we'll start with the pharmacology, the pharmacokinetics, and teratology of thalidomide and analogues with Dr. Dave Erickson from the CDC.

DR. ERICKSON: Do you want me up there?

DR. GROFT: Audience preference? Why don't you come up here and then you're a little bit more visible and the microphone is probably a little bit better.

DR. ERICKSON: Thanks very much, Steve.

I was the moderator for this Section A on pharmacology, pharmacokinetics, teratology, and analogues. I felt at that time, and still feel, a bit out of my league. I'm an epidemiologist, and it seems that the participants knew what each other were talking about, but I had a hard time following it.

I got the idea from Dr. Sterling, and Dr. Shannon, and Dr. Trapnell that there seems to be a consensus we know a lot about the pharmacokinetics of thalidomide. There's also a need for some really very basic pharmacokinetics data. For example, one very practical unknown is what is the minimum therapeutic dose. This would be really important if one could use a lower dose than those doses which are now typically used today, because of the sedative properties of the drug.

There also seemed to be a consensus that we need some sort of animal model, for neuropathy in particular. There is a lot which is known, but a lot which is unknown. The basic mechanisms, pharmacological mechanisms, for both the toxicities and the potential beneficial effects seemed not to be well understood and people are groping around in the dark to some extent.

I was really very interested to hear about Celgene's work on analogues. As I got it, and I hope the panelists could jump in and help me if I make a real mess of this, but as I got it, Celgene has developed a class of analogues which appear to have very, very powerful effects on TNF alpha and maybe on some other aspects of the inflammatory process. But in their assays, most, if not all, of the many, many compounds they worked with appear not to have teratogenic potential, at least in small animal studies, small numbers of rabbit studies. I think that's really very exciting. If, in fact, drugs with the beneficial properties of thalidomide could be developed that don't have the teratogenic and possibly neuropathic potentials of thalidomide, that would be really wonderful.

I just want to take advantage of having the podium for a minute and get on a hobby horse of my own that's connected with this. That is, you need to know that an analog, for example, isn't teratogenic. That's just the beginning, and I want to relate to the group here a story about valproic acid.

Valproic acid is a weak teratogenic in the sense that it is thought to cause spina bifida in about 1 to 2 percent of women who are treated with the drug for epilepsy. This fact was discovered and published in 1982 in Lancet. Rober published this in the Lancet and two years later, a little less than two years later, Heinz Nall from the Federal Republic of Germany published a report in Neurology that the 2-ene version of valproic acid, sort of the first metabolite of valproic acid, in an animal model had the anticonvulsant properties of valproic acid, but did not have the teratogenic properties of valproic acid. They suggested in that time in 1984 that perhaps this 2-ene version of valproic acid could have a place or be an alternative in the treatment of human epilepsy.

It's 1997, it's 13 years, and nothing has happened. No company has sought fit to go to the trouble to bring this drug to the marketplace. My understanding is that it is all because of the patent structure, laws that we have in this country and in Europe.

I was interested to hear the Celgene representative, Dr. Stirling, say that they had sort of wrapped themselves up in patents for all of these new compounds. Maybe that will help to hasten the replacement of thalidomide with a nonteratogenic alternative, if in fact it exists, but I'm still dismayed that we don't have something to replace valproic acid when it appears, at least in good animal models, that there is something that is highly likely to be as good an anticonvulsant as valproic acid without the teratogenic effects.

I've been wondering whether there are other incentives that need to be put in place in this country and in Europe, or maybe disincentives of some sort that will help to encourage the development and marketing of nonteratogenic drugs. I think somebody said in this meeting before the desire for normal children is universal. It's really a tragedy when we have opportunities to avoid exposing fetuses to toxic substances that we don't take advantage of them.

Thank you.

DR. GROFT: Thank you very much, David.

If you'll hold your questions, if any, until the end of the session, I think it would help to move things along.

Dr. Mervyn Elgart will be next, speaking about the dermatology discussion group. Dr. Elgart agreed to fill in for Dr. Maria Turner who, because of travel commitments, was unable to join us. So you did double duty today. Thank you, Mervyn.

DR. ELGART: Good afternoon. At our session on dermatologic uses of thalidomide, Dr. Maurer talked about prurigo nodularis in AIDS patients and found that a significant number of these patients had an improvement in their itching with the use of thalidomide. It was interesting to note that here is a drug which causes some nerve damage, that we don't know how pruritus is carried along the nervous system and how it's appreciated, but that this medication did seem to have an effect on pruritus, at least in many of the HIV patients.

Dr. Rae talked about the use of thalidomide in erythema nodosum leprosum. This is a reactive pattern in patients with leprosy, generally patients who have been treated for multibasalary leprosy and who develop an erythematous, pinkish, sometimes necrotic type of reaction, and the kinds of responses that were seen with thalidomide over a number of years.

The third talk was by Dr. Fleischer regarding Behcet's disease in his dermatologic clinics in North Carolina -- I can't remember the name -- and their improvements both in the aphthous stomatitis, severe necrotic aphthous stomatitis, as well as some of the other ulcerative portions of this disease.

Lastly, I spoke about pyoderma gangrenosum, a neutrophilic ulcerative disease sometimes associated with inflammatory bowel disease, and how our four patients seemed to respond to thalidomide.

It was interesting that these are diseases that are really characterized by us physicians not knowing the etiology of the disease, not having very much information on pathophysiology. Three of the four diseases seem to be associated with proliferation and migration of neutrophils, and yet other diseases in which neutrophils play a significant part don't seem to be affected by thalidomide.

So we discussed the use of thalidomide in the treatment of these diseases. We talked about possible mechanisms of action, but this was the blind leading the blind, basically. We didn't come up with any conclusions.

Clearly, each of the speakers felt that the trials which had been done were uncontrolled trials and that controlled trials were necessary. It was noted that side effects were generally nonserious. There were no serious

hematologic abnormalities. There were some neurologic problems, some persistent tingling, some numbness, but in general the results of neurologic testing did not correlate well with the clinical appearance of these neurologic findings. By and large, there were no other problems. Somnolence was fairly minor, and most patients took the medication at night.

The session closed with a discussion of other possible uses of thalidomide, including chronic erythema nodosum, sarcoidosis, and several other diseases that have been in the literature. In general, people were pleased with the results that they got from thalidomide and were anxiously awaiting more and better controlled studies in the use of dermatologic indications.

Thank you.

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

If after we're finished I could get a copy of the comments and the summaries, that would be helpful.

Dr. Phil Fox from the National Institute of Dental Research will talk about the immunology and rheumatology working session.

DR. PHILIP FOX: Thank you, Steve.

In the session, we were talking about autoimmune connective tissue diseases and inflammatory disorders. Four talks were given.

The first dealt with lupus erythematosus and covered both the systemic form and, in probably a little more detail, the chronic cutaneous form of lupus erythematosus, often called discoid lupus, both the localized and generalized form.

The second talk dealt with Sjogren's syndrome, and for those of you who may be not as familiar with that, it is an autoimmune xancronopathy, a multisystem autoimmune disorder, but the major manifestations involve the salivary and lacrimal glands. Although it is not particularly well-known, there are at least a million people in the United States, it is believed, that have Sjogren's syndrome.

We had a talk on thalidomide and rheumatoid arthritis, and also a potential use for thalidomide in inflammatory bowel disease.

This was a really interesting session, I think. I believe that these represent in many ways what we were talking about as to where the potential for thalidomide is going and, some might say, really the most problematic uses for thalidomide. These are chronic, debilitating, and disabling diseases, and while there may be mortality certainly associated with any of them, in general I would tend to characterize them more as life-altering than life-threatening. Therefore, one clearly has to have a certain high standard in terms of risk and benefit.

It also needs to be pointed out that for each of these conditions there is no universally effective treatment, and that the available treatments themselves have serious side effects, which is something we have to put into the equation.

In terms of the current situation, only for discoid lupus, chronic cutaneous lupus erythematosus, is there clear evidence of efficacy of thalidomide in that there are a number of series that have been published, controlled studies, that have looked at the use of thalidomide. In all the other conditions, their use is based on either theoretical considerations or on case reports. In the case of chronic cutaneous lupus, there is in this number of publications between a 50 to 90 percent improvement, and this is in resistant cases. That is, cases that have been resistant to all other forms of therapies. In general, the response is rapid and have definitely been able to show steroid sparing effects in combination therapies.

The mechanism of action is not known for that condition, nor for any of the others we talked about. There are

currently clinical trials that are either in progress or in the late planning stages for each of these other conditions. There have been a number of trials that were done. Dr. Lee talked about one that she conducted in rheumatoid arthritis which, basically due to a number of side effects, was terminated early.

One point that came out in looking at these conditions -- and I think as well this has bearing on many of the other conditions that people are proposing -- is that these are diseases or syndromes that have a very wide spectrum of disease expression. Therefore, it's important to select patients with care. Clearly, even looking at systemic lupus patients, as Dr. Klippel pointed out, this can range from patients who clearly have endstage renal failure, and I mean are very, very sick, with a variety of other organ system involvement, to patients who have rash and arthritis, not that that's a minimal problem, on the other hand. Clearly, there are big differences here and one has to consider that when patients are selected for clinical trial and for therapies.

What do we need to know? Well, we need to know the mechanism of action of the drug. I have a feeling every group will probably talk about that, but a more important point was made that it is not just the mechanism of action of the drug globally, but we need to know the mechanism of action in specific conditions.

For example, in three of the four conditions that were discussed, there is a theoretical story, a hypothesis, if you will, in which elevation of TNF alpha plays a role in the pathogenesis of the disorder. That is at this point, in all of these, theoretical. In some cases, for example in rheumatoid arthritis, probably it is a stronger case than in others.

But it's going to be important to look at mechanism of action in a specific condition. It probably will not be the same in all cases. That seems obvious given the spectrum of diseases that seem to be benefitted by thalidomide.

It is also important that we determine the best dose, which may be equal to the lowest dose, and additionally, and somewhat differently, however, it's important to know about maintenance dose. In all of these conditions, they're chronic, and we're anticipating long-term treatment. It's obviously going to be exceedingly important to see if one can minimize potential side effects by lowering the dosage. Again, it's critical that controlled, well-designed clinical trials be conducted so that we move past the anecdotal case report stage into true measurement of benefit and efficacy.

In terms of the future, there were a few other diseases that were mentioned as being good candidates or possible candidates for clinical trials, and these included scleroderma, Crohn's disease, and ulcerative colitis. For at least the last two, there are a number of, again, anecdotal reports, but quite compelling anecdotal reports, in particular that were shared by one of the speakers.

We also felt that it's exceedingly important, and there was a fair amount of discussion about peripheral neuropathy, that one determines the true incidence and severity of peripheral neuropathy with thalidomide treatment, and to find out whether it in fact is dose-related. What that leads to, of course, is we need to make a determination as to the best monitoring for peripheral neuropathy. Is there a standard instrument? It would be wonderful if there were, or at least if one could agree on certain forms of even physical examination, so that one would be able to compare studies.

We have a potential new toxicity that came up, that was mentioned. This came from Dr. Lee's study, where three of seven patients who were given active drug developed tremor. From the other people, many of whom had a lot of experience in giving thalidomide for a long time, that was not something that had been reported or seen. So I sort of throw that out. I don't know if that was mentioned in any of the other sections, but it's something that we might want to keep an eye on.

Additionally, I think it's important, if we're going to pursue the tumor necrosis factor story, that we look at the site of the disease and not at the convenient site, which is the circulating blood. There was actually a very interesting point made if one uses, as an example, looking at levels of tumor necrosis factor in the gut mucosa, where it is elevated in inflammatory bowel disease, as opposed to looking in the peripheral blood where it is not. So it's going to be important to look at tissue sites and not just at circulating levels.

Finally, of course, I would have to put this in as a researcher, and it was mentioned earlier, it is going to be important that we have better animal models to really begin to look at some of the mechanisms of thalidomide in diseases, a general need I think for most conditions.

Thank you.

DR. GROFT: Thank you very much, Phil.

Our next section will be looking at the hematological and oncological uses. **Dr. James Pluda** from the National Cancer Institute. Jim?

DR. PLUDA: Thank you.

We had presentation of five clinical trials or uses of thalidomide in hematological and oncological malignancies. The first was by Georgia Vogelsang, and she was discussing the use of thalidomide in chronic graft-versus-host disease. In her initial studies, what they found is in taking patients who were either high-risk for or had chronic GVHD, where there is normally less than 20 percent survival according to historical controls, they dosed thalidomide in doses ranging from 200 milligrams four times a day to as high as 400 milligrams four times a day. What she found was that in a cohort of approximately 40-some-odd patients, they saw a 59 percent response rate, and an overall 64 percent survival rate, which was quite interesting in light of what the historical survival was.

She reviewed the literature and there had been a number of other studies that had been performed and reported, many of them much smaller, both supporting the activity of thalidomide on chronic GVHD as well as refuting this activity. One larger study was a study of 80 patients performed at the City of Hope, looking at patients with chronic GVHD. They reported, basically, what they called a negative study. They said they only saw a 20 percent response rate, but interestingly, what they did see was a 54 percent survival, which is still higher than what historical controls are. So right now, the jury is still out as to whether or not thalidomide is going to be a useful drug in GVHD.

There were some other studies that she mentioned that were negative. In particular, one using thalidomide for prophylaxis for GVHD. That is, patients with acute GVHD that were treated and then given thalidomide in a prophylactic setting, and that was a negative study.

So although it's unclear whether or not thalidomide has real activity in this disease, my take of the literature and of the presentation from Dr. Vogelsang is that I think we do have encouraging evidence of potential activity, and clearly warrants further study of thalidomide in this very severe complication of transplantation.

One of the ongoing studies that she has right now is a study looking at thalidomide plus cyclosporine plus PUVA, which is psoralen and UVA light in patients with chronic GVHD. So far, out of 27 patients, 17 have responded. So I think although we do not have clear-cut randomized controlled studies, I think what we can take away is that there are some evidences that thalidomide may be useful in this disease and clearly warrants further study.

We then proceeded to talk about the use of thalidomide in solid tumors. The basis for the use of thalidomide in solid tumors was its antiangiogenic activity. This was first reported by Bob D'Amato in 1994 in the rabbit cornea micropocket assay, and there appears to be compelling data that it is a hepatic metabolite of thalidomide.

Doug Figg presented some very interesting data in a rat ring aorta model, that it appears that thalidomide needs to be hepatically metabolized to what may be an apoxide form in order to have its antiangiogenic activity. It also appears that mice and rats do not have the appropriate liver enzymes to do this and, therefore, we do not have a good oncologic model for the use of thalidomide as an antiangiogenic inhibitor in cancer, because almost all of our cancer models are in mice.

It also was theorized that the teratogenicity of thalidomide may very well be due to inhibition of angiogenesis during organ and, particularly, limb bud formation and elongation, and that potentially one of the reasons this may not have been picked up initially was if the studies were not done in species that were sensitive, such as rabbits or dogs or monkeys, but were in fact done in rats or mice, you would not have seen any teratogenicity in preclinical studies.

So based on the antiangiogenic studies, activities of thalidomide, four studies were initiated. The first one that was presented was by Howard Fein, which was a study of thalidomide in relapsed high-grade gliomas. In high-grade gliomas, the response evaluation is very difficult. The neuro-oncologist essentially will accept stable disease, because radiographically it's very hard to determine shrinkage of an irregular tumor from scans. They will, in fact, accept lack of clinical progression as evidence of response, since in most people's hands these relapsed tumors inexorably progress and ultimately lead to the death of the patient.

So in this study, Howard actually was able to see, and this was using doses of 1,200 milligrams per day, two partial responses out of 32 patients where there was clear-cut shrinkage by at least 50 percent on MRI scans of lesions, in one case a biopsied-positive lesion; two he called minor responses, which are shrinkages, but not 50 percent shrinkages; and 12 patients, or 38 percent, that had stable disease for at least eight months. Three of these 16 patients are still on therapy nine, 11, and 12 months after the initiation of therapy. Considering that upfront glioblastoma multiformi has a median survival of approximately eight to 12 months, and that these were relapsed patients, that's fairly remarkable.

What we take away from this study is that although it's not a controlled study in a tight population of patients, clearly, it appeared that thalidomide was having some biological effects on these tumors and definitely warranted further evaluation in tighter controlled trials.

The second study was presented by Doug Figg from the NCI. He was looking at a study of low dose versus high dose, 200 milligrams versus 1,200 milligrams, of thalidomide in patients with hormone refractory prostate cancer. He was also attempting to get biopsies. One of the interesting facts that Doug brought out was that in vitro and when using PSA as a response, which is a problem in prostate cancer, you always have to wonder does your drug have an effect on PSA production in and of itself that would negate the abilities to use PSA.

What he was able to demonstrate was that in an LN cap line in vitro, which is a hormone-sensitive prostate line, thalidomide actually upregulated via ELISA and via RNA PCR. They were actually able to show that there was upregulation of PSA in these cells by the parent compound thalidomide.

Now, that becomes relevant because they have nine patients on their low dose and 10 patients on the high dose, and they do have a number of patients who, although not having a 50 percent decline in PSAs, did in fact have drops in their PSA which you can honestly say, or at least you can speculate based on his in vitro data, was not due to a direct effect of thalidomide on the prostate cells making the PSA, but may in fact have been an overall antitumor effect.

He also remarked that they saw some shrinkage in soft tissue disease, although nothing that would constitute a formal PR, but also they did not see sustained and prolonged maintenance of these effects. That is, that most patients did relapse and ultimately progressed within two or three months.

So although there was a suggestion of biological activity, and the study is still ongoing -- they've only enrolled nine or 10 in each level and they're enrolling many more patients -- there were no clear-cut evidence that in hormone refractory prostate cancer thalidomide was having any major response rate.

The next trial was presented by Dr. Robert Yarchoan, and this was a trial of thalidomide in Kaposi's sarcoma patients. The way this trial was done was patients started out getting 200 milligrams, and then every two weeks the dose was titrated upwards to a maximum dose of 1,000 or whatever the patients would tolerate.

To date, there are nine patients enrolled on this trial, there are now four partial responses, and although it's difficult to assess responses in KS -- they are using the modification of the AIDS ACTG criteria for KS

response -- Dr. Yarchoan and his group do have a track record of being conservative in their calling of responses and in fact being accurate, having been recently involved in having one of the seminal studies that was used by the FDA for approval of taxol for KS.

So the four out of nine, or 44 percent response rate, is actually something that was surprising considering the trial was originally set up to determine stable disease and not responses. So although, again, it's very early, there is a suggestion that we're seeing biological activity and we clearly believe it deserves further therapy.

The issue of what's the appropriate dose of thalidomide to give did come up, particularly in light of mention by Dr. Yarchoan of a British study that was presented at the AIDS malignancy meeting last spring where they treated patients with KS in England with 100 milligrams of thalidomide and reported an approximately 40 to 45 percent response rate.

One of the reasons is we don't have a good animal model, so it's very hard. We don't have a good way of assessing what doses are necessary in animals to inhibit tumor growth and, therefore, trying to extrapolate to humans. We also don't know what metabolite is actually responsible for the activity of thalidomide and, therefore, we can't measure it. We can't do dose-responsing of that. Also, there may be differences in metabolism between individual patients depending on age and also depending on drugs that they may be taking, such as hepatic activating agents like the anticonvulsants in the glioma patients.

So, therefore, what we had attempted to do was rather than miss activity by giving too low a dose and concluding that the drug didn't work, we chose to give the maximum amount of drug that we felt we could safely give and, if there was activity, we could always then go back and try and determine a more optimal dose. But in these preliminary studies, we did not want to miss activity, which is why we went with the higher doses.

Interestingly, in these patients, and in particular the AIDS patients, there really was no peripheral neuropathy noted. In Dr. Fein's group with patients out to 12 months, they did not see peripheral neuropathy. In the nine KS patients, some of which have completed 52 weeks of therapy, there was no peripheral neuropathy. Many of these patients were on neuropathic agents, antiretroviral agents, and also HIV itself can cause neuropathy and these patients may have a subclinical background of peripheral neuropathy, and yet peripheral neuropathy was not a problem.

One of the main problems that was in fact seen was constipation. This occurred mainly in the cancer patients where prophylaxis was not instituted at the same time. If prophylaxis was instituted at the time of dosing, it wasn't an issue. It really wasn't much of an issue in the AIDS patients because, in general, many of these patients tended to have diarrhea and actually came in and reported improvements in their bowel function because the thalidomide actually helped their diarrhea.

The last study that we had presented was a study by Said Baidas of thalidomide in breast cancer. It's a randomized study, again looking at low-dose versus high- dose thalidomide. It was just too early to tell what was going on. They only had five or six patients enrolled on the study on the two arms and there wasn't enough data really to get a feel for whether the drug was having activity one way or the other.

Thus, I think what we can take away from the session is that there are data at this time that would suggest that, in some of the tumors that we have looked at, thalidomide is having a biological effect. I think the two tumors where this is most compelling are in glioma and in Kaposi's sarcoma, and that, clearly, thalidomide warrants further evaluation. The oncologic community would be very interested in the evaluation of analogues that did not have the sedation and some of the other side effects, but yet still maintained the antiangiogenic activity of thalidomide.

Thank you very much.

DR. GROFT: Jim, thank you very much.

Our session, **Dr. Larry Fox** from the National Institute of Allergy and Infectious Diseases will talk about the

infectious disease aspects and treatment with thalidomide.

DR. LAWRENCE FOX: I had the privilege of chairing a session where a great deal of clinical work has already been done, and it was actually difficult to get people out of the room at the end. We could have used more time to talk.

The discussion in the infectious diseases section focused on four problems that probably have a common underlying immunopathogenic mechanism. We talked about tuberculosis, and especially tuberculosis in the setting of co-infection with HIV, HIV aphthous ulcers, HIV wasting syndrome, and AIDS dementia complex. They all have as a component of their pathology an inflammatory response causing ancillary tissue damage. So in addition to the usual antibiotic therapy, antiretrovirals, or antituberculosis agents, there's obviously a place for some sort of immunomodulation, and we talked about, of course, thalidomide in this context.

In AIDS dementia complex, the least amount of clinical work has been done. All we had is anecdotal information to discuss. To make the story very quick, this happens in about 20 percent of AIDS patients, so there's a good deal of need to come up with something to treat people with. It involves inflammation modulated by the microglia and by invading macrophage, which then become a source for further HIV propagation.

But there is a disparity sometimes between the viral burden that's seen and the degree of dementia that takes place. Some patients have a very high degree of infection and yet have relatively little dementia. Other patients have a fairly low degree of infection and have a great deal of dementia. It seems to be a function of the immune response. The greater the inflammation, the greater the dementia.

In studies of using immunomodulation -- again, this is strictly anecdotal -- there's been some evidence of efficacy, and certainly when using highly active antiretroviral therapy we see dementia resolve. We do see markers of inflammation also resolving.

To get on to the studies where we actually have a good bit of information, in the study of effect of thalidomide in tuberculosis, Gilla Kaplan discussed studies that she has done, studies in Thailand in TB, and in TB in patients that also had HIV. Here, TNF levels, tumor necrosis factor levels, rise dramatically with TB. They fall with treatment. They're even higher in patients with co-infection. It was found that when thalidomide was used to block TNF production, patients gained weight much more rapidly than those that were simply treated with antituberculosis drugs.

There's also an excellent rabbit model for CNS TB, which is a very, very severe disease with an extremely high degree of mortality, and which particularly tends to affect children, especially in the Third World. In a rabbit model, near 100 percent mortality was reduced to 100 percent survival of the animals using thalidomide in addition to antituberculosis drugs, and studies are about to begin in South Africa in children. So we have a good bit of clinical evidence that there's a place for thalidomide and possibly other immunomodulatory agents in the case of tuberculosis, especially tuberculosis in patients co-infected with HIV.

The mechanisms, the dosing, the timing all has to be worked out. Remember that all thalidomide is not the same thalidomide. There are many, many sources of thalidomide in the world and they are probably not bioequivalent, and some of the attempts to extrapolate from one study to another as to efficacy and safety problems may be simply complications of different sources of thalidomide being used.

Also keep in mind that adverse events vary depending upon the background disease which is being treated with thalidomide. If you group patients by their background disease, there is usually a fairly uniform rate of adverse events in response to thalidomide, particularly in terms of peripheral neuropathy. In some cases, it's nearly zero. In other cases, it's nearly 100 percent. So we have to work out that bit of the puzzle also in terms of why does the background disease affect the likelihood of different adverse events occurring.

In HIV wasting syndrome, a number of studies have been done. We had a great review by Morris Schambelan, who has done some of the work himself. As you're probably aware, attempts have been made to treat this syndrome simply by increasing the patient's food intake, increasing their appetite. This leads to a lot of fat

increase and does not restore the lean body mass, which is the main problem in this syndrome. When you drop down to less than two-thirds of your ideal body weight measured by lean body mass, you die. Simply replacing fat is not sufficient to keep people from dying.

Human growth hormone has been very successful in restoring the lean body mass, but this is extremely expensive and not all patients respond. We've seen less HIV wasting in response to highly active antiretroviral therapy with triple therapy, but we're seeing a lot of breakthrough now and it's going to continue to be a problem.

The study done in Thailand, as I mentioned, looked at the effect of thalidomide in weight gain in terms of TB and HIV infection. There have been studies done in Mexico that were reviewed for us yesterday where great efficacy was shown in thalidomide in reversing HIV wasting, so much so that the drug has been approved for that use in that country.

Celgene in this country has an ongoing study. We discussed the preliminary results, looking at the data from eight weeks. This is a placebo-controlled trial, and there has been preliminary evidence of efficacy gains in lean body mass, but paradoxically also a bump in HIV viral RNA is seen in the peripheral blood, about 0.3 logs. This is not enough to be clinically significant. This is barely enough to be reproducible, but the question is why is that happening, and we have not yet got an explanation for this, especially since in the TB study the viral burden was seen to go down.

Gilla Kaplan suggested a mechanism for this. In TB, the primary source of HIV may be HIV replicating in long macrophage, where we know that we are very able to inhibit TNF production and that, in turn, inhibits viral production. In other settings, the T cell may be the primary source of HIV, and thalidomide does not seem to inhibit HIV replication in that setting. It doesn't seem to be TNF-driven. In fact, there's been some evidence that thalidomide may activate T cells, which may account for the small bump in HIV RNA that has been seen now in two studies, and also in the aphthous ulcer study, which I'll mention in a moment.

One of the things that we have unanswered is what will happen with a background of highly active antiretroviral therapy and thalidomide, because all these studies go back a couple of years and we had then a heterogeneous group of patients. Some are getting no antiretroviral, some are getting one or two drugs, and very few of them have been getting protease inhibitors. So all of this has to be revisited in the setting of highly active antiretroviral therapy.

Jeff Jacobson reviewed for us the results in ACTG 251. I had the privilege of doing the interim analysis in that study, along with three other collaborators, and we recommended closing the acute phase of the study prematurely. Not prematurely, but earlier than it was scheduled, because of efficacy. We saw such dramatic improvement in the aphthous ulcers in the patients treated with thalidomide compared to controls that there was no longer any need to continue that phase of the study. We're now looking at a follow-up to see how long patients on maintenance therapy continue to remain free of aphthous ulcers. So there's clear evidence of efficacy in treatment of HIV aphthous ulcers.

The issues of safety, the issues of optimum dosing, have yet to be resolved. Here, we saw a rise paradoxically in serum level TNF alpha and TNF alpha receptor, accompanied by small increases, a little less than 0.5 log, in HIV plasma RNA levels, similar to what was seen in the wasting study, so we are left with not only the problem of how to explain the HIV rise, but the problem of how to explain the rise in TNF, since this was the mechanism that we expect would have accounted for the healing of the aphthous ulcers. As has been mentioned already, one answer is that we need to look at the tissue at the site at which we're seeing healing and not simply at that convenient spot where you can draw from the peripheral blood.

While the evidence of clinical efficacy of thalidomide in the treatment of these diseases is very promising, more studies are needed to answer many questions, and we're left with a number of exciting things to look at in the future. We're going to need to look at pharmacokinetics. We're going to need especially to look at pharmacokinetics in women, since they've been very much underrepresented in these studies so far, and there are the obvious problems that we've been talking about for the past two days about doing that. Not only do we

have to look at the optimal dose, but we have to look at some way of figuring out what is the equivalent dose in different sources of thalidomide, and this will come out of the pharmacokinetics studies, in part.

Looking at wasting, we're going to have to consider combination therapy for wasting most likely, similar to what's been done now for HIV. We may need something that combines an appetite stimulant with an anti-TNF agent. We'll also have to consider looking at the mechanisms that are involved in wasting where intercurrent opportunistic infections lead to a drop in weight, and then the patient simply fails to regain weight often, rather than necessarily having a steady erosion of weight. Perhaps we should look at studies in which, when patients develop opportunistic infections, we then intervene with an anti-TNF treatment.

Also a problem in all of these studies is going to be looking for the instance of peripheral neuropathy. It has been reported to be about 20 percent in HIV patients treated with thalidomide, but that is based on a very limited number of patients. It will probably vary depending upon the degree of disease progression and it will probably vary depending upon the source of the drug.

We don't even yet have a sure way of knowing the optimum way to look for this. Do we need to measure SNAP, do we need simply clinical exam, or is it practical to insist on instrumentation? Even at the NIH, we would now be unable to do more studies than we're already doing looking for peripheral neuropathy if we had to use instrumentation on all of our patients instead of simply clinical exam. So we don't yet have the standard determined as to how best to monitor for this severe adverse event.

So, it's exciting. We have a lot of clinical studies that have already been done in infectious complications, particularly with HIV and TB, great suggestions of efficacy, and a lot of work left to be done looking at safety issues.

DR. GROFT: Thank you very much, Larry.

I think, hearing the responses back from the various panels, that we've achieved the goal, at least initially, of identifying some needs and many of the potential uses -- not all the potential uses -- that will come in time.

I'd like to open it up to questions, if anyone from the audience would like to ask a question of any of the chairs of the breakout sessions.

Dr. Trapnell?

DR. TRAPNELL: Carol Braun Trapnell from FDA.

One thing that hasn't really been said by anyone, but I keep thinking about it as I'm sitting here listening, is the source of funding for all this research that everyone has identified that clearly needs to be done. I guess I would like to say that if there's some kind of final report or recommendation from this conference, that we include perhaps some encouragement of funding for this kind of research, because these are orphan diseases in many cases and the basic pharmacology and animal model work needs to be done.

I think there's a big question about where this kind of funding would come from. I think if we at least say that we encourage that, it would probably at least help somewhat.

DR. GROFT: Any comments from any of the panel members?

DR. PLUDA: Hear, hear.

DR. GROFT: I think that's what we were hoping to do as we were enlisting partners for sponsorship of the meeting to identify potential needs and future opportunities for research, that the institutes would become aware of research that needs to be done and should be done that would advance the potential applications for thalidomide. So I think we have some very good partners right here on the stage with us. I don't know how deep the pockets are, but they're here anyway.

Any other questions? I know it's been a long two days and as we approach brain-dead stage -- yes, sir. Please identify yourself.

MR. VAN NUFLIN: Ray Van Nuflin. I'm a KS patient. What I want to know is, has any work been done with thalidomide on HIV-negative KS patients?

DR. PLUDA: Not that I'm aware of at this time. Part of the problem is that there really aren't a lot of HIV-negative KS patients, and to do the controlled clinical trials is a bit more difficult in order to get these patients into one center or a group of centers where we can actually do a controlled trial is more difficult. My impression would be that if we could demonstrate activity in KS, it would make life easier in order to try and get the drug available for the HIV-negative KS patients as well.

DR. GROFT: Any other questions?

DR. LONG: One of the points I made in my statement, some of you were not here, so with regard to the registry, with respect to the demographics of people taking the drug, women, African-American, Hispanics, et cetera, I feel there should be -- of course, in AIDS we find there's a differential access to certain treatments. I wouldn't want to see one type of population getting, say, their growth factor and another getting thalidomide for wasting or whatever. There should be equal access.

Also, the third-party payer issue which comes up. What drug is going to be paid for that's used for wasting? Is it going to be nerve growth factor? Is it going to be thalidomide? There's this disparity thing. Could you answer that type of question?

DR. PLUDA: Are you referring to access to clinical trials and whether third parties will pay for --

DR. LONG: Well, not only access to clinical trials, but even after drugs are approved certain people have access because of their knowledge, their input, and they have access to much more drugs than everyone. Even though the drugs are approved, certain drugs go on formularies and others don't, so there is this differential access. I think the registry should look into some of the demographics of who is getting thalidomide if the drug is approved.

DR. PLUDA: Well, you've also mentioned third- party payers, perhaps, as a suggestion for the next meeting that we get some of the insurance companies involved.

DR. GROFT: Yes, that was one of the many groups that I think have been identified as potential participants at a future meeting. We'll have to go back after this and look at where we are and what we want to do with the results of the meeting. Larry's laughing and thinking.

We'll figure something out of where we have to go after this as far as our next action. I know there's been a lot of talk about publication of the proceedings and the like to get the information out. I think, as many of us agree and I don't want to say too much about this, we can't spread the word enough.

Mervyn?

DR. ELGART: At the present time, of course, this is a drug which is not approved and, therefore, no third-party payers will pay for it. Once the drug is approved, if it is approved for wasting in HIV, then all of the other indications that we've been talking about are off-label uses. Again, in many pharmaceutical groups associated with HMOs or with third-party payers, by regulation they don't pay for off-label.

Now, they don't always know when the use is off-label, and they haven't got a good system of catching up with that, but when drugs become expensive, they particularly go out and seek those off-label indications. For instance, the use of Retin A in non-acne patients, some of the insurance companies require that you certify what the disease is that you're treating. I'm sure that this will become more prominent as drugs become more expensive and as off-label use becomes more prominent.

DR. FERGUSON: John Ferguson from NIH.

I think this has been a most extraordinary couple of days for several reasons. This drug brings up something for everybody here -- for medical science, for a large number of medical specialties, but also for the social, legal, ethical, and government -- something for everybody to chew on. I'm very excited to hear many of these presentations, and I think a lot has been accomplished. I'd really like to congratulate the organizers of this for a great job they've done.

I have a question that I haven't quite heard answered. In whose lap does the shepherding of this process sit?

DR. GROFT: The approval process or --

DR. FERGUSON: Well, I understand that the FDA will have to approve it, but once that's happened, and it is likely to, then who oversees it? Where does the overseeing of all the things that have been brought up on how to take care of this from our society standpoint, where does that sit? Does that sit in the FDA? Does it sit with the manufacturers?

DR. WOODCOCK: I'm Janet Woodcock. I'm from the FDA.

I think it's a good question. I was going to address it in my closing remarks, because I think it's the responsibility of all of us. That's one reason the organizers put together this meeting, because every group represented here, from the patient groups, to academia, to government research, to government regulation, to consumer groups, to lawyers, and to companies doing drug development, all are going to have to contribute if we're going to make this go forward correctly, I think. It can't be just the responsibility of one group.

DR. GROFT: If there are no other questions, I would say thank you very much to the panel.

I was heartened by a number of comments that came back in to me walking through the hallways of how much a lot of people gained from the interactions with each other. Really, that's the purpose of the workshop is that we're able to connect people together to see how things can be done, what needs to be done, and then move forward.

These are not the concluding remarks. Dr. Woodcock will present them. If people would like to stand up for a minute or two until we switch chairs, we'll go right into it, if that's okay.

Thank you.

(Applause.)

DR. GROFT: For the wrap-up, after everything is said and done, and we figure out what we've heard and where we're going, we thought the most appropriate person would be Dr. Janet Woodcock, the director of the Center for Drug Evaluation and Research.

Before turning it over to her, I don't know if Terry has any concluding remarks?

MS. TOIGO: No, I was out at the registration desk.

(Laughter.)

MS. TOIGO: No, I think back to how I got started in this, and that was offering to help Janet on thalidomide back about a year ago. We've spent a lot of time over the past year. I'm at FDA in the Office of Special Health Issues, and people often ask what a special health issue is. In our mandate it says AIDS, cancer, Alzheimer's disease, and other serious and life-threatening diseases. It seems that a lot of the diseases that we've talked about over the past few days relate to things that our office works with.

We primarily work with patients and patient advocates, and clearly, we hear many calls for access to promising and effective drugs, and our discussions with people are in trying to explain to them the need for clinical trials, and how FDA tries to help people with access to products, but how in that process that it's critical that we gather the information that's necessary to determine whether or not these drugs are safe and effective. I think this conference has helped us in trying to do that.

It's been a pleasure to work with Dr. Groft and others at the National Institutes of Health, and we look forward to continued collaboration.

DR. GROFT: As director of the Office of Rare Diseases, it's very nice to come to a meeting and not have to explain what a rare disease is. So that's a good feeling.

I got involved in this somehow last year. I received a phone call from an investigator who said he was unable to obtain an IND for the use of thalidomide. I thought, that's not too unusual. That would be expected that the IRB is going to require certain things.

But then as I made a couple phone calls out to my friends and colleagues at FDA, I began to realize that there already is an extensive system in place for people to obtain an IND or to get onto a clinical protocol already in operation, and so we quickly referred the individual and got things started there.

But then it became really apparent that we needed to do something to tie together the federal movement and action that would be responsive to the public's needs. Naturally, being a fine bureaucrat that many of us are, you go to a working group, or in this case it was an interagency working group of FDA and the Centers for Disease Control, and ask for volunteers from the institutes. They all provided several people who attended today and have participated and gave us guidance and direction as we went along. I just can't thank them enough for this almost a year's worth of activity that we started. I believe last October 2nd was our first meeting.

I'm sure all of those people, I'm sure everyone in this room probably, has suffered through as many sleepless nights as I have during the past year trying to deal with this issue. It's a hard issue. When we look at the outcomes, not necessarily the benefits, but the bad potential outcomes, it's scary, but I think with all of our shared responsibility, we can do -- I guess back in the 1960s and late 1950s, Dr. Frances Kelsey and her colleagues did it right. I think all of us today want to do it right, too.

I can't say more. I'll turn it over to Janet.

DR. WOODCOCK: Thank you.

Well, I want to say, I think it was appropriate that a storm broke and there was thunder and so on outside during the discussion of all the new clinical uses of thalidomide, because this is really what's happening. It describes the clinical interest in it. Really, those presentations reflect the challenge that's ahead of all of us.

We've had a lot of very germane suggestions and discussion over the past two days about what should be done. I want to reiterate what we were just talking about, that it is our mutual responsibility now to make this happen, make these suggestions happen. For the researchers, the pharmaceutical discovery groups, and the research laboratories, it's finding safer analogues, it's understanding the mechanism of action, to the extent that's possible, pathogenesis of the toxic reactions, finding animal models, looking at the pharmacology. These are major challenges, and as Carol said, we need to look for funding for those. Maybe go through collaborations or whatever to make sure these get done.

It is excruciatingly important that the various potential uses that have just been mentioned be evaluated for their safety and efficacy in clinical trials or in some kind of clinical evaluation that's capable of letting us know whether the drug works for that condition and what the safety profile is. This is going to require a partnership again, this time between the companies, academia, and probably FDA, and government in general to make this happen, particularly in these very rare diseases in some cases.

I would urge those who are looking at diseases that are chronic where thalidomide would be considered as a maintenance therapy -- and this is just an aside -- to consider randomized withdrawal trials for maintenance. This is one way where you can use a small number of patients and yet get extremely valid results, I think, and you can do repeated cycles of that.

Another challenge that is before us right now, and has been before us, that is going to continue whether or not the drug is actually approved is the safe distribution, the safe study, of thalidomide. Obviously, we've heard over the last couple of days major concerns about the teratogenicity and peripheral neuropathy. We don't have standard monitoring for these peripheral neuropathies, as you've heard, and that's a problem because we don't know how to evaluate whether it's developing or not.

Right now, as you've heard, there are investigational uses going on. There's an access program going on, single patient uses. FDA has worked hard to facilitate that with manufacturers to make sure these INDs that are held by investigators allow the drug to be distributed safely for these uses under an investigational new drug application, but there are limits on this as far as how much control there is over the distribution.

We've worked extremely hard also, and I want to emphasize this because I think there might be some misunderstandings, to eliminate the distribution through uncontrolled channels such as buyers clubs, either by talking to buyers clubs, or sending them warning letters, or in a recent case taking legal action against a group that was distributing thalidomide through uncontrolled channels. This also is facet of this that needs to be kept under control if the drug is going to be distributed safely, investigated safely.

If the product would be approved for an indication, I can't emphasize enough that for drugs that are approved and on the market, there is still ongoing risk-benefit assessment. FDA has a postmarketing surveillance system. The CDC has mechanisms for surveillance in many cases. Many drugs are carefully looked at after approval to make sure that the safety results in practice, in use of the drug, are as predicted or remain safe enough that the benefit outweighs the risk. So that postmarketing surveillance, if in fact thalidomide would be approved for something, would be an extremely important aspect of continued availability, distribution, and investigation of thalidomide, and would be, again, a responsibility of everyone.

One of the most important things to me actually is education. There's a whole population out there that needs to be educated even now, when the drug is not approved, but is being used for a wide variety of conditions and is out there. We heard from the behavioral scientists that we really need to educate with behavioral objectives in mind. We need to make sure we change our direct behavior. We need to have certain results in our messages.

We need to work with professional societies of physicians, dentists, nurses, pharmacists, and other health care providers. We've got to work with the health educators and, I agree, we need to work with managed care. Managed care is a growing force in delivery of health services, obviously, to the U.S. population and has a say now in what drugs people get, and can be a force for educating all the groups I just mentioned about the safe use of products. We need to make sure there is continuing medical education for all these different parties. We also need to reach out to the patient groups, and make sure they are fully informed about this, both risks as well as evolving data on clinical efficacy.

For all these groups, we need a consistent and clear message, I think, from the interested groups so that there isn't a lot of confusion, and I think there's another group that really could help us, which is the news media. I think the public in general needs and deserves to be informed about this in ways that they can comprehend, in a balanced manner so that an understanding of the word "thalidomide' is again something that the people can recognize and know what it means.

So those I think are the tasks in front of us. Each of us can apportion whatever responsibility we're willing to take on, but I really do appeal to everyone here. I thank you for coming and giving this your attention. I thank all the co-sponsors for putting so much effort in this, and I thank all the other people -- the patient groups, the health professionals, the subspecialists, and so on -- for coming and helping contribute to this effort.

Thank you very much.

(Applause.)

DR. GROFT: If there are any questions, Dr. Woodcock will attempt to answer them for a few minutes. She does have a meeting to get back to shortly, but I think we're all content to close the meeting and say thank you very much for your attendance.

Thank you.

(Whereupon, at 4:01 p.m., the meeting was adjourned.)

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