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P R O C E E D I N G S

DR. HULKA: This morning we are meeting for the Fertility and Maternal Health Drugs Advisory Committee to the FDA this morning. Our discussion on Accutane will last until about 10:45. I will say specifically that the reasons for our meeting here to discuss this is to bring our Committee up to date on what has been called "the Accutane campaign", intended to reduce the use of Accutane and, thus, reduce exposure of any fetuses to the drug. Then, after getting the information, the Committee will provide comments concerning this campaign, specifically for the use of this drug by women of reproductive age. We have a series of speakers on the program who will be speaking on the various aspects of Accutane.

Before we go ahead with that, Dr. Corfman has a few comments that he would like to make to you.

DR. CORFMAN: I would like to note that we have made a change in the dates for the coming meeting. They are tentative dates and they are in the back of the agenda which you received. So the next meeting is scheduled for October 26th and 27th. Then the date for February has been put forward one week to accommodate one members who could not make the 15-16 date. Then we are scheduling a meeting for a year from now, for June 21 and 22. So if anyone has problems with that, I would like you to let me know so that we can

take care of it during the meeting.

I would like to acknowledge that Dr. Carl Peck is here. He is the Director of the Center for Drug Evaluation and Research; and Dr. James Bilstad, who is the Director of the Office of Drug Evaluation II. They are here for the Accutane discussion. The Committee has actually been asked to address this issue at their request and perhaps they would wish to participate in the discussion. I hope that is the case.

As far as the meeting goes this morning, so far we only have four agencies who have said they wish to speak. The American Academy of Dermatology did call me and make arrangements but there is no speaker here. So it seems to me that we have plenty of time to have all four agencies give their presentations during the one-hour time period that has been assigned to this. Does anyone else wish to speak besides ACOG, CDC, Public Citizen and Teratology Society?

(No response)

At the beginning of the coffee break, I would wish those who wish to speak during the open hearing on lactation suppression to come up and tell me so, so we can apportion that time and then later in the day also for tomorrow morning's session.

That is all I have to say, Dr. Hulka.

DR. HULKA: Going by alphabetical order, the

speaker for ACOG will come first, Miss Laura Feldman.

PRESENTATION BY LIRE FELDMAN

MS. FELDMAN: The American College of Obstetricians and Gynecologists, an organization representing more than 28,000 physicians specializing in the delivery of health care to women, is concerned about the serious effects of Accutane therapy on the developing fetus and strongly believes that pregnant women and their offspring must be protected from the hazards of such exposure.

As ACOG indicated in an April 26th, 1988 letter to the Food and Drug Administration, we believe for such protection to exist the following process must be used: A pregnancy test be performed; the patient be counseled about the potential effects of the drug on the fetus; and family planning options be discussed with the patient, including contraceptive information and prescriptions as indicated. When prescriptions are refilled for Accutane, particularly for teenagers, the physician should again undertake the process outlined above.

ACOG does not believe that the availability of Accutane should be restricted by either removing it from the market or classifying it as an IND drug. Moreover, ACOG would be concerned with the precedent of removing or restricting women's access to useful and valuable drugs that are potential teratogens. We believe the effect of the recent

changes in labeling should be evaluated prior to any changes in Accutane's status. Thank you.

DR. HULKA: Any questions of Miss Feldman? If not, we will go on with David Erickson, CDC.

PRESENTATION BY DAVID ERICKSON

DR. ERICKSON: Good morning. I am happy to be here to discuss the important issue of Accutane embryopathy with you. About a year ago I spoke before the Dermatologic Drugs Advisory Committee on this matter and I appeared at another hearing just last month. What I will say to you today is very similar to what I said to that committee on those two occasions.

I am the Chief of the Centers for Disease Control's Birth Defects and Genetic Diseases Branch. The mission of our program is to search for causes of birth defects and to prevent unnecessary morbidity and mortality due to these diseases.

I am here today because I believe that the birth of babies with defects caused by fetal exposure to Accutane is unnecessary. Obviously, if this drug was not available, these defects would not occur. I believe that babies are still being born with Accutane embryopathy. Therefore, I believe that it is time for a new and effective approach to preventing fetal exposures.

The approach to prevention that was taken in 1982,

when FDA decided to allow the marketing of Accutane, was that of strong product labeling and of physician and patient education. The approach, unfortunately, has failed to prevent the birth of babies with major handicapping defects. In fact, it seems to us that there is evidence to suggest that the rate of fetal exposure did not decline to any marked degree after renewed warnings were made in 1985. We have no information available today to suggest that this pattern has changed over the past year despite the very strong new warnings.

As I said before, we think it is time for a new, much more aggressive approach to preventing babies being born with defects due to Accutane exposure. We feel that a successful approach will involve much more than further warnings and more education.

Because the problem could be markedly reduced by having better contraceptives available, we are quite pleased with the recent recommendation of your Committee to approve Norplant. If the Commissioner should act favorably on the recommendation, and we hope that he does, it will provide the potential to reduce the number of in utero exposures substantially.

But we do not feel the problem will be fully solved by the availability of better contraceptives. Not all women treated with Accutane will use them, and even though they

could be very effective, they do fail occasionally. We think that an approach to a more nearly complete solution will require a restricted distribution to substantially reduce the number of fertile-age women who use Accutane.

We feel pretty strongly about this issue simply because it is a matter of our perception of the balance between the risks and the benefits. I think that policy-makers need to address explicitly the very difficult issue of equity, to make an accounting of the risks and the benefits of Accutane use, to balance the interests of babies with the problems of persons with skin disorders. These policy makers need to decide how many persons cured of cystic acne by Accutane is a fair and equitable balance for each baby born with a serious physical and/or mental deficit.

I want to share with you some estimates that we have made that will help to put this issue of equity into concrete terms.

(Transparency)

This graph shows our estimates of the numbers of live born babies that would be affected by Accutane embryo-pathy for varying numbers of drug users. Each of you on the Committee has a copy of this graph in the back of the handout that I provided.

We present estimated affected numbers for 3 different yearly rates of contraceptive failure, 20 percent,

3 percent and 0.3 percent, the latter being the approximate failure rate of preparations like Depoprovera and Norplant.

(Transparency)

The assumptions used in arriving at these estimates are the following: That about 33.5 percent of women aged 15-44 are not fecund and that 14 percent had never had intercourse;

that no treatment would be started during pregnancy;

that all courses of Accutane treatment would be 5 months long;

that the pregnancy rates would be the various contraceptive failure rates;

that a little more than half of women who have had an inadvertent exposure during pregnancy would elect to have the pregnancy terminated;

that the fetal death rate (early and late) would be on the order of 46 percent. A rate of 10-15 percent spontaneous abortion is considered usual but Ed Lammer's data suggests a spontaneous abortion rate of 40 percent. To that, we have arbitrarily added a stillbirth fetal death rate of 6 percent;

finally, that 25 percent of exposed fetuses that survive to live birth will have serious malformations.

(Transparency)

This slide shows estimated numbers of babies who

will be live born with serious malformations. It is obvious that a marked reduction in the number could be achieved by reducing the number of users. If the drug were used by only 4000 women per year, we would expect somewhere between O-13 affected babies to be live born in the U.S., the lower number (0), if all women were using a very low failure rate contraceptive, and the higher number (13), if all were using a high failure rate contraceptive method. The number 4000 is presented because that was the estimate of the number of fertile-age female severe cystic acne cases made last year by Dr. Graham, of the FDA.

Data are also presented in the graph for larger numbers, up to 70,000, which is the approximate number of current users. At this level of use, we would expect the birth of somewhere between 3 and around 220 malformed babies, depending on the mix of contraceptive methods used by Accutane users.

It is obvious that having more effective contraceptive techniques available would go a long way towards achieving the objective of reducing Accutane embryopathy. But we believe that a restricted distribution system to reduce the number of users is also needed.

I think a decision to depend on better contraception alone, without active intervention to reduce the number of users, is a decision to leave the number of affected babies

at an unacceptably high level.

(Transparency)

I will take the last few minutes of my presentation to describe to you CDC's ideas of what would be an acceptable limited distribution plan that would make Accutane available to all persons in need of the drug, including potentially fertile women. We believe that this could be done as a result of FDA action or as the result of a voluntary effort by the manufacturer. The plan, as a minimum, should include the following features:

First, the distribution of Accutane would take place through a very limited number of institutionally-based centers. These centers would be responsible for seeing that protocol is followed by prescribing physicians.

A center review committee would require certification by the physician who wishes to use the drug that the patient has severe acne that is resistant to other forms of treatment before releasing the dug.

There would be innovative approaches to education about the dangers of the drug to the fetus and about the facts of contraception.

There would be a center oversight procedure that would require certification that women who are treated are at minimal risk of becoming pregnant during and shortly after treatment.

Prescriptions would be limited to one-month supplies of the drug. To receive continuing treatment, the patient would need to return to her physician to have a reliable pregnancy test performed. The system would also be designed so that women would return at an appropriate time after completion of treatment for a final pregnancy test.

Our goal is to prevent fetal exposures but failures will occur and fetuses will be exposed. So we believe that each center should have a system for adequate counseling of women who do become pregnant while using the drug. Some women will elect to continue their pregnancies, while some will elect to have their pregnancy terminated. Induced abortion is an intervention that has been used in Accutane-exposed pregnancies and probably will continue to be used so long as Accutane is available for use by fertile women.

Finally, there should be an evaluation of the prevention strategy, including a national registry of patients who have exposures during pregnancy, with a follow-up of pregnancy outcomes. The restricted marketing approach that we recommend would make follow up and evaluation feasible. Without such an environment, we think it would be very difficult, if not impossible, to devise an adequate and unbiased evaluation system.

That concludes my presentation. Thank you again for the opportunity to be here. I will be glad to answer any

questions that you might have.

DR. HULKA: Are there questions? Dr. Erickson, I would like to ask a question on one of your figures, the one on the different contraceptive methods and their failure rates and the resulting number of malformed children.

(Transparency)

Yes. Are these failure rates failure rates that apply to the 5-month treatment period?

DR. ERICKSON: Yes.

DR. HULKA: Then would you specify which contraceptive methodologies each of these apply to?

DR. ERICKSON: Yes, the 20 percent failure rate is, by our understanding, the typical in-use failure rate for something like spermicides; 3 percent for the pill; and 0.3 percent for failure rates. Those failure rates are yearly failure rates but the numbers that are in the graph have been adjusted by 5/12.

DR. HULKA: So the 3 percent failure rate applies to the annual failure rate for the pill?

DR. ERICKSON: Yes.

DR. HULKA: For oral contraceptives. The 0.3?

DR. ERICKSON: That is our understanding for a preparation like Depoprovera or Norplant. These data come from Trussell's review of contraceptive failure rates.

DR. HULKA: The reason I highlight this point is

because you have a great variability in terms of the results of malformed children. If 60,000 women are using the drug, you are talking about anywhere from 3 possible malformed children for a very successful contraceptive up to 189 for a basically inadequate contraceptive and I think that point ought to be highlighted.

DR. ERICKSON: Yes.

DR. HULKA: Other questions? Jim?

DR. SCHLESSELMAN: Dr. Erickson, does the CDC have an estimate of the number of malformed births that were Accutane-induced over time?

DR. ERICKSON: No, we do not. I believe Dr. Stadel will probably touch on what has been reported to the FDA. As a rough ball park estimate, I think what we know in the way of reported cases is something on the order of 80. But we believe that to be only the tip of the iceberg. There is no active search for babies born with these problems.

DR. HULKA: If there are questions from the floor, would you please stand up at the microphone and introduce yourself?

DR. ROSA: Dr. Rosa, FDA. One slight adjustment on that figure, that is the figure for women who become pregnant while they are using Accutane. Actually, we have another third of these pregnancies of women who start Accutane when they are already pregnant.

DR. HANEY: There are some other drugs that are teratogenic in humans that are used frequently and I would like to get some feeling for the relative magnitude here. Danazol is used in infertile women who are trying to get pregnant, given to women who are pregnant and given to women who inadvertently become pregnant. It is a contraceptive by itself. So it is probably going to be a greater proportion who are inadvertently given it during pregnancy. But do you have some feeling for the number of serious birth defects that that drug generates in a year?

DR. ERICKSON: No, I am sorry, I do not.

DR. HANEY: How about any of the other human teratogens -- diphenylhydantoin, DES, etc?

DR. ERICKSON: I am sorry, I do not have estimates. I guess the major drugs of concern would be the anti-epileptics. In the past there have been concerns that uncontrolled epilepsy might in itself be dangerous to the fetus.

DR. NIEBYL: But I think it is fair to say that the order of magnitude of the risk of Accutane exposures is much higher. If a patient is exposed to Accutane in the critical period, what is your estimate of the risk of malformations? What number would you give?

DR. ERICKSON: We would say 25 percent for serious major malformations, which is on the same order as the risk with thalidomide.

DR. NIEBYL: Whereas with Dilantin it is probably 2 percent at most. So you are talking about a much more likely event with Accutane. With Danazol they are few and far between that have even been reported. It is my understanding that it is a completely different type of problem, with masculinization of genitalia which is surgically correctable, whereas these are major defects of both mental and physical handicaps. So I think we are talking about a much more potent teratogen with Accutane than any of the other drugs that are currently widely used.

DR. HANEY: I think you are exactly right about its attack rate. I would not, however, characterize what happens with Danazol as a mild, inconsequential, easily surgically correctable --

DR. NIEBYL: Right, but these are far worse.

DR. HANEY: Well, you know, eight operations and a child in a psychiatrist's office for the remainder of their lifetime who does not understand their gender identity, does not seem to be mild either.

DR. NIEBYL: No. No.

DR. GRAHAM: David Graham, from FDA. Regarding anticonvulsants versus Accutane and the risk of birth defects, you should also bear in mind that the pregnancy categorization that FDA assigns to these drugs is different. Accutane bears a category X, which states that the benefit to

the patient never outweighs the risk to the fetus, whereas, anticonvulsants carry a category D classification which specifies that in certain situations the benefit to the patient may outweigh the risk to the fetus.

This is important to recognize, especially when talking about anticonvulsants because with anticonvulsants in a pregnant women we are really talking in a sense about treating two patients. If a woman has serious seizures which could be life-threatening she not only jeopardizes her own life but her unborn child. It is a very different comparison that I think the Committee should be aware of. Thank you.

DR. HULKA: We will go on to the representative from the Public Citizen, Andrew Holmes.

PRESENTATION BY ANDREW HOLMES

DR. HOLMES: I am Andrew Holmes. I am with Public Citizen. I am a pediatrician with a subspecialty in preventive medicine and that is why I am here today.

Accutane is a more potent teratogen that thalidomide, yet it can be prescribed as readily as penicillin. This has resulted in a tragic epidemic of birth defects and abortions through fear of birth defects. Birth defect reports have plateau'd after an initial peak in 1984. There is no evidence that this epidemic is abating.

We are heartened that Accutane is now on the agenda of the this Committee, the advisory committee that is best

qualified to evaluate practical issues of Accutane's teratogenicity. It is unfortunate that it took seven years from the time Accutane was approved.

In May of last year., Public Citizen petitioned the FDA to take measures to stop the epidemic. It is with regret that we report that the FDA, last month, rejected those parts of our petition which would have limited prescribing to suitably qualified physicians who would sign a statement that they would only prescribe Accutane to women with severe cystic acne unresponsive to more benign therapies and would agree to do initial and monthly pregnancy tests.

The FDA conceded that it may have the legal authority to adopt the recommendation but it refused to use this discretion, stating, in the words of Commissioner Young, that this "would constitute an unprecedented intrusion onto the doctor-patient relationship."

We ask members of the Committee to consider just what sort of calamity it should take to intrude onto the doctor-patient relationship in order to protect patients.

I want to go through the status quo. There has been a singular lack of progress on the part of Roche over the last few years. The new blister packs, announced over a year ago, have only just reached the market. There is not yet any adequate postmarketing surveillance. By proceeding with the rejected protocol for postmarketing surveillance,

Roche has conspicuously flouted an FDA directive. The promulgation of biased data gathering is tantamount to a disinformation campaign.

The FDA has, in a partial denial of the Public Citizen petition, bought into Roche's obstructive strategy by referring to the study without mention of the flawed protocol, in a justification of its decision. Dr. Young, in his letter to Public Citizen, stated: "A survey has been conducted by Hoffmann-La Roche to identify the rate of pregnancy exposure among women prescribed Accutane and to help the Agency determine the effectiveness of the total intervention program undertaken to date."

This is in spite of a protocol being rejected by its own scientists, after review by its own epidemiology and two independent reviewers. One of the reviewers was Dr. Barbara Hulka, current Chairman of this Committee. The other was Dr. James Schlesselman, also on this Committee. The basis for rejecting the protocol was that because of its voluntary nature, enrollment is likely to be low and biased toward physicians who were adhering to proper prescribing and pregnancy-prevention practices. Thus, it is likely that the pregnancy exposure would be underestimated. This is, in fact, acknowledged as a potential problem in the survey protocol, written by the Slone Epidemiology Unit, and a part of the Roche briefing package to members of this Advisory

Committee.

Prescribing patterns for Accutane are essentially unchanged. It continues to be grossly over-prescribed for all groups but, most importantly, it continues to be grossly over-prescribed for fertile women. As we heard from Dr. Stadel, at the Dermatologic Advisory Committee meeting last month, the data sources are too imprecise to determine minor trends.

There is no evidence that the incidence of Accutane-induced embryopathy has decreased. This can be seen in the voluntarily reported birth defects during 1985-1988 which, though fewer than in 1983 and 1984, are steady at 10, 9, 11 and 8. I need not remind you that the voluntarily reported birth defects are only a small fraction of those actually occurring.

There are no hard data on the number of spontaneous and induced abortions consequent to Accutane exposure. The scant information that is available indicates the rates are high. The Michigan Medicaid study suggests that the rate of spontaneous abortion after first trimester Accutane exposure is 40 percent (twice the background rate). In that study, 60 percent of the first trimester exposures that did not abort spontaneously resulted in induced abortions.

The Company's advice to physicians and the label on the blister packs, while suitably strongly stated, says that

potentially all exposed fetuses can be affected, without stating the actual published observed risk, which is 25 percent for major physical malformations. This obstructs the process of informed consent, with the likely effect of coercing decisions to induce abortion.

Conclusions -- the rate of Accutane prescribing does not appear to have changed significantly in the last few years. Most importantly, first-time Accutane use by women of childbearing age has not declined from the levels of three years ago.

A year from now, we are not going to know if pregnancy exposures have been reduced because we do not have an adequate data collection system. As it stands, we will have no way of knowing whether the blister packs, just introduced, actually work to reduce pregnancy exposure. Our only reasonable information is prescription numbers, and blister packs are a post-prescribing intervention.

Focusing on the number of birth defects evades the issue of the number of spontaneous and induced abortions consequent to Accutane exposure. Abortion should not be regarded as a satisfactory outcome for pregnancies exposed to Accutane.

We should not lose sight of the fact that there are other major morbidities associated with Accutane use. Our group has received calls from members of the public who have

suffered major side effects after prescription for relatively mild acne or before other therapies have been given an adequate trial.

Responsibility for adverse outcome for Accutane use has been shifted from Roche, the manufacturer and marketer, to the prescriber and patient. This is in the face of Roche being obstructive to the process of gathering postmarketing data and misleading the public in its product warnings.

Recommendations -- there must be immediate restrictions to reduce prescribing to only severe acne that has not responded to more benign therapy. Our petition outlines a workable set of such restrictions.

Although the FDA has rejected the part of our May 17 petition which would impose such restrictions, the Agency does not deny that it has the legal authority to implement such tighter restrictions.

Postmarketing surveillance with rigorous follow-up should be an immediate requirement. The protocol should be submitted to and approved by the FDA in consultation with independent reviewers.

If the FDA finds that it does not have the legal authority to impose rigorous 100 percent follow-up in postmarketing surveillance, and the Company does not agree to do this voluntarily, then the FDA should immediately call for legislation which would allow for this.

Upon future review of Accutane use, its continued availability should be contingent on hard evidence that it is being used appropriately and with a clear, major reduction in drug-related morbidity.

Finally, product warnings to physicians regarding the outcome of pregnancy following Accutane exposure should include the actual measured relative risk of Accutane-induced birth defects. Information should also be provided about the effects of dose, gestation and duration of exposure on pregnancy outcome.

In summary, the failure of Roche and the FDA to more severely restrict the use of Accutane, the failure to conduct acceptable surveillance to determine the extent of pregnancy exposure and the failure to accurately inform women who become pregnant while using Accutane of the actual risk of major birth defect must be challenged by this Advisory Committee.

Accutane has an important role in the treatment of severe acne but it is imperative that it be used responsibly. There is substantial irresponsible use of Accutane at present. It is our position that unless there are immediate prescribing restrictions, such as those we outlined in our petition one year ago, and an effective monitoring system is implemented, Accutane should be removed from the market. Thank you.

DR. HULKA: Are there any brief questions?

(No response)

Thank you. We will move on to the Teratology Society, William Scott, Jr.

PRESENTATION BY WILLIAM SCOTT, Jr.

DR. SCOTT: Good morning. I am William J. Scott, Jr. D.V.M., Ph.D., Professor of Pediatrics at the Children's Hospital Foundation, University of Cincinnati College of Medicine.

This morning I am representing the Teratology Society. We have presented testimony to the Dermatologic Drugs Advisory Committee regarding Accutane on two previous occasions, and appreciate the opportunity to speak with this Committee this morning.

The Teratology Society is a professional organization of basic scientists, pediatricians, obstetricians, toxicologists and other health sciences concerned with the etiology and prevention of birth defects and other aspects of abnormal development. Members of the Teratology Society are from academia, government and private industry.

As a professional society, we have been concerned with the teratogenicity and other developmental effects of retinoids. Many, if not most, of the studies demonstrating such effects of retinoids have been conducted by members of the Teratology Society. Our public affairs committee is

preparing statements on Accutane and Tegison for publication. My remarks this morning summarize the recommendations in the Accutane statement. The statements to be given have been reviewed and approved by the council and the public affairs committee of the Teratology Society.

The Teratology Society believes that malformations caused by Accutane are preventable. Despite the national publicity concerning the teratogenicity of Accutane following last year's Committee hearing, pregnant women continue to be exposed to Accutane.

Currently, we see three obstacles to the prevention of birth defects caused by Accutane: One, a large number of women in the age range of 12-44 years old are being treated with Accutane. Two, oral contraceptives, the most efficacious currently approved contraceptives in the Unite States, have typical failure rates of about three percent. Three, the lack of recommendations for the close monitoring of early detection of pregnancy.

The manufacturer and the FDA have estimated that women aged 12-44 have received 65,000 new Accutane prescriptions during 1988. This number of prescriptions seems to be well above the published estimates of the incidence for recalcitrant cystic acne. Your Committee and the Dermatologic Drugs Advisory Committee may be in a position to assess if there is over-prescription of Accutane.

This number of users, coupled with the limitations of the currently available contraceptive methods in the United States, creates a significant problem. A number of scholarly papers have been published on contraceptive failure in the United States. Trussell estimates, based on all available studies, that the typical failure rate of oral contraceptives is three percent. Other reviews have been recently published by Mishell, in The New England Journal of Medicine, and Grimes recently published another review in The Journal of the American Academy of Dermatology, focused on dermatology practice.

It is not difficult to estimate that several hundred women could become pregnant during the treatment period with Accutane even while using an oral contraceptive. This estimate is based on the current number of new prescriptions of 65,000 women each year and a failure rate of approximately 3 percent for oral contraceptives.

Injectable progesterone type implants are available outside of the United States and have been shown to be very efficacious in preventing pregnancy. The observed failure rates of injectable progesterone and implants have been estimated at 0.3 percent, about a lo-fold improvement from oral contraceptives for typical failure rates. If all fertile female patients using Accutane would also use an injectable progesterone or an implant instead of oral

contraceptives, this could reduce pregnancy rates resulting from contraceptive failure by about 90 percent.

The recent recommendation of this Committee to the FDA to approve implants in the United States is a step in the right direction. Until such products are available, the use of multiple contraceptive methods should be considered. Recommending the concurrent use of barrier methods with oral contraceptives may be an important behavioral modification.

The possibility of contraceptive failure underscores the need for monitoring for pregnancy. For a drug that carries a category X labeling, it would seem logical that the prescribing physician would like to discontinue therapy as soon as the contraindication emerges.

Clinically available ultra sensitive pregnancy tests would detect pregnancy at or shortly before the anticipated missed period. We see two advantages for including repeated early pregnancy detection. First, having to return for a pregnancy test and a new prescription on a monthly basis may provide another behavioral modification about the careful use of contraceptives. Second, those patients that would consider discontinuing an Accutane-exposed pregnancy, as suggested in the current labeling, would face a simpler and safer procedure than the ones available after 12 weeks of gestation.

The Teratology Society supports and encourages the

educational programs developed by the manufacturer to make women aware of the risk of Accutane use during pregnancy and to assist prescribing physicians in the pregnancy prevention program. The Society would like to encourage the FDA and the manufacturer to continue to support efficient and unbiased surveillance of pregnancy exposures among female Accutane users. We believe that any pregnancy occurring to female Accutane users should be considered a failure of the pregnancy prevention program and should be carefully evaluated to determine the reason or reasons for the failure and to develop additional strategies to prevent such occurrences.

Therefore, the Teratology Society offers the following recommendations to this Committee, the Food and Drug Administration and the manufacturer:

One, efforts should be made to decrease the number of Accutane prescriptions to fertile females.

Two, the extreme hazard associated with Accutane exposure during pregnancy necessitates that female users be provided with the most effective means of contraception, for example, long-acting progesterone type injections or implants.

Three, monthly pregnancy testing should be performed in fertile female patients and Accutane prescriptions should only be continued if there is a negative ultra sensitive pregnancy test.

Four, an active and unbiased surveillance of

Accutane use among female patients should be continued and every occurrence of pregnancy among Accutane users should be evaluated to determine the reasons for the failure in the presence of the pregnancy prevention program and to develop additional steps for preventing such occurrences.

These are interim recommendations, with the hope that they will be effective in preventing pregnancies in female patients being treated with Accutane. Your Committee and the Dermatologic Drugs Advisory Committee should review the surveillance data in a reasonable period of time to determine if these measures have been effective, that is, prevented pregnant women from being exposed to Accutane. If such measures are not effective, this Committee and the Dermatologic Drugs Advisory Committee will be faced with implementing stronger measures to prevent exposure to Accutane during pregnancy, such as restricted distribution. Thank you.

DR. HULKA: Are there questions? Yes?

DR. MCDONOUGH: May I ask, Dr. Scott, do we have any data on Tegison in psoriasis? Even though that is not something on the agenda here, it seems to me that the analogy is fairly good. That is, we have basically a disorder that may vary from mild to very severe being treated basically with a drug that is in the retinoid category.

DR. SCOTT: Yes, as I said, we are preparing a

position paper on Tegison as well. Dr. Rosa can certainly speak more to the case reports than I can. It certainly is a serious animal teratogen. Reports from Europe, I think, of exposure to Tegison and subsequent birth defects present a much larger problem in that Tegison has a very long half-life in human beings and there have now been reports of malformations when exposure to Tegison was a year prior to conception. So Tegison is a problem but, to my knowledge, in this country there have been no children born with malformations attributable to Tegison. But I would submit to Dr. Rosa to give an authoritative answer to the question.

DR. MCDONOUGH: And the half-life of Accutane?

DR. SCOTT: It is on the order of hours or days.

DR. HULKA: Thank you very much. We now go on to two speakers from the American Academy of Dermatology. Each will speak for five minutes. Dr. Maria Turner?

PRESENTATION BY MARIA TURNER

DR. TURNER: Good morning. I am Maria Turner, Professor of Dermatology of George Washington and the Children's National Medical Health Center. I am also Chairman of the Task Force on Therapeutics of the Academy of Dermatology and a member of the ad hoc committee that set up guidelines for the use of Accutane for the Academy of Dermatology.

I am pleased to represent more than 7000 physician

members of the Academy in my comments. We appreciate the opportunity to once again discuss the importance of isotretinoin or Accutane and to review with you actions the Academy has taken to ensure that this important drug is made available to the thousands of individuals who suffer from severe cystic acne.

Severe cystic acne produces profound, permanent scarring of the face, neck, back and cheek and until the introduction of isotretinoin no predictably effective treatment existed. It should be noted that cystic acne is usually not a self-limited process. It does not disappear at the conclusion of adolescence. Unfortunately, it can persist for years during the course of adult life.

In spite of the fact that there were treatments for this disease before the introduction of isotretinoin, the responses to systemically administered antibiotics, sulfonamides, sulfones, anti-inflammatory agents, hormones and high doses of vitamin A were unpredictable, incomplete and temporary at best.

This was true even if these drugs were given in sequence or in combination. These drugs also had many allergic and unwanted side effects. A number of these older, pre-isotretinoin treatments were contraindicated during pregnancy and the question exists as to whether some may have reduced effectiveness of birth control procedures.

Dermatologists know that there are no alternative treatments for severe cystic acne that offer the same improvement and cure as isotretinoin. In fact, we could never speak in terms of a cure until the introduction of this drug.

Please allow me to show you a few slides that will actually show the spectrum of severe nodulous cystic acne.

(Slide)

This is the usual type of patient who comes with severe nodulous cystic acne. This is a patient of mine who has had acne for about five years, who underwent all types of conventional therapy and really did not get better until Accutane. Conventional therapy consisted of all the mentioned treatments in the previous paragraph.

(Slide)

This is to show you the spectrum of nodulous cystic acne. This is a 14-year old boy who had very severe, acute onset acne, who had fever and bone pain. This particular patient was one of the original patients who was put on Accutane therapy because nothing that we did would help him. He had to leave school and actually was pretty toxic from so-called fulminant acne.

DR. CORFMAN: How old was he?

DR. TURNER: He was 14.

(Slide)

And to show you that we are not really talking of just small pitted scars that can be covered with cosmetics, I thought this was a very rare case but I can tell you that just in the past month I had a similar patient, a 20-year old young man who still had active acne, who had been on Accutane and who had keloids such as these. He was so embarrassed, he would not let me take a photograph.

(Slide)

This is to show you what Accutane can do.

(Slide)

After 16 weeks of Accutane therapy this gentleman, who has very severe nodulous cystic acne looked, like this. Again, it is not a perfect example. It is not perfect skin. But I am sure anybody can see that Accutane is a really important medication in the armamentarium of the practicing dermatologist.

There are a great number of medications that must not be given during pregnancy and isotretinoin is absolutely among them. The Academy has consistently stressed this issue, along with the manufacturer, and will continue to do so.

In spite of these concerns, the members of the American Academy of Dermatology, experts who know this disease, its natural disease and the ineffectiveness of alternate therapies, conclude that the benefit-risk ratio

justifies the present and continued use of Accutane with appropriate warnings and protection against pregnancy during therapy.

As a result of the April, 1988 hearing before the FDA Dermatologic Drugs Advisory Committee and the subsequent correspondence with the Food and Drug Administration, a number of actions were taken by the Academy to underscore the effects of this drug if administered during pregnancy.

In May, 1988, the president of the Academy sent a "dear colleague" letter to the entire membership, reporting on measures that need to be taken. Just prior to the approval of the guidelines, the FDA formally requested the participation of the Academy in a broad educational campaign and this was undertaken at the annual Academy meeting, as well as in the Journal of the American Academy of Dermatology.

In March of this year the Academy again wrote to its entire membership asking for its cooperation in the Slone Epidemiology Unit study of female Accutane users which would enroll such patients, track their progress and evaluate the effectiveness of the FDA-Hoffmann-La Roche pregnancy prevention program.

DR. HULKA: Your time is up. Any questions?

DR. BARBO: How many times would a young woman, if she has this severe problem, be given a course of the treatment, which is five months. Is that right?

DR. TURNER: Yes.

DR. BARBO: How many times might she need that in her lifetime?

DR. TURNER: Most of the time one course is sufficient. Speaking from my own experience, and I work in a tertiary care center, a referral center, probably of 100 patients I have used it on, I have only had to give it more than once about four or five times. It is really that effective. It is not perfect at the end of one course but it is controllable by the usual means of topical medications. They are still not perfect. They still have to have some type of treatment. I do not aim for a perfect cure.

DR. ROY: Do you agree with the estimates that of the 65,000 individuals or prescriptions administered only 4000 or 5000 truly are in the subcategory of intractable, refractory cystic acne and, therefore, how can you account for why the Academy is not successful in self-limiting its use?

DR. TURNER: There are a couple of points that we need to talk about. One is that it is very difficult to set up criteria. In fact, we do not have strict criteria for what is severe nodulous cystic acne. The pictures I showed, definitely everyone would agree are nodulous cystic acne. But there are others that are not quite so severe and I think if you just consider the ones that are as severe as this,

maybe that is a correct estimate. But I can tell you there are others who are not quite so severe that would increase this number lo-fold, if not more, but who are also resistant to conventional therapy and when I say conventional, that includes high potency antibiotics for ever. So you are kind of trading a for ever treatment with a four or five-month course of treatment.

DR. MANGANIELLO: Just to follow up on Dr. Roy's question, could you give us specifically what the incidence of severe cystic acne is in the United States?

DR. TURNER: I do not know that anybody can do that. Dr. John Strauss, who has devoted his entire professional life really to acne, has estimated that practicing dermatologists see half to two patients a month who need Accutane, who have severe enough acne to need that. If we have about 6000-6500 practicing dermatologists, that brings the number up to about 36,000-144,000 patients, which really puts us in the ball park of the number of prescriptions that are being written for Accutane.

DR. MANGANIELLO: In he information that was supplied by Roche they had indicated that from 1982-1983, there was a low of 90,000 prescriptions in 1982 to a high of 340,000 in 1983, averaging out over that year of time about a quarter million prescriptions that have been filled for Accutane. With the American population of about 250 million,

that would be 1/1000 people who would be candidates for taking Accutane.

As a gynecologist, I obviously see a different patient population but I would assume that I would be seeing some individuals who had been taken care of by dermatologists at some point in time and I do not think I really see that number of individuals with that specific problem. I realize that the patients whom you see are in need of treatment but I just kind of want to have a better idea of exactly what the scope of the problem is.

DR. TURNER: Well, the way I explain that very big number of prescriptions is that, remember, Accutane was recently introduced and there was this pent up demand for it. You know, all of us had a stable of patients who were waiting to get treated. Accutane had been in use in Europe for years before and we knew about IND studies going on and you can see that it levelled off after that.

Then, again, there was a lot of publicity, both in the scientific press and in the local press, regarding the availability of this cure for cystic acne which brought patients in by droves. I will tell you, I had that experience and it was not easy to take the time to explain everything and make sure that they had had good, conventional therapy before starting them on this medication.

DR. NIEBYL: That brings up an important point

because the dermatologist now finds himself in the role of counseling about contraception in a busy schedule when people are wanting information. Does the dermatologist do the contraception counseling or do you usually insist that a patient go to an obstetrician-gynecologist? For example, is the pregnancy testing done in the dermatologist's office as it is in the obstetrician's office? Patient compliance, if they are sent elsewhere to get a pregnancy test, may not be the same as if it is done on the spot.

DR. TURNER: What we discussed with Roche and what we kind of practice now is that we do send patients for contraceptive counseling to a gynecologist, in addition to our own counseling. The initial pregnancy test is done by the gynecologist and the subsequent pregnancy tests are done by the dermatologist. Personally, I do not write another prescription until I get that test back. I may have been lucky but in all this time I have never had a problem.

DR. NIEBYL: Well, you have been lucky.

DR. MCDONOUGH: You are at a tertiary center. Do you feel that there is any way that the use of this drug could be limited? I mean, it has been limited in other countries. Do you think that is feasible? Is that an option?

DR. TURNER: You know, the question is, is that an option and you would have to say, yes, it is possible that that could be an option. However, it was an IND for a few

years before it was even available to me and you could see that there was this pent up demand because a lot of patients would have had to travel very far and if we want to keep them under such surveillance, seeing them every month, then I think it would make it much more expensive and much more 'difficult.

I personally think that if doctors are not educable, rho else would be? I think if we really made a point of educating physicians, which we are doing right now and have done in the past, but more so right now, then we can, I think, make big inroads into decreasing exposure to this drug.

DR. NIEBYL: But it has been on the market since 1982 as category X. Surely, the doctors would have been educated by now. I guess my worry, if I were a dermatologist and somebody put this huge box of things on my desk and I did not really know that much about contraception, I am not sure that that should be a dermatologist's responsibility. Gynecologists spend a lot of time talking to patients about contraception. They have spent years learning about it. I would wonder if there is an issue in terms of what types of contraceptive failures have occurred. Do you know if it has been compliance in not taking the pill or not using the contraception?

DR. TURNER: I know personally of one failure that

was a birth control pill failure. The patient had taken her pills, or supposedly had, and still had a failure. That was not my own patient.

I agree with you about the contraceptive advice. I do sit down with my patients but I also do send them to gynecologists for contraceptive advice and for the first pregnancy test and then I reinforce that at every visit.

DR. MCDONOUGH: I just wanted to ask one question about treatment. For example, will the oral contraceptives make cystic acne worse or better? That is, would you give Accutane and an oral contraceptive at the same time.

DR. TURNER: My own experience is that it probably has a neutral effect. In the old days when birth control pills had higher proportions of estrogens, they were really terrific for controlling relatively mild to moderate acne. But oral contraceptives that are now available, I find, have a neutral effect on acne and I would not hesitate to give them oral contraceptives at the same time that I have them on Accutane.

DR. HULKA: Other questions? If not, we will go on with Dr. Mary Spraker, also representing the American Academy of Dermatology.

PRESENTATION BY MARY SPRAKER

DR. SPRAKER: Panel members, I speak today as a concerned pediatrician, dermatologist, practicing pediatric

dermatologist, Board member of the Society for Pediatric Dermatologists and chairman of the Academy of Dermatology's tack force on pediatric dermatology.

I feel, as a pediatric dermatologist, because of my double areas of interest, that I understand the issues that pertain both to the fetus and to the patient with acne. To remove Accutane from the market or to severely restrict its distribution, to me, would belittle the suffering that patients have who have this disease.

Acne is not lethal and it is not life-threatening but it does profoundly affect lives. All of us remember friends and acquaintances and patients with severe acne and what it has done to them and continues to do to them throughout their lives.

We no longer see many young patients with severe acne because of Accutane. Accutane's effect on severe acne is truly miraculous. It is a wonder drug for these patients. In one month the patient begins to look better. In a mere 16-20 weeks the patient is markedly improved and 90 percent of patients clear with 1 course of Accutane. So a very small percentage of patients receive an additional course of therapy and this is not done for months later. There is a washout period between courses.

Even more wonderful, most patients remain in remission when the drug is discontinued. We have never had a

drug like this before. There is no patient more gratifying to treat. I can so severely change their lives that patients are always grateful.

Now, it was known at the time the drug was first introduced in the United States that it was a potent teratogen in animals and so it was not to be used in pregnancy. This was emphasized by Roche. When, unfortunately, pregnancies did occur, confirming the human teratogenicity of the drug, we, in dermatology, were certainly made aware of this development.

For example, at our annual meeting, which is attended by 80 percent of all practicing dermatologists, there was great discussion in multiple seminars, fora and symposia about what could be done to prevent these pregnancies.

I have an ethical dilemma when I face a patient with severe cystic acne. What can I do to make sure my female does not become pregnant? I certainly warn her. With the new pregnancy prevention program, Roche pays for a visit to the gynecologist for contraceptive counseling. I repeat the warning of pregnancy at follow-up visits. I emphasize the need for adequate contraception. Is it ethical for me to insist she take oral contraceptives if she insists her current contraception is adequate? Occasional patients have serious complications from contraceptives. Isn't it right

that the patient participate in this decision?

Ironically, Accutane is almost a fertility drug, just the opposite of a contraceptive. Suddenly, a young woman who is physically very unattractive is attractive for the first time in her life, changing her social life drastically, often in a way she is not prepared for.

All drugs have side effects, including lethal side effects. Penicillin and other antibiotics kill. Many other drugs damage the fetus -- Dilantin, alcohol. Our neonatal intensive care unit is currently filled with the infants born to cocaine and crack addicted mothers. Vitamin A is as damaging or more damaging than Accutane, yet, it can be purchased over-the-counter.

The suggestion that Accutane usage should be decreased by 20 percent, I feel is arbitrary and impractical. The drug has never been approved for mild acne. So which of my severely involved patients do I not treat and what do I say to that person?

As Dr. Turner alluded to, Dr. Strauss, who is a past president of the Academy of Dermatology and a noted international authority on acne, has estimated that about 2-5 percent of all women with acne might warrant therapy with Accutane at some time. We do not feel that the only epidemiologic study cited, that estimates a very low incidence of acne, is accurate. There are all kinds of problems with that

particular study that I do not want to take the time to go into. Unfortunately, we do not have good epidemiologic data regarding the true incidence of severe cystic acne.

I will play the devil's advocate and say that if we agree that there are only 2100 cases that warrant therapy, there are 7000 dermatologists in the country. That would imply that each dermatologist sees less than half of a female patient per year warranting therapy. This does not make sense to me. I am at a university teaching center. I only see patients part-time. I do not have a big acne practice because I see a lot of pediatric dermatology patients. Most of the Accutane I think is probably used in the community rather than in a university because that is where the acne patients are concentrated but even I use Accutane for at least 5-8 female patients a year.

If we estimate that the average dermatologist in the United States sees perhaps one-half to two patients per month of childbearing potential who might require Accutane, and this is probably a conservative figure, then between 36,000-144,000 such women might be candidates for Accutane each year. This is not out of line with the 70,000 prescriptions that are currently prescribed.

The regional center idea, to me, is impractical. There are too many patients who would need to travel too far, too often and this does not seem to solve the problem. Even

in the controlled IND setting there were 5 pregnancies in 100 women in one series. Never in the history of drug prescribing has more been done to educate physicians and patients regarding the teratogenicity of a medication.

Because the FDA, Roche and concerned physicians and individuals worked together, we have developed what I think is a wonderful new and creative approach, the pregnancy prevention program. We should not overdo the good we have done and create more problems.

What do I do if Accutane is removed from the market or is severely limited and a patient with severe acne comes to me? Do I say, well, go to Canada or Mexico for therapy? Then when she comes back with the drug, is it ethical for me to do follow-up studies?

As physicians, we can guide our patients but we are not gods or have the power to completely to control them. We should respect the fact that our patients must take some responsibility for their own actions.

DR. HULKA: Are there questions?

DR. MCANARNEY: Dr. Spraker, what percentage of physicians prescribing Accutane are dermatologist and what percentage are primary care physicians?

DR. SPRAKER: I believe the figure is 70 percent. I think Dr. Cunningham, from Roche, will present very accurate data subsequently about that. Any other questions? Yes?

DR. MANGANIELLO: When you speak about severely limiting the access of Accutane to patients to just tertiary care centers, wouldn't it be possible not only to include tertiary care centers but to designated centers with dermatologists or large group practices where there would be a kind of team approach to monitor the use of Accutane?

DR. SPRAKER: With the new pregnancy prevention program you have to sign on the line and check the boxes that your patient qualifies for therapy. If my patient were sent to a center, and I assume our university may very well be such a center, I would be in the same situation but I would have a drawback in that I would not have been the one that had treated that patient all along. So seeing the patient for the first time, I would not have a good feel for what therapy they had been on before. I would not know the patient because I had not followed her for a long time. so I would not have as much rapport. I would not have a good feel for which patient I think is reliable and which patient I do not think would be reliable.

There was a suggestion that ten centers be involved. So if we say that perhaps there are 70,000 patients treated, that is 7000 patients per center.

DR. MANGANIELLO: That is pretty restrictive. You know, I think there could be more than 10 centers in the United States; there could be 50, 100, depending upon what

the needs are. As specialists, we are asked to do what you said is impossible to do all the time. We have patients referred to us. Information is given by referring physicians and we have to more or less decide what treatment is appropriate and what treatment is not, even though we may not have seen the patient, except for one time, while she was being cared for by her primary care physician.

It is not clear to me, if you had geographically located distribution centers, that that would not be an appropriate way of monitoring the use of the drug, not restricting access to the patients. Yes, you would restrict access to certain physicians but I would certainly not want to take care of an oncologic patient; I would not want to do open heart surgery. There are certain restrictions that I think people should more or less abide by. We have our privileges in hospitals restricted all the time.

DR. SPRAKER: Well, first of all, it is a little bit unprecedented to limit a drug like this when you can get vitamin A over the counter. I am more concerned about that. Vitamin A was used instead of Accutane but Accutane is a vitamin A-like drug and it is thought that vitamin A has many side effects, more than Accutane. So I am more concerned about restricting that.

I guess I am not sure I see much advantage in restricting the drug to the centers because I am not sure

that the additional amount of hassle is going to provide much benefit. Even in that controlled IND setting there were 5 pregnancies in 100 women. So there is hard data that that approach did not work in the past.

DR. WENTZ: Vitamin A versus Accutane -- is not Accutane somewhat more potent than vitamin A and would we not, therefore, have seen a remarkable epidemic of birth defects? And is that not something that is perhaps off the subject here? We are talking about Accutane.

DR. SPRAKER: Dr. Cunningham may be able to answer that question more accurately, but vitamin A has more potent side effects, for example, of hepatic toxicity. It was not uncommon years ago that when we used high doses of vitamin A that the patients needed to be hospitalized for hepatitis. Eskimos do not eat polar bear liver because of the vitamin A in it.

So it had a lot of toxicity; it is thought to be a teratogen. It does not work as well in acne. It helps if you use very high doses but it is not nearly as effective. The reason Accutane was developed was to try to discover a drug that worked better, that did not have as much toxicity.

DR. WENTZ: Let's go back to Accutane and responsibility. You made the statement that we are not gods. I think we all agree but I do think that we take responsibility. You have made a very poignant point that you have a close

relationship with your patients; that you have a feel for which patients need Accutane and whose lives will be severely changed -- I think were the words you used.

But I have a difficulty with responsibility when the dermatologist who knows the patient is going to ship the patient off to a gynecologist, who has never seen the patient before, and ask that gynecologist to go through a number of things there in order that the patient be protected from the dermatologist's drug. Do you not think then that there should not be some better arrangement, such that the dermatologist who knows the patient, who has a feel for the patient's quality of life, if you will, should not also have the responsibility of taking the time and, if you will, getting the learning necessary to prevent pregnancy in these patients?

DR. SPRAKER: I think that that is certainly expected of the dermatologist. Indeed, a new layer was added when it was strongly suggested, if we adhere to the pregnancy prevention program, that, in addition to that, we enforce the message by asking our patients to see the gynecologist too. In fact, Roche feels that that is so important that they are willing to reimburse the physician for that visit. I see it more as reinforcement.

You know, we are at a tremendous risk for malpractice when we treat a fertile woman with this drug. All

of us are well aware of that and we are nervous about it. So I do not think that there is a responsible physician who does not take this very seriously when we talk to the patient about the pregnancy issue. What more can we do?

DR. WENTZ: What is your explanation for the 5 pregnancies in the IND study of 100 women?

DR. SPRAKER: I cannot answer that question. I was not involved with that.

DR. HULKA: I think we will have an opportunity to hear from the sponsor on that.

I would like to close this open part of the meeting today unless someone else wishes to speak. But before we go on to our formal agenda, I would just like to ask if there is anyone from the FDA, specifically Dr. Troendle, who is here representing Dr. Sobel, or Dr. Bilstad or Dr. Peck, who would like to make any comment before we go ahead with the formal presentations.

(Drs. Troendle, Bilstad and Peck shake their heads)

There are no comments at this point in time. I would also like to mention to the Committee that we do have a discussion time set up at the end of the Accutane presentations. We have no formal questions and answers but we will go around and ask each of you to present what is your thinking about the prescribing and use of Accutane, just so that we have that for the record. Dr. Corfman has told me

that we may in the future have an opportunity for a longer and more formal discussion of this whole topic. But for today, we will each give our comments.

Now we will go ahead with Dr. Ridgely Bennett, from the FDA, who will tell us about the use of Accutane by women of reproductive age.

PRESENTATION BY RIDGELY C. BENNETT, Jr.

DR. BENNETT: This briefing on the use of Accutane, an established teratogen, is provided in order to inform the Fertility and Maternal Health Drugs Advisory Committee of current FDA policies regarding this drug.

These policies are aimed at significantly reducing the possibility of pregnancy occurring in women of reproductive age while they must take the drug. Accutane is indicated for the treatment of severe, recalcitrant cystic acne and a single course of therapy for 15-20 weeks has been shown to result in complete and prolonged remission of disease in many patients.

Because of significant adverse effects associated with its use, Accutane should be reserved for patients with severe cystic acne who are unresponsive to conventional therapy, including antibiotics.

The current physician's package insert for Accutane contains a boxed contraindication and warning section at the very beginning of the insert, in large, bold type, which

states that Accutane must not be used by females who are pregnant or who may become pregnant while undergoing treatment. There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking Accutane in any amount, even for short periods. Potentially, all exposed fetuses can be affected.

Accutane is contraindicated in women of childbearing potential unless the patient meets all of the following conditions:

One, she has severe, disfiguring cystic acne that is recalcitrant to standard therapies.

Two, she is reliable in understanding and carrying out instructions.

Three, she is capable of complying with the mandatory contraceptive measures.

Four, she has received both oral and written warnings of the hazards of taking Accutane during pregnancy and the risk of possible contraception failure, and has acknowledged her understanding of these warnings in writing.

Five, she has had a negative serum pregnancy test within two weeks prior to beginning therapy. It is also recommended that pregnancy testing and contraception counseling be repeated on a monthly basis.

Six, she will begin therapy only on the second or third day of the next normal menstrual period.

Major human fetal abnormalities related to Accutane administration have been documented, including hydrocephalus, microcephalus, abnormalities of the external ear, such as micropinna, and small or absent auditory canals, microphthalmia, cardiovascular abnormalities, facial dysmorphia, thymus gland abnormalities, parathyroid hormone deficiency and cerebellar malformation. There is also an increased risk of spontaneous abortions.

Effective contraception must be used for at least one month before beginning Accutane therapy, during therapy and for one month following discontinuation of therapy. It is recommended that two reliable forms of contraception be used simultaneously unless abstinence is the chosen method. If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy.

Accutane should be prescribed only by physicians who have special competence in the diagnosis and treatment of severe, recalcitrant cystic acne or experience in the use of systemic retinoids and understand the risk of teratogenicity if Accutane is used during pregnancy.

Similar contraindication and warning statements appear also in the current patient brochure for Accutane. I will give you a brief chronology regarding Accutane from the time of its initial approval, in 1982, until March of 1988.

Dr. Evans, who will follow me, will then bring you up to date regarding more recent events.

In January of 1982, the Dermatologic Drugs Advisory Committee recommended approval of the Accutane new drug application. In April of 1982, the package insert was reviewed by the Dermatologic Drugs Advisory Committee. Teratogenic effects occurring in animals were known and stated. A paragraph cautioning against use during pregnancy was included.

In August of 1982, an FDA Drug Bulletin announced FDA's approval of Accutane and discussed its contraindication during pregnancy. In September of 1982, Hoffmann-La Roche introduced Accutane into the marketplace with a warning in the package insert that it had caused birth defects in animals and that pregnant women should not use the drug.

In July of 1983, Roche sent letters to half a million physicians and pharmacists informing them of the first reported cases of human birth defects. In August of 1983, Roche sent letters to half a million physicians and pharmacists regarding a revised package insert reflecting new clinical information, and sent pregnancy warning stickers to pharmacists for placement on patients' prescription bottles that warned pregnant women not to take the drug.

In September of 1983, FDA provided background information for use by the media to inform the public and

reinforce the birth defect potential of Accutane, with appropriate warnings against its use by pregnant women. In October of 1983, the Dermatologic Drugs Advisory Committee heard a citizen's petition by Public Citizen Research Group, a consumer activist group, advocating mandatory patient package inserts. The Dermatologic Drugs Advisory Committee recommended stronger warnings about teratogenicity in both physician and patient package inserts.

In November of 1983, an FDA Drug Bulletin reported the occurrence of major human birth defects with the use of Accutane and again warned against use of Accutane in pregnancy. In January, 1984, pregnancy warnings in the package insert were changed to boldface type and the occurrence of human birth defects was added.

In 1984, Roche sent letters to physicians and pharmacists about additional clinical and safety information and included a revised patient brochure. Also in March of 1984, an FDA press release announced the additional birth defect warnings and alerted blood banks not to accept blood from Accutane users. In April of 1984, Roche sent letters to physicians and pharmacists about a new trade package that incorporates patient information literature and pregnancy warning labels.

In May of 1984, Roche made a presentation to the Dermatologic Drugs Advisory Committee reporting 20 cases of

birth defects associated with the use of Accutane and revising the package insert appropriately. In August of 1984, another FDA Drug Bulletin updated the birth defect reports and discussed the latest changes in the package insert.

In October of 1984, Hoffmann-La Roche sent physicians and pharmacists new clinical and safety information that had been added to the package insert and patient brochure. In November of 1984, the Dermatologic Drugs Advisory Committee was brought up to date about adverse events. Further revisions to the physician package insert and patient brochure were discussed. In December of 1984, Roche placed advertisements in JAMA and the Archives of Dermatology providing guidelines for use of Accutane in females.

In June of 1985, another mailing was sent by Roche to physicians and pharmacists about the most recent revisions of the package insert and patient brochure. The package insert placed the use and pregnancy contraindication in a prominent box and strongly recommended the use of contraception and pregnancy testing.

In August of 1985, another FDA Drug Bulletin was distributed to all health professionals regarding the package insert revisions for Accutane. In October of 1985, two articles were published in The New England Journal of

Medicine discussing the use of Accutane and the occurrence of birth defects, based on reports to Hoffmann-La Roche and the FDA. In June of 1986, Hoffmann-La Roche mailed physicians and pharmacists the most recent revisions to the package insert for Accutane. In June of 1987, the most current package insert was distributed.

In February of 1988, FDA and CDC staff notified the FDA Commissioner of their concern about the number of cases of Accutane-induced birth defects. In March of 1988, FDA issued a "Talk Paper" about four new cases of serious birth defects associated with Accutane and announced an upcoming Dermatologic Drugs Advisory Committee hearing on Accutane, to be held in April of 1988.

Dr. Carnot Evans, group leader of the Dermatology Section of our Division of Anti-Infective Drugs, will now continue the briefing.

DR. CORFMAN: Before Dr. Evans begins, I would like to point out to the Committee that Dr. Bennett attended the Dermatologic Drugs Advisory Committee meeting for the Committee. Some of you were asked if you could make it and none of you could, including the Chair. So he is really representing your interests and he and Dr. Evans are here to update you on the status of the "Accutane campaign".

PRESENTATION BY C. CARNOT EVANS, Jr.

DR. EVANS: Dr. Bennett has given you a chronology

of some of the aspects of Accutane which, of course, is a drug which has had considerable oversight and regulation over the past ten years.

As you are aware, an IND was submitted ten years ago and many of us in the Agency, as well as the Roche Company, have lived with this drug for this period of time. It has posed a serious and complicated problem for us.

In February of 1988, which is one year ago, something happened which had a major impact on our oversight in the Food and Drug Administration. A position paper was prepared by the members of the Division of Epidemiology and Biostatistics of the Food and Drug Administration, which was a lengthy, involved document.

It concluded, number one, that Accutane is, indeed, over-prescribed; number two, that pregnancies in Accutane-treated females were continuing; three, that severe birth defects (62 had been reported at that time) were continuing to be reported; finally, that the regulatory interventions by FDA at that point, and in their view, had not had a substantive effect.

This had a major impact on us at the Agency, as you can imagine, and we had several in-house meetings to address these points. It was decided, after a number of conferences, that we would tighten up our interventions and that we would present the problems to the Dermatologic Drugs Advisory

Committee, which was to convene three months hence.

When the advisory committee met we had several questions to pose for them, the most important of which I will give you: The first one was, should Accutane be removed from the marketplace? The unanimous opinion was that, no, it should not. It was felt that the benefits outweighed the risks and, in addition to that, there was no reason that male patients who would not be the subject of fetal toxicity should be deprived of this product.

I might also say that there was also the consideration of vitamin A, which is available over-the-counter and which is a known fetal toxic agent in high amounts, and which has also been reported and, in fact, is in the literature as being effective in very high doses in the treatment of severe cystic acne.

The second question that was posed to the advisory committee was is there some way that we can label this drug so that we can get reasonable interventions? One of these was that possibly we could label the drug that it should not be used at all in women of childbearing age. This would have the beneficial effect of leaving it on the market but it would also make physicians who prescribe it very well concerned about who they gave it to since it was "contraindicated in women of childbearing years." Of course, this would mean that it would be available to postmenopausal

women, as well as male patients.

The Committee rejected this for several reasons. They felt that this was not the appropriate way to address the problem. Instead, they recommended several things: They recommended that we should consider informed consent prior to using Accutane. They recommended changes in the labeling and there was a suggestion that maybe a picture of a malformed child would have a severe enough impact so that the product would not be used as often as it had been in the past. It should be labeled to indicate that only physicians with special competence in the use of the drug should have available Accutane for use. It was indicated that we should give consideration to some type of limited distribution.

What has the Food and Drug Administration done since that time? The first thing that was done is that we formed an Accutane monitoring group, which is very similar to the AZT monitoring group that we have had in place for some time. This is an inter-office coordinating body to look over the details on a regular basis with the Roche Company, as well as others, to make sure we have adequate oversight.

We are now requiring Roche to give quarterly reports on adverse effects and pregnancy exposures; the amounts of drug that are manufactured and drug use data; and advertising and educational programs.

We have also been active in assisting Roche in the

development of labeling, their pregnancy prevention kit, blister pack and epidemiological surveys that we will hear about later.

The physician labeling has been updated with a number of things, as Dr. Bennett mentioned and which I will not repeat.

You are aware that Accutane has a category X label, meaning that the drug is known to cause birth defects. We are also requiring that the non-pregnancy symbol appear prominently on the beginning of the label, as well as in the PDR. This, of course, is a silhouette of a pregnant patient with the red circle and the cross, which means "do not use."

The goals of these activities are to, number one, reduce prescribing; two, eliminate pregnancy exposure with Accutane use; eliminate birth defects and eliminate the need for abortion.

You heard from representatives of various groups who were interested in giving you their views on what we should do in the oversight of Accutane. One that gave views, not represented today, was the American Academy of Pediatrics. They recommended that Accutane prescribing not be limited to any specialty or subspecialty groups. They recommended that the American Academy of Pediatrics'implement an effective educational program on risks and benefits of Accutane. They recommended that the American Academy of Pediatrics urge the

AAD and the AAP Section on Dermatology to conduct a study to determine the incidence of severe cystic acne; they urged the FDA to evaluate more effective means of contraception for females using Accutane and they urged the FDA to strongly establish a standing committee to closely monitor and advise on drugs that are potential teratogens, and that the task force reconvene in one year to reevaluate the changes in patient tracking and results. If the new prescriptions to females have not been reduced by 20 percent, the American Academy of Pediatrics should entertain recommending that FDA devise a more restrictive scheme for Accutane prescribing.

I think we all recognize that there has been insufficient time to determine the effects of the interventions that we have imposed. While we have not asked specific questions of you, we would appreciate constructive comments and we hope that together we will be able to get a reasonable solution to this vexing problem. Thank you.

DR. HULKA: Are there questions?

DR. MCKAY: You mentioned earlier in your presentation that Accutane should be available for male patients regardless. Is there any evidence whatsoever that Accutane could affect spermatogenesis?

DR. EVANS: There is evidence that it does not.

DR. HULKA: Further questions?

DR. ROY: Do you think that since September of

1988, when the pregnancy prevention program was launched -- we have no data whatsoever to have any feel for whether it is working or not? Do you think it is just too early?

DR. EVANS: The answer is that it is too early. There are differences of opinion and you will hear later in the program from some of those folks who have the hard data.

DR. HULKA: I suggest that we go on to the sponsor, the representative from Hoffmann-La Roche. This is Dr. William Cunningham.

PRESENTATION BY WILLIAM CUNNINGHAM

DR. CUNNINGHAM: Good morning. Madam Chairman, members of the Advisory Committee, ladies and gentlemen, I am William Cunningham and I am the director of medical affairs at Roche Dermatologics, which is a subsidiary of Hoffmann-La Roche. Thank you for the invitation to be here today. I will limit my comments to 30 minutes as we earlier agreed.

I would also like to introduce in a few moments Dr. Alan Shalita, who will give you some information about the medical aspects of Accutane, further amplifying the comments of Dr. Turner and Dr. Spraker.

(Slide)

This is about the fifth time that I have stood in front of a committee such as this, either the Dermatologic Advisory Committee or this one and, of course, we have had a lot of interaction on the subject of Accutane, as Dr. Carnot

Evans mentioned, over the past several years. It is a concerted effort that we would like to present today. We have had interaction and taken comments from many of the groups who have already spoken today.

Our goal at the Company is to reduce the risk of malformations. We feel that human malformations is the central issues. We do feel that we are seeing some progress, however, in the other areas. We do see some downward trends in usage. In fact, even in early 1989 we see some decrease in the number of users. We have a lot of prescribers out there who are just plain not interested or too afraid to prescribe the drug, which raises some other questions. But, in fact, I think we are seeing both anecdotally and in fact some decrease in usage of the drug.

Of course, we share your concern about the seriousness of the malformations and we have made every attempt to examine every strategy and every solution that has been proposed, no matter where it came from, very carefully. So we feel we have tried to keep as open an attitude as possible about what can be done about this situation.

The pregnancy prevention program was initially launched in September of last year. It has come out in parts and the most recent addition has been the blister package, which was only launched a few weeks ago. We discussed this, of course, back in April of 1988 and it was implemented along

the way as we have had the approvals and ability to produce blister packages, for example, and we do feel, as Dr. Evans has mentioned, that it needs some time to make its full impact.

(Slide)

Now I would like to go to today's agenda and I have asked Dr. Shalita to address the medical role and we will be giving you some status reports on the pregnancy prevention program, its implementation and its effects; the epidemiology of both the pregnancies and usage of the drug; the next steps which we feel will be coming in the next few months in terms of the impact of the follow-up survey and the impact of our other activities.

But first I would like to ask Dr. Shalita to give you a little bit of evidence on the medical utility of this unique drug. Dr. Shalita is Professor and Chairman at the State University of New York, the Department of Dermatology.

PRESENTATION BY ALAN SBALITA

DR. SHALITA: Thank you, Dr. Cunningham. Madam Chairman, members of the Committee, although I have been asked to speak to you on behalf of the sponsor, I could just as easily be here on behalf of the American Academy of Dermatology, where I serve as the chairman of the retinoid committee and the council on communications. I am also secretary of Professors of Dermatology and have served on the

residency review committee and various other national committees for organized dermatology. I am one of the original investigators of this drug, as many other acne drugs, because I have devoted my investigative career to the study of the pathogenesis and treatment of acne.

I would like to give you a little bit of perspective about cystic acne and perhaps correct some information about the statistics of what this disease represents.

(Slide)

First of all, I think that it might be useful to you to have some understanding of the factors that are involved with the pathogenesis of the disease and how one can influence that with the various categories of drugs that are available to us.

I think the prime defect in acne is that at puberty there is an androgen-modulated increase in the sebaceous secretion, which gives you an increase in sebum production. That could be inhibited by oral estrogens in the past which counteract the effect of androgens and, in some cases, low doses of steroids to inhibit adrenal androgen. But also this is profoundly affected by isotretinoin.

There is a proliferation of follicular microflora, principally an organism known as Propionibacterium acnes, which can be affected by broad spectrum antibiotics, all of which are bacteriostatic rather than bacteriocidal, and can

be affected by some topical drugs. The population of this organism is dramatically decreased, if not totally wiped out, by oral isotretinoin because this organism is lipophilic and the lipid environment created by sebum is diminished so that this organism can no longer survive.

There is an abnormality of keratinization of the follicular wall which is only affected, among oral drugs, by oral isotretinoin. It is also affected by topical tretinoin. Finally, there is a marked inflammatory response in the more severe forms of the disease, which could be modified by relatively high doses of oral glucocorticoids, by sulfones and by isotretinoin.

I think it is fairly evident from this chart that the only orally administered drug that affects all four major parts of the pathogenic pathway is oral isotretinoin.

(Slide)

I thought I would give you a quick picture of the spectrum of disease that cystic acne represents. I think some people think that cystic acne is only on the face. This is cystic acne in a different form. These are all lesions which more than meet the criteria of 4 mm or larger, combined with other lesions, which are also quite disfiguring. These numerous milia-like lesions are common in a mature, adult woman.

(Slide)

This is a rosacea form of cystic acne. This woman also had large nodules and cysts on her back and chest.

(Slide)

Here is a young woman whose cystic acne was induced by external agents, the use of hair pomades.

(Slide)

Here is another form of cystic acne in a younger adult woman. You can see this very large nodule here and one adjacent to it, and a preponderance of lesions on the chin and the long angle of the mandible.

(Slide)

This was one of the patients from our original study with severe nodulous cystic acne of the face. The economic and emotional impact is best illustrated by this patient, who was an aspiring actress and was unable to even obtain work as a waitress in a restaurant because of this disfiguring disease. She cleared completely is now in the road company of a major Broadway production.

(Slide)

This is just a side profile showing the kind of scarring that results. This is the same patient.

(Slide)

Obviously, this is a disease that affects males as well. I was emphasizing the female patient because of our concern this morning.

(Slide)

The actual statistics that we have been able to gather from a survey done among professors of dermatology in the country is akin to what Dr. Bennett told you before. An average of one new patient per month per dermatologist in this country would give you somewhere in the neighborhood of 80,000 new cases of nodulous cystic acne in women per year.

This is cystic acne with sinus track formation. What happens is that the two inflammatory lesions that you see here merge beneath the surface of the skin by a sinus track and these lesions keep filling up with purulent exudate and are very difficult to treat.

(Slide)

This is an example of the kind of ice pick, pitted scarring that can result from severe inflammatory forms of the disease even when it is non-cystic.

(Slide)

And to demonstrate that this disease also affects the trunk, as well as the face, here you have numerous cystic lesions on the back and shoulders.

(Slide)

This is just a closeup of one side.

(Slide)

Here is a more extensive case in another patient with severe scarring.

(Slide)

This is the kind of ulcerative necrotic debris that can occur over these lesions, with secondary infection frequently being common and resulting in very severe, pronounced scars.

(Slide)

This is acne keloidis, limited primarily to our black patients but fairly common, with severe hypotrophic scarring.

(Slide)

Finally, not to belabor the point but I will show you just a before and after photograph to demonstrate the efficacy in the disease of severe nodulous acne.

I would like to conclude by a very brief anecdote. Last year I was interviewed on Cable News Network about acne in adult women in general and asked to review a whole series of treatments that are available. We were talking mostly about oral contraceptives and hormonal problems in adult women. Dr. Sonia Freedman interviewed me, who is a very astute interviewer and physician.

At the very end, after having gone through all of the therapies, I mentioned that when all else fails one can use Accutane but that it has severe side effects, including birth defects. I was interrupted by the interviewer. She said, yes, doctor, we have many drugs that have severe side

ffects. It is our responsibility to become more educated onsumers. Thank you for your attention.

PRESENTATION BY WILLIAM CUNNINGHAM

(Slide)

DR. CUNNINGHAM: I will skip through some of the lides in the interest of brevity, but I will give you what ur objectives have been for the last year.

Our goals in 1988 were to limit the use of this drug o the severest types of acne; to exclude pregnancy by pre- reatment pregnancy testing and pregnancy testing throughout herapy and through ensuring contraception. We feel this is he major part of our pregnancy prevention program.

(Slide)

Since April of 1988, we have revised the package nsert extensively. The pregnancy prevention program was egun to be launched in September of last year. The blister ackaging was launched early this month. Extensive communi- ations have been had with the dermatologists and the rest of he medical community and with multiple organizations hroughout the year and we have had extensive interactions rith other organizations nearly on a daily basis.

(Slide)

The program is essentially in three parts. One is he package insert revision. The second is the pregnancy revention kit that you see in front of you. I would

encourage you to look through that to see some of the components of it because I am not going to dwell on any one of the forms. The third part is the blister packaging, which we feel is the final approach to the patient.

(Slide)

The "avoid pregnancy" symbol is throughout our pregnancy prevention program and throughout the patient brochure and throughout the kit. The package insert revision was mentioned before by Dr. Bennett. The size is much increased over the past one. It is essentially double size print. Warning of fetal risk is reemphasized. You cannot read this on the slide but you can if you look in the pregnancy kit in front of you.

For example, six criteria must be met. The patient must have the severe disease. They must be capable of understanding the treatment and capable of signing a written consent form. Many aspects of this, we feel, were ground-breaking in terms of other drugs and we feel are rather innovative and we continue to look to other possibilities. So essentially the drug is contraindicated in females unless each of these criteria are met.

(Slide)

Abstinence or two forms of contraception are recommended. We talked about that earlier. I need not dwell on it. We emphasize strict contraception with the use of

this drug.

(Slide)

Only experienced practitioners should use the drug. We have felt that in some cases, family practitioners, in areas where dermatologists are not available, could use this drug. We do not promote to them specifically but we feel we do have to inform them that they should be experienced in the use of retinoids. This is a prerequisite for the use of this drug.

(Slide)

The consent form is part of the package insert. It is attached to it. It will appear in the PDR. If you do not have one in the kit, you can take it out of the PDR and xerox it and have the patient sign it. There are ten specific places the patient must initial and then sign and the physician must sign it, put a copy in the chart and the patient takes one as well. So we have really tried to tie up the legal aspects of this.

(Slide)

In summary, the "avoid pregnancy" symbol appears throughout the patient and physician material. The contra-indication and warning is very large. It is very clear. It underscores the fetal risk aspects many times. It contra-indicates the drug in fertile females unless all six specific criteria are met, and recommends two forms of contraception

and use by experienced practitioners, and incorporates a consent form. It is quite an extensive package insert.

The revision was communicated, shortly after its approval in August, to all the dermatologists in the country on September 2 and all of the physicians, over half a million, on September 9. We have done this as a matter of routine every time we have had new information on the product. We routinely send that information at least to all the dermatologists and, where applicable, to all the physicians in the country.

(Slide)

The kit is in front of you. There are a couple of copies on the table and we have another one in the back. It is a rather extensive program.

(Slide)

It has multiple components, the first being the patient qualification checklist. The patient must meet all of these criteria and the physician should go down this list with each patient or, otherwise, not prescribe the drug for that particular patient.

(Slide)

The patient brochure has been updated and, again, it is in the kit. It is rather extensive. It has been revised multiple times in the past several years as we have learned about the risk of fetal malformations and about other

side effects.

(Slide)

We have English and Spanish patient information in the kit and, as well, we have an 800 number both in English and in Spanish. So anybody who does not get the information clearly enough from their physician could get it through the 800 number and we have other provisions, as necessary, for the patient to get as much information as they need.

(Slide)

Contraceptive information is included in the pregnancy prevention kit. We agree with the suggestion that dermatologists should be familiar with this. I think it is mandatory, in fact, that the dermatologists understand this. We have an optional program, which I will mention in a moment, where obstetrician or family practitioner consultation could be obtained. That is another ancillary way the patient could get adequate contraception information.

(Slide)

The contraception referral program I referred to just now is a voluntary program. We have felt that this is a very good option for patients who need additional information or in situations where the dermatologist does not feel they can adequately inform the patient on contraceptive use. Roche will pay for the initial pregnancy test and the contraceptive referral when performed by a family practitioner

on contraceptive counselor of the OB/GYN type. We feel that this is an ancillary part of the program and we do feel, of course, that the dermatologists should be very familiar with contraceptive information.

(Slide)

A patient self-evaluation test is included. The patient is supposed to take this test. If they fail even one of the questions and the physician sees that, he is not supposed to put the patient on the drug. We emphasize that every single criterion must be met and every single exam question answered correctly, otherwise the patient should not get the drug.

(Slide)

The consent form, as I mentioned before, has about 10 or 11 places for the patient to initial. If they sign this, they have, obviously, complete information about the drug, about its side effects, about the risk of malformations and about the appropriate use of contraception. Otherwise, the physicians place themselves at great legal liability when they use this product. I might add that they probably place themselves at great legal liability if they do not use this product under certain circumstances. That is how restrictive our program has become. The consent form also includes a third sheet which is a possible sign-up for the possible survey, which I will mention in a moment.

(Slide)

So in summary, the kit includes all of those forms. I will not go into them again, in the interest of time, but they are in the kit. We feel that it is a rather innovative program. We would like to keep our options open in that regard. If you have some specific suggestions for improvement, we would like very much to hear those.

(Slide)

The prevention kit was launched to all the dermatologists, starting around September. In February and March, when we polled the dermatologic community, as we have been doing at regular intervals, we found that 95 percent of the dermatologists have received the kit. Of those who have it, 55 percent have used one or more components in the last couple of months.

Why didn't everybody use it? Interestingly enough, some evaluate the patients with the kit or without it and they do not have occasion to use the product. So 36 percent actually have not evaluated patients. I think we are seen anecdotally as well a great hesitancy on the part of many dermatologists to use the product.

(Slide)

When the patient is evaluated using the kit, interestingly enough, 22 percent of the patients do not get the drug. So we think that we have, in fact, cut down some

of the prescribing by the use of the kit at the very beginning of the program.

(Slide)

The blister packaging was introduced in early May. We have already had some positive feedback on that. I have one in front of me and you have a couple at the table. It opens with some difficulty. It is child-resistant and it has taken us some time to get over that hurdle. I must say that we have incorporated just about everything we can think of in this, including all of the patient information that they need; the highlighting in red and with pregnancy symbols throughout. I think it is quite dramatic. Even from the back of the room you can see the kind of kit we are talking about here.

This is the only way the drug is available now when the existing supplies run out. We have had some technical difficulties getting this made because of the heat-sensitive capsules. But it is out now and your patients are going to start getting this. Eventually this will be the only way a patient can get this drug.

It has the line drawing of the malformation. It has extensive warnings in red about the risk of fetal malformations. Every time you take one of the capsules you have to press it through one of these "avoid pregnancy" symbols. Again, if you have some suggestions on this for

something more to be done, we would like to hear them. But I think we have just about covered all the bases.

Inside, folded up in it, is an enrollment form for the follow-up survey. So if the physician does not enroll the patient in the follow-up survey, we hope that the patients will enroll themselves. In fact, we are finding out that a substantial number are self-enrolling since the blister pack has been available.

(Slide)

I have already shown you some of these features. As I mentioned, the patient information is integral to the packaging. There is no way you can get this drug without this package. It tells you everything you need to know, including all the avoid pregnancy information.

(Slide)

The pregnancy warnings in red are throughout.

(Slide)

The pregnancy symbols, as I mentioned, are throughout, as well as on the back of the blisters so that you cannot get a capsule without seeing that.

(Slide)

And the line drawing of the malformations can be seen. I would be glad to pass this around to the audience too if they would like to see it.

(Slide)

The enrollment form for the follow-up survey is included. With that, I think we have come about full circle in terms of what we think we can do as a final step to intervene in the patient receiving the drug. Hopefully, they do get complete information from the physician but if they do not, for some reason, we think that when they receive this package from the pharmacist, this will make a substantial impression.

(Slide)

In terms of communication, I will not belabor it except to say that we have followed up extensively with our dermatologic and other colleagues on all the problems associated with the malformations.

(Slide)

We have extensive professional representation in the field. We have made a total of over 20,000 visits now to all of the dermatologic prescribers and those prescribers of Accutane whom we have identified as being substantial prescribers. We have sent letters to every physician asking them if they prescribe Accutane. If they do, we then visit them. If they do not prescribe Accutane, we do not detail them; we do not advertise to them. We do not want the product used outside experienced practitioners. But we do visit them if they do use the product. As you see, we have had extensive representation. Most of these visits were in

September and October. For example, over 10,000 were to detail the pregnancy prevention program kit. So the kit was gone through in detail with the physician prescriber.

(Slide)

We have presented this issue many times. I, myself, am asked to comment on this all around the world. The American Academy of Dermatology has been very supportive on this in inviting us and having their own members present the issue of teratogenicity as the important aspect of Accutane. I might emphasize that the conference on retinoids and teratogenesis was a major conference sponsored by Roche, held last month in Westchester, with representatives from all around the world talking about the very basic aspects of teratogenicity and its prevention. We are very interested in the research aspect of this.

(Slide)

This is not the usual ad that one would see in a medical journal but this is the way we advertise Accutane now in terms of its problems. We do not emphasize efficacy; we hit them with the problems that they are going to encounter. Here again, this is for the dermatologists who see the pregnancy prevention symbol and the problematic nature of prescribing is emphasized.

(Slide)

This appeared in the dermatologic literature, as

cited here.

(Slide)

To the family practitioner and the general audience, I do not think one can be more dramatic in terms of what this drug is, that is, it is contraindicated in females.

(Slide)

This is the ad that is run in the following journals, The American Medical News, the AMA, Family Practice News, etc. This is the kind of advertising that we are doing, solely this kind of advertising.

(Slide)

We have had, as I mentioned, extensive interactions with the American Academy of Dermatology and the pediatric groups , the obstetricians and gynecologists, the professional pharmacy associations and, of course, we have had extensive interaction with the Slone Epidemiology Unit to develop this follow-up survey.

(Slide)

I realize there are some aspects to this that are not completely agreed upon but we feel that we live in the real world and that we have to face the situation as it is now and deal with what we can right now. So we have introduced this follow-up survey.

(Slide)

In terms of patients, we feel that the trend is

downward. Here is a graph of usage of the drug in new female patients, starting in 1985 when the latest peak occurred. There is a 29 percent decrease, based on PDS data sources, until 1988. I would like to tell you what happened in 1988 and 1989, and the trends are downward as well. Our factory units are down compared to previous years and, in fact, recent PDS data analysis for the first quarter in 1989 showed data that showed a decrease in usage compared to the first quarter of 1988.

Interestingly enough, it changed in the male-female ratio. In the past the ratio has been about SO-50 and in the latest survey of PDS it was 59-41, something of that order. So that is 60-40. That is admittedly soft data. I do not pretend to stand here and defend this epidemiologically. That is not our goal. Our goal is to look at the general trend and we feel that that is downward.

(Slide)

In terms of the pregnancies, I think you have this information in your submission, the total number of malformations is 76. We feel that these numbers are closer to reality than the other estimates. I have personally testified in at least half a dozen lawsuits. We have over a dozen lawsuits pending on this very issue in the Company. The American Bar Association has made this the "hit" drug. I think if we had 1000 malformations, the lawyers would let us

know about this and I do not agree with the estimates of 1000 such malformations. This is a drug where reporting is quite substantial. We have an increase in reporting of adverse reactions with this drug over 1985 data. So we have a constant level of reports of adverse reactions and the malformation rate, although it is not at zero, is substantially lower than it was 1983 when we had 25 malformations reported; or 1984 when we had 14. In 1988 (sic), as of April 30th, we had 2. Admittedly, there is a lag period. We do not pretend to be at our goal yet. We think we are going toward that goal and we are not there yet.

The bottom line of the total number of pregnancies I think is also possibly downward but, again, I agree with the critics who say that this is not complete information. This is a spontaneous reporting system. We do not pretend to have absolutely complete data. But given the focus on this drug, we do feel that these numbers are closer --

DR. CORFMAN: Can you elaborate on the elective abortion rate?

DR. CUNNINGHAM: I think I would say again the same on that, that the elective abortion rate, in fact, is not different from the general population. It is not above the general population. In fact, most of our data indicate that we have less of a problem of pregnancy abortions, etc., with this drug than in the general population. But I do not say

that this number is the absolute number. That is clearly an estimate and elective abortions are not completely reported to us, nor are all pregnancies. But we do feel malformations are much more complete in their presentation to us.

(Slide)

I will briefly go through the survey, essentially just to focus on the fact that we have a voluntary survey. We recognize the possibility for bias in that but we feel it is the best we can do for the present time in a pilot way to see if we can start to get a handle on these numbers.

We are going to look at the pregnancy rate and awareness of the teratogenic risk, etc., and pregnancy outcomes in the survey.

(Slide)

I will show you schematically how the patient can get enrolled. They can either become informed of the survey through their physician and, hopefully, they will do that. Of through this blister pack they can self-enroll.

Once they are enrolled, they receive a one time fee of $10 for doing that. They are then followed up either with a telephone or a mail contact throughout the total follow-up period, which is a total of 11 months. We have tacked on those additional months so that we can see what happens after the drug is discontinued but we realize it is a voluntary survey.

(Slide)

This is our enrollment at the moment. We have steadily crept upwards and the enrollment has substantially changed in terms of its composition since the blister pack introduction a month ago. So we do feel that that last part of our program has started to have some effect and we are finding that approximately 30-40 percent of the enrollment now is through the blister package.

(Slide)

In terms of next steps, I will take about two more minutes to summarize and give you what we feel the next steps will be. The blister packaging has just been there a month. So we think it is going to take some time to make its full impact but it is starting to have an impact through the parameters that we have been able to look at.

The Slone follow-up study -- remember, this is kind of a unique study. We just started it a few months ago. It got off to a somewhat rocky start with controversy. So it is not exactly the way we would have liked to have gone but, again, we are trying to deal with the real world situation here and we do feel that the impact will come later.

We have an extensive CME program which we have started to implement, which will be continuing with the American Academy of Dermatology endorsement, as well as all of the other communications which you see. We will continue

to mail to everyone and advertise very specifically on the issue of contraindications. We have extensive pharmacy interactions ongoing at the moment. We will be continuing to present these aspects of Accutane to the practicing physicians through our professional representatives.

I think you should also know that when the professional representative calls on a physician, they are instructed to emphasize the pregnancy prevention aspect of Accutane, not the efficacy. We do not need to sell efficacy with this drug. That is clearly not what we are doing at the moment either.

I would say, in summary, that we intend to monitor the situation and revise this program as necessary. I think that we have implemented something that is doable, that we can live with, that we can hopefully make a significant impact with. But we would like to take your suggestions seriously and implement them where practical.

We would also emphasize that we have what we feel 'is a model example of cooperation with the Food and Drug 'Administration. We have not always agreed on some specific points. We have talked about those points and we have tried to find a solution to the problem.

So in summary, I think that we have a situation where we are approaching our goal of reducing the risk of malformations to the minimum. We are showing a substantial

decrease in usage of the drug, which is a hopeful sign. We feel we are approaching our goal with a very innovative and creative and, where necessary, to be revised pregnancy prevention program. Thank you.

DR. HULKA: Questions?

DR. MCKAY: I notice that you do not have any communications, at least formally, with the American College of Nurse Midwives. Would not low income women perhaps be more likely to be seeking nurse midwifery care and family planning clinics? What kind of information is disseminated to them?

DR. CUNNINGHAM: I think that is a good suggestion. At the present time, we are looking at the Dermatologic Nurses Association, for example, as a start. We have learned a lot as we have gone on with this. First of all, we have learned that it is not always the physician who counsels the patient; it is frequently a nurse. In this situation it is perhaps a midwife. So we will be looking at all of those options, yes.

DR. WENTZ: Would you provide us information about the pregnancies? I would be particularly interested in the age of the patient; whether this was method or user failure. What types of things have you collected that you can tell us?

DR. CUNNINGHAM: I think I would summarize by saying that the situation, as we see it here, parallels the

general situation in the United States population. That is, pregnancies occur. They are unwanted. Sometimes they are the result of not using adequate contraception. Sometimes they are the result of not knowing what contraception means. Sometimes they are the result of method failure and sometimes, in this situation, they are the result of starting the drug before the pregnancy test is obtained or about a third of the patients historically with this have been pregnant at the time of initiation of therapy. So we think that the mandatory pregnancy testing at the beginning, with meticulous history taking, etc., is very important.

I think the point that Dr. Spraker made on this is important to emphasize in this regard. I have had a lot of concern about this drug going into a regional distribution system, for example, to regional centers because, in my experience and I practice dermatology every week in New York, when you do not have a patient's confidence you really cannot guarantee -- well, you can never guarantee completely but you really cannot have a good sense if they are going to go home with your message. If they come across the State of Iowa, I doubt if they are going to tell you about their sexual habits and their use of contraception and their intent in terms of this. We have had some intentional use of this drug to precipitate situations where an abortion would be required.

So you see the whole spectrum of activity here

essentially. What we have tried to do is focus the responsibility where it belongs -- on the physician and on the patient. These two people are really in partnership on this issue. We do not feel that the third parties and the distribution schemes, and such, really get to the heart of the problem, that is, the physician and patient.

So have I answered your question? A substantial number are pregnant before they get the drug. Some people use contraception rather poorly and they do not use it properly and get pregnant. Others use it and they get pregnant. The Norplant and the Depoprovera suggestions are worth thinking about in this regard in this very special circumstance. Yes?

DR. HULKA: I wonder if Dr. Shalita is here.

DR. CUNNINGHAM: Yes, he is.

DR. HULKA: I would like to ask you a question about this indication, the serious cystic acne. By the time you are prescribing Accutane for individuals with this condition, they apparently already have serious, irreversible skin damage. I wonder if there is any experience with the use of Accutane for less serious acne where there would be the potential to prevent this serious, irreversible skin damage.

DR. SHALITA: What a few of us have done, some of the original investigators, is that we have taken some of the

younger children and families where there is a very, very strong family history of severe cystic disease, where the father has a lot of scarring, where we have already treated one of the older siblings -- we have not really had one before they have developed acne and we are a little reluctant to go very young with it but we have treated 14, 15 and 16-year olds.

DR. HULKA: I am speaking about more modest forms of the disease currently --

DR. SHALITA: Yes, we have treated them before they have gotten severe cystic disease to see whether or not one can modulate the course. The results have been good. That is not the problem. The problem is that the less severe disease to begin with, the more likely they are to get a recurrence. That may have to do with the concentration of drug that is actually delivered to the skin. It is like penicillin getting to inflamed skin.

DR. HULKA: Thank you.

DR. HANEY: Dermatologists have been treating psoriasis with methotrexate for a long time. That is a potentially hazardous drug as well. Do you have much feeling or experience why this same issue for methotrexate has not blown up?

DR. SHALITA: Yes, I think that the problem with methotrexate is a real one. It is also a teratogenic drug.

In general, I think that you are treating an older population. You just have to do the comparison between the number -- Bill, how many birth defects have we seen with Tegison?

DR. CUNNINGHAM: We have not seen any in the United States. We have had a few, especially in the premarketing time.

DR. SHALITA: In general, you are treating an older population of patients.

DR. CUNNINGHAM: In response to your previous question in terms of what we know about pregnancy, interestingly enough, with Accutane the pregnancy curve is bell shaped, it is a few 13 and 14-year olds and a few 45-year olds and the majority are in the 20-40 age range. It is just bell shaped. Women at 40 are still getting pregnant.

DR. SCHLESSELMAN: Dr. Cunningham, we saw this morning numerous very graphic portrayals of the benefits of Accutane therapy and equally graphic portrayals of benefits appear in one of the patient information brochures. Why is there no equally graphic portrayal of an adverse outcome?

DR. CUNNINGHAM: I could show you some pictures that I have been able to get from textbooks of fetal malformations, which I use during my presentations. But we have not had access as a Company to pictures of malformed infants. Some of the cases are in litigation and we do not have access to them. Others are held by one of the primary investigators

who has been reluctant to give us the pictures to use on any of these forms.

DR. CORFMAN: There is a drawing on the blister package.

DR. CUNNINGHAM: There is a drawing, yes.

DR. SCHLESSELMAN: There is a difference between a drawing and a photograph.

DR. CORFMAN: Of course.

DR. EVANS: We have found that legally this was impossible to do. There are legal implications with this and this is the reason for the graphic representation.

I would like to respond to one of the questions as to why we have not had problems with methotrexate and etretinate the way we have with Accutane. Accutane is a one of a kind drug. This is a drug which does something that no other drug will do, which is untrue of methotrexate and is untrue of etretinate. For severe psoriasis we have a number of other treatments which are available. This is not true of severe of cystic acne which has not responded to other types of treatment.

DR. MCANARNEY: Dr. Cunningham, as a pediatrician, I am concerned about the issue of understanding the materials that are presented. In working with adolescents we make sure that the materials are directed toward a fifth grade reading level and I would think probably young people would be

reading these materials, as well as people whose educational level may be truncated, for whom these materials would be quite complex.

So my question to you is have you considered the possibility of having somebody review your materials for understanding? Are they too sophisticated for the population to which they are directed? And is there any information on how this is handled with adolescents? Are the parents involved in terms of the informed consents or do the youngsters sign the consents themselves? I have a number of questions about the issues of the understanding of the materials, the actual consent and who is doing the consenting, and that may be a whole other topic we ought to be thinking about.

DR. CUNNINGHAM: It is a major topic. I think in terms of understanding, you probably realize that we are in a unique legal, regulatory and practical situation where the complexity of the scientific issue is one thing, where the regulations about how things should be is another, where legal constraints are a third. There are some practical aspects to that. We have looked at it. Our indications are that it is at about the highschool level, which is probably a bit too much for some.

That is the. reason we have some backup systems, however. The 800 number, for example, gives some access to

other ways of hearing the message. Again, hopefully, the message is getting across not just in writing to the patient but verbally from the physician or the counselor, whoever that may be.

In terms of the use of the consent form and minors, I think that is more or less a case by case situation. We do not, as a Company, have an official policy on that. I think you will find there is a great disparity, probably even around this table, about what you do for consents for minors, whether you have the patient involved. I know there are a lot of issues about everything from birth control information to abortion and any surgical procedure on that. But I do not think we are unique in that regard but we do not have a specific policy on that. We think that here again the physician, patient and in this case perhaps parent needs to be involved. We do not state the specifics of that.

DR. ROY: I think this blister pack is wonderfully put together but I wonder whether it is not too large. You said something about the compound being heat sensitive. I would suspect that some individuals would probably just pop out all of the ten pills and put them in something a little easier to carry. Would that impair the efficacy of the drug?

DR. CUNNINGHAM: No, probably not. We have been marketing in bottles of 30 or 100 in the past. They are heat sensitive and they will stick together a little bit but even

when they are stuck together after being in the sun, or something, they are not impaired. They are not any more toxic than they are to start with.

It is an interesting point about is this too complicated. Again, where do you draw the line between full disclosure -- you want as much information as is necessary to be there, but then you do not want so much there that they do not use it. We have had this criticism of the prevention program. Some people say this is too much; this is unrealistic; we are not going to do it. You know, it is a balance. That is the case with this blister package. We have tried to cram everything in there that we could to, again, be the final interrupter, if you will, of therapy if it is appropriate for the patient but I need new glasses to read some of the fine print; it is pretty small.

DR. ROY: I think one of the central issues are the numbers of cases of malformation. You have stated that you believe that the reported numbers, the ones that we have been provided, are accurate. Dr. Erickson earlier said that he thought it was the tip of an iceberg -- we are at polar differences here.

DR. CUNNINGHAM: We had this discussion a year ago when I think that Dr. Lammer made the most salient point, that is, he said that this is not a numbers game. So I do not really think that I nor Dr. Erickson want to get into

that sort of discussion. The issue was not how many; the issue is, you know, if it is your child that is affected, that is one too many or if it is one that you know of or have had experience with or prescribed the drug for. Every single one is obviously a terrible tragedy.

So our emphasis has not been on the numbers but on the problem of malformation. We want to get the number down as low as practical. I think everyone realizes that this is the real world and it may not reach zero immediately or next year but, on the other hand, I would like to put in perspective that we do not believe, from many sources including our legal side, if you will, which is relatively vulnerable in this area -- we do not believe that there are a thousand, as the original estimates were made from the Medicare data base in Michigan. But, again, I do not think I would want to make that the issue today. I think the issue is pregnancy prevention, malformations and how do we get to the root of that problem, not how many are there.

DR. MCKAY: What would a package of Accutane capsules cost to the patient?

DR. CUNNINGHAM: I would put it in terms of the total cost of about five months of therapy, saying it is about $400-500 for the total cost of the therapy. We have had a lot of questions about that. I think the point that was made earlier that this is a single course of therapy for

90 percent of the patients is worth emphasizing, rather than a 2, 3, 5, lo-year course of therapy with tetracyclines, for example, which are obviously much less expensive per unit.

DR. HOLMES: Dr. Cunningham, I wonder if you could tell us how you plan to explain to us how there has been a reduction in the number of pregnancy exposures this time next year? I am asking this because, as you know, the protocol for the postmarketing surveillance study that is being conducted was rejected in draft form, in its first submission and in its second submission and you have continued with that.

DR. CUNNINGHAM: I think I can answer that very easily. In life, one always has the existing situation and then the new situation. Here we have an existing situation where we have a data base of some reliability, although not completeness, since 1982, since the product was marketed.

I have mentioned that the adverse data reporting has been relatively flat throughout the period, about 3.4/1000 patients treated, and we know the exact numbers of that per patients treated. So that adverse reporting has remained constant. If that remains constant, we do not see why the pregnancy rate should decrease or change out of proportion to the reporting of hangnails and earaches and stomach pains. So we feel that we have a base there that we can look at for the future.

On the other hand, the Slone study will be put in

place this year and we will have subsequent years to look at something. I think that in the real world that is what we are facing. We do not start out with knowing exactly how many pregnancies we have today in any system, whether it is a complete restriction of the drug or not, because one does not know what the previous rate was.

So in response, I think we will be looking very much toward what has been a reliable system, although somewhat incomplete, for degree of change rather than a completeness of change.

DR. HOLMES: What is the enrollment of women?

DR. CUNNINGHAM: The present enrollment rate varies somewhat by month and week but the rate last year was about 130 women per week. The total usage of the drug last year was about 65,000 new females.

DR. HULKA: Thank you.

DR. HOLMES: Would you express that as a percentage, please?

DR. CUNNINGHAM: It is about ten percent I think.

DR. HOLMES: Do you think that is sufficient?

DR. CUNNINGHAM: I think we could debate this probably until the Committee meeting is finished tomorrow afternoon in terms of whether that is complete. Obviously, it is not complete. We have addressed this with the Accutane working group within the FDA extensively. So I probably need

not dwell on it here. It is a sample. It has the potential for bias. It is the best we can do at the present time.

DR. HULKA: I would like to suggest that we stop this part of the meeting now and take a break. Fifteen minutes from now we will reconvene, at ll:OO. Then we will continue with the discussion of Accutane.

(Brief recess)

DR. HULKA: The next person to speak is Dr. Bruce Stadel, with the FDA. He will be speaking on the use of Accutane by women of reproductive age in 1988.

PRESENTATION BY BRUCE STADEL

DR. STADEL: Thank you very much. I am going to move fairly rapidly through some of my early slides because to understand the concerns about use in 1988, it really has to be viewed in the context of use up to that time. So we do have the 1988 initial slides in that context.

(Slide)

We are trying to track the drug for the Agency, and it is a drug that is not supposed to be used in pregnancy. There is not supposed to be pregnancy exposure because of the risks associated with it.

(Slide)

This is our estimate of the male to female ratio for cystic acne and the female incidence. This is, admittedly, a rough estimate. I would offer, however, that it is based

upon population-based data, the National Health and Nutrition Examination Survey; that the criteria for defining acne are very well described and detailed in the report and that the examinations were done by a cooperating group of 200 dermatologists.

We have had to estimate incidence by just taking the prevalence with the available published estimates of a duration of 8-9 years. So it is, admittedly, a rough estimate but it is a data-derived estimate, whereas, the figures that I have heard otherwise seem to be mainly anecdotal.

(Slide)

This, very quickly, is the total use in mentions in thousands; total use in new start rates from the National Disease Therapeutic Index for Accutane over the years. So despite the publicity and concern, the rate of use continues and you can contrast this against the estimated annual incidence I put up before. So even if that figure were substantially underestimated, we are talking about orders in magnitude of difference; we are talking here about 50,000-60,000 starts per year.

(Slide)

Again, percent of total Accutane use in women is close to 1:1 ratio, whereas, the best estimate is closer to 6:1 ratio for cystic acne in men to women. I might also add

that we have seen other data from other sources to support that for more serious acne, from a recent publication of the British Medical Journal.

(Slide)

So these have been our figures at the time this slide was prepared, that 80-90 percent was being handled by dermatologists and even though it was being handled in the specialty, it appeared from our data at the time, based upon the estimate of 5000, to be a very, very large excess if one accepted that definition of indication, with the conclusion that the majority were being treated for milder acne than seemed to be the indication.

(Transparency)

Again, one other data base, the PDS data base, also gives a ratio of nearly 1. That is really the only purpose of showing this, just to show a second data base giving the same ratio.

(Transparency)

I think this slide is important in placing things in context. This population figure is millions. The exposure incidence is number per thousand per year. This is the experience in these countries, aggregating data from 1982-1987. What we have done then is to say how many fold greater is the use in the U.S. compared to Sweden, U.K. and Germany. You see that the excess is a multiple in the range

of 6-8-fold greater use in the age range 15-44 in the United States than in other countries of comparable developmental and medical care level.

(Transparency)

This transparency focuses down on this. In Sweden, where we have recently had communication with the Department of Drugs concerning a considerable study that they have done to examine Accutane use in Sweden, where it is handled through a licensure system, the columns show you the numbers treated of women 15-44 and the totals; the number in the U.S. ; and then the number of patients treated per thousand per year. So you have in this slide a nearly lo-fold greater use in women 15-44 in the U.S. than in Sweden. These are data confirmed by the Swedish Department of Drugs.

I might comment in this context also that when they examined geographical variation in Sweden, what they found was that the differences in the rate of use in different regions -- Stockholm versus others in particular -- was not highly predicted or correlated with the differences in the size of the population. It correlated best with the differences in the numbers of dermatologists in the different cities. So it seems that the difference in the rates of use was more a function of prescribing than of the number of people in the population who were potential recipients.

(Transparency)

This is just briefly to remind you that Accutane syndrome reporting, if you look at the right-hand column, has been pretty stable since 1985. Despite a great deal of concern about the syndrome itself, it really has not changed very much.

(Transparency)

I would emphasize skepticism about the idea that these birth defects are reported with the kind of completeness that Dr. Cunningham suggested. The whole experience with the spontaneous reporting system is that under-reporting is enormous. For example, in DVT-associated deaths, reporting was estimated at less than 10 percent. Similar very low reporting rates have been noted for highly publicized occurrences such as deaths from deep venous thrombosis in oral contraceptive users, in Britain, where reporting, despite a great deal of publicity, was less than 10 percent of what had been derived off population-based figures.

You also have to remember that there is an average reporting lag of about five months, to which must be added the gestational lag for the fetus involved and that you really cannot track pregnancy exposure by watching birth defects because it can be driven by abortion rates. So given the pregnancy category of the drug, we have focused our attention on the issue of pregnancy exposure.

(Transparency)

This moves then right here to the pregnancy exposures that were reported to Roche, which they provided to us, which have again been pretty stable from about 1985 on.

I would comment here that there were nine pregnancy exposures reported in the first quarter of this year. All exposures occurred late in 1988. Of the nine, the records indicate that all but one or two were either already pregnant women exposed or became pregnant within one month of initiating use. With regard to contraception, one was an apparent OC failure; three reported they had been using barrier rhythm methods; one thought she was infertile and was not using anything; one thought her partner had a vasectomy. The others were uncertain.

(Transparency)

So this gets us to where there was a great deal of concern through these early years with the reports of birth defects or pregnancy exposures, with very high levels of use relative to orders of magnitude in relation to the indication and experience in other countries.

This is difficult to read. I put it up simply to illustrate that we are dealing with specific people as well as numbers. This report of a birth defect came to us in May of 1988. The child had no left ear; hydrocephalus; a deformed right ear. The indication was described as mild acne and the comments said that the dermatologist did not

know about the pregnancy and that the obstetrician did not know about the acne.

We think that this anecdote does help to illustrate some of our concern with fragmentation of information, the feedback and the ability to track the situation.

(Slide)

As you know, the objectives have been to eliminate the pregnancy exposures.

(Slide)

This slide shows you the use by quarter in 1988. Towards the end of the year there is definitely a drop in total use but, to the extent of the available data which are based upon small numbers, there has been no pattern with new starts. We have been concerned about this because most of these pregnancy exposures occur early.

(Slide)

This is an estimate of possible pregnancy exposures in 1988. If women on Accutane had been using contraception the same way as population-based data in the article Mishell had applied, if all of these women had been using oral contraceptives, I estimate this figure would still have been over 600 pregnancy exposures in 1988.

(Slide)

This pretty well wraps it up. If there were 1200 exposures, 40 percent would have been drug-induced spontaneous

abortions. Of the remainder, the induced abortion rate would probably, from our estimates, have been about twice as high as the general induced abortion rate, for obvious reasons. Of those reaching delivery, about a quarter would have some birth defects.

(Slide)

My last comment here pertains to the postmarketing study efforts, as has been discussed. I will not go into this. However, the enrollment rate is too low for me to consider it seriously providing useful information on analyzing pregnancy exposure and I submit that it could be actively misleading because of the selective nature of the enrollment.

(Slide)

So I would conclude with the last slide here that says that use appears to continue to greatly exceed the indication. When I look at the first quarter 1989 data, it does not persuade me that there is a pattern of meaningful decrease. Pregnancy exposure continues to be high and I do not think this postmarketing study is adequate.

(Transparency)

This is a very close look, month by month, of NPA data for new Accutane prescriptions by dose, month and year. This is a valuable adjunct to NDTI and PDS data because, especially in NDTI, the projections for new use are based

upon such small numbers that they have a very high variance. This shows you that there is a seasonal pattern with new starts. I look at this as not persuasive that the new start rate is changing in the kind of orders of magnitude that have been discussed here with regard to the use of the drug. Thank you very much.

DR. HULKA: Questions for Dr. Stadel?

DR. HANEY: Dr. Stadel, do we know if the incidence of cystic acne is the same in genetically homogeneous populations, like Sweden, and the known heterogeneity in our population? Do we know that they are the same?

DR. STADEL: No, we do not know that. I mean I would have to have a fairly elaborate comparative study to say that I knew that.

I showed the data simply because I am trying to place our experience in some kind of perspective with other countries with similar levels of development. I do not have the ability to tell you whether a weighted average by Hispanic, black and white ethnic derivation, for example, would affect these. I would think it very unlikely that it would be that order of magnitude.

DR. HANEY: Is it a genetic disease?

DR. STADEL: I do not know. You mean specific to an ethnic group as defined by Europe versus the United States? I do not know. I would be very surprised.

DR. GRAHAM: David Graham, FDA. I can add one point to that. There has been one study that I am aware of that is published looking at racial differences and cystic acne in man. In that study they concluded that the prevalence of cystic acne was 10 times greater in white men than in black men. So that is one published piece of information that suggests that prevalence is lower in blacks than it is in whites. If you go back to your ethnically homogeneous populations in Europe, where they do not have substantial black populations, if race is a factor, that would tend to give them higher prevalence than in the United States where we have a substantial black population contributing a lower prevalence.

DR. HULKA: Do we have additional questions from the Committee?

DR. EVANS: I would like to reply to the question about genetic predisposition. I think, undoubtedly, there is. Dr. Shalita mentioned that earlier. With these patients there is a strong genetic tendency.

DR. MCDONOUGH: Within families?

DR. EVANS: Yes.

DR. MCDONOUGH: I just wanted to ask does anyone know what has been the experience in the United Kingdom in the distribution of this drug, where they limit it to certified dermatologists? What is happening in countries

like Sweden, where they have not allowed it to be dispensed? Is it sort of black market?

DR. STADEL: It is used in Sweden. That is the report I showed you from the Department of Drugs.

DR. MCDONOUGH: Oh, all right.

DR. STADEL: In fact, as I said, it is used at about one-eighth of the rate that it is used here. It is used through a licensure system. It is the only country from which I have been able to obtain a detailed analysis of usage, which was sent over to me recently. The figures that I showed you for the U.K. and for Germany are based on less detailed data; they are based on IMS data on sales compared to the population size. But they correspond fairly well between those different countries.

DR. ROY: Bruce, could you just reiterate how many prescriptions you are saying are written annually in this country?

DR. STADEL: Well, we said the new start rate in women of reproductive age has run about 60,000-65,000 per year. That is from the NDTI data. Those NDTI data are estimates based upon small numbers and they have a high sampling variation but the pattern has been constant in the new starts from 1983-1988. Although the variance is large for each individual year, when you look across the whole pattern, it does seem to be fairly stable at that rate.

DR. GRAHAM: David Graham, FDA. I can provide a little more information to that. The total number of women treated in the United States, by NDTI from 1982 to the present, is about 400,000, and with the PDS it is 450,000 or so. If you just divide that by the time on, you can see that it is about 70,000 a year.

DR. HULKA: Thank you, Bruce. What I would like us to do now is what I mentioned earlier about going around the table, starting with Anne Wentz who is looking so puzzled, to make some comments in terms of our reaction now to prescribing and the various issues that have been addressed here in any relevant domain that you feel is appropriate.

DR. WENTZ: I think we have seen convincing evidence that there is over-utilization, although the indication for utilization apparently is in the eyes of the beholder.

I think another area that distresses me is that we are learning some lessons about communication. I think I counted 26 communications and I would be very curious to know how many of these communications are simply thrown away by the busy physician. Perhaps a study showing how many of these are actually read would be useful to all of us.

But the major thing I think I have learned from this is a real concern -- it was known ten years ago that this drug is teratogenic and it should have been known because

population statistics have been available for what the pregnancy exposure would be and what the pregnancy rates would be. What I am so puzzled about and one of the things that concerns me is why ten years ago this meeting was not being held, a meeting in which we planned for communication; we planned for patient education; we planned for physician education; we planned for responsibility and for accountability. So my look of puzzlement is really puzzlement of why we are hearing about this today and why we did not hear about it close to ten years ago.

DR. NIEBYL: Can I answer briefly that question or at least make a suggestion that ten years ago the pregnancy tests were not nearly as accurate in ruling out a pregnancy as they are now? So some of that has evolved as a technology that is more reassuring to the person who is about to prescribe the drug. Now a negative serum-sensitive pregnancy test really does make it extremely unlikely that a patient is pregnant.

DR. WENTZ: Only if the patient begins the medication within three to four days --

DR. NIEBYL: Right. I am talking about the one-third of patients who were already pregnant when they started the drug. I would hope that the serum pregnancy test requirement, for example, will eliminate that one-third.

DR. SCHLESSELMAN: Well, this is obviously a very

effective drug and it is obviously a potent teratogen. I think that it is disturbing to know that despite the best intentions of the Company and very strong and repeated efforts to prevent pregnancy exposures to Accutane, we still have pregnancy exposures to Accutane occurring and Accutane-induced birth defects resulting.

I guess I, for one, am a little bit skeptical of what more is likely to be accomplished by providing further paperwork, if you will, to the prescribing physicians. I think since all of us are caught up in reading and value education, we tend to believe in that. But I think despite all of the information that has been put out by the Company snd the best efforts that the Company uses to prevent pregnancy exposures, as long as the drug is marketed there will be pregnancy exposures and probably, consequently, Accutane-induced birth defects.

So despite the claim that this is not a matter of numbers or that we should not be considering numbers, I would disagree with that. Whenever one weighs risks and benefits one has to consider numbers. What puzzles me is the very great disagreement that I have heard with regard to the indications for use of this drug. It is startling to hear the wide divergence in figures reported, say, by the FDA versus the Company.

I think when you go back and hear the statement

that the Dermatology Advisory Committee weighed risks and benefits in reaching the decision to allow continued use of Accutane, I, for one, am skeptical about whether there was really good evidence on which to weigh the risks, given the divergence in views that we have heard thus far with regard to risks. I, for one, cannot understand how one could have really come to a rational view about benefits and risks -- benefits, certainly. I think that is very clear. But with regard to risks, I think that, to my mind presently, is very much in doubt.

DR. ROY: I think all of us have to sort of add to what has gone on, or try to. The thing that disturbs me about what I have heard is once again the disparity in terms of numbers. I think you cannot get away from numbers. I am very concerned that even with this effort to prevent pregnancy, these pregnancies will occur and will be underreported and the malformations associated with them, as has been described.

I think that despite that, we still need to make the best efforts we can to try to get better data, such as are the malformations more likely to occur in those who start the medication already pregnant versus those who get pregnant while on the medication? I think some of the intervention strategies may be better if we had more clear data on that point.

DR. NIEBYL: I would reiterate the issue that has been noted about the conflicting data. But I guess I would like the opportunity to respond to specific questions. I do not really know enough about this Committee to understand why most of the time we get specific questions and today we have just had some "information". Are we being asked for specific advice as to what to do? In which case, perhaps this could be reviewed at a later date as a series of specific questions to the Committee and we could go back and read the data from the different sources and try to make some sense of it.

In the meantime, perhaps we could get some more information one year out in terms of the pregnancy prevention program and whether it has had any impact. That would be a prerequisite. Then maybe after one year of this new program, if it has had an impact, we could review it as a specific question.

DR. CORFMAN: I would say that is excellent. If you want to recommend that, we might be able to bring it back to the Committee at another time.

DR. NIEBYL: Maybe give one year or some fixed time for the new program, new efforts to prevent pregnancy and see if it has had any impact.

DR. CORFMAN: But the purpose of today's meeting is simply to brief the Committee in a brief period of time on what is going on with the Accutane campaign and to solicit

your individual comments. That is the purpose of today's meeting.

DR. MCDONOUGH: I think this is a major, major problem that we are going to have to deal with, not with respect to just isotretinoin but with all the vitamin A congeners, because there is no doubt that they are teratogenic, not only on the basis of empirical data here but just the known biology of retinoid and the retinoid receptors, and so on, during early embryonic development. I think it is unequivocal and it certainly even justifies concern for the mega-doses of vitamin A that are sometimes deliberately prescribed or taken during pregnancy.

Of course, the second issue is that there is no doubt that the drug is unequivocally effective in severe cystic acne and that the real problem is indiscriminate prescribing. I have sort of even heard here today that one can sort of extend the indications really sort of beyond severe cystic acne into other various categories. So it is a real challenge whether you can actually regulate through various means, through education and finally even through medical-legal constraints the distribution of this particular drug.

I think the Company has done an exemplary sort of stab at this to try to see whether or not you, in fact, can do this. I think that this is perhaps an appropriate

occasion to plan to look at this a year later to see even what is going on in terms of trends. Maybe it is not even possible. The numbers of birth defects may, in fact, continue and they may continue to increase and you may find that all the constraints that one can put in, including the medical-legal ones which I think are really considerable -- there is considerable pressure on the physician and, in a way, on the Company to make this work. That may be one of the things that may, in fact, make it work ultimately.

DR. MCKAY: In considering the pregnancy prevention program, one of my major concerns in waiting a year is how many congenital defects is that worth? Who is going to pay for all the deformed babies while we wait to evaluate the program? I am not talking about just economic costs but the social costs, the parenting costs.

I am really concerned about the fragmentation of care and dispensing these kits to dermatologists, for the most part, who are not the ones who apparently primarily do the contraceptive counseling. It seems as if there has to be a great deal more restriction on the prescribing and also the correlation of contraceptive assistance with prescribing of Accutane.

DR. MCANARNEY: I would like to make comments in two areas. The first will be objective, hopefully; the second may be a bit more subjective. Certainly, we have

heard today that severe cystic acne is disfiguring. Those of us who are clinicians see this in our practices. I primarily take care of adolescents. We recognize that there are both short-term and long-term physical and psychological sequelae.

We have also heard that the treatment of this condition is absolutely critical in order to prevent the physical and psychological sequelae that we have heard about. We have heard that Accutane is effective for the treatment of cystic acne but that there is a down-side with regard to teratogenesis.

I would like to raise the question of whether there are any other drugs on the horizon that are being developed which might ultimately replace Accutane. We have heard nothing about that this morning and I do not believe that in our materials we hear about whether there are going to be any other modalities potentially that will be equal.

If there are not, and for argument we might say that, then I think we have to begin to address many of these issues that we are considering today.

First, we heard about the issues of prescription practices being a problem. That is a focus that I think certainly could be attended to.

Secondly, we know that prevention of pregnancy in any groups is a problem, particularly in the groups that have this particular problem -- certainly the adolescents for whom

I care, trying to help them prevent pregnancy, as you well know, is difficult at best. So we are talking not only about the adolescent population but young adult population for whom we recognize, in general, that prevention of pregnancy is a problem.

We have heard about the issue of monthly pregnancy tests. I would ask the manufacturer whether there is any possibility of combining the packaging of Accutane and contraceptive pills, for example -- bit the bullet and see if that is possible. I think there are some serious implications here. I would also say that improving of the surveillance with regard to the teratogenesis has been addressed.

Those are the objective things. I would like to hear somebody address if there are any other drugs on the horizon. If not, then I think the issue of really focusing on Accutane becomes even more pressing.

Now with regard to the more subjective issues, I have raised the issue with regard to the adolescent because that is really what I do most of the time. I am still concerned about the informed consent; about whether, indeed, the young people who are using this drug are well informed and whether the materials are effectively directed toward them.

There are a number of concerns that I have with regard to delivery of health care in this country. Perhaps

that is another political issue but we are hearing about fragmentation of care. We are asking whether dermatologists can give contraception; we are asking about whose responsibility that is and, I guess, as somebody who originally came out of a primary care background, I am saddened by this because the complexity of what we are seeing is reflective partially of the health care delivery system we live in. That is part of the subjective issues.

But basically, can somebody please address the issue of whether there is any other drug being developed on the horizon? If so, what is the time frame with regard to that particular modality?

DR. MANGANIELLO: This morning we realized that cystic acne is a debilitating disease and I do not think anyone is questioning the effectiveness of Accutane. I do not think most people would recommend that it be taken off the market. I guess the main concern of our Committee today is basically the effects on the inadvertent exposure to the fetus.

I think if the Committee is going to get this again at some future time, rather than being reactive, there should be proactive guidelines which are set down to try to get to the answer of the problem.

I work in New Hampshire and there you "live free or die" so I moved to Vermont, where it is a little bit less

black and white --

(Laughter)

-- and there is no system that really is ever perfect to prevent or protect every single individual that you are going to be treating.

This morning I was really in favor of having limited access, basically limiting the number of centers that would be dispensing the drug. I guess I could compromise with that and live with the fact that if a physician were actually licensed to administer the drug, if he were trained specifically in counseling patients and administering the drug, being willing to follow mandatory guidelines that have been set forth today, that would be an acceptable guideline. But I also feel that there should be included in that mandatory surveillance of patients who are administered Accutane.

Finally, we are going to be speaking about further additions to the guidelines, such as monthly pregnancy testing and monthly distribution of the drugs. Thank you.

DR. HANEY: Not to belabor the point, it is an efficacious drug unequivocally, the only effective agent in practice. I think contraceptives must always be viewed as use effective, not just effective. This population, like all populations, cannot count on that. This one in particular is difficult.

I do not think I heard anything that the drug should not be available. The question is how to make it as safe as possible. I would like some information in general, if I were the FDA, and I am certainly interested also, one, what is the real incidence of this disease? I do not get a good feeling for that anywhere. Two, I am amazed that there is a 6:1 ratio for the disease and a 1:1 ration in prescriptions. Some of that may be attributable for the need for women to have a more improved cosmetic appearance than men. But I would still maintain that there is a lot of uncertainty about what that means.

I do not accept that methotrexate is not a problem. There is a segment of that population that is young and there ought to be some information -- maybe we are just not seeing this; not paying attention or whatever, but there has to be some data about methotrexate.

I think Dr. McAnarney's comment about birth control pills is not so wild and far-fetched. Propione (phonetic) acetate, used in Europe for hirsutism, is formulated with 50 micrograms of ethinyl estradiol. Effectively, it is a contraceptive, controls bleeding and reduces androgen exposure. It is the best combination product I can think of, short of what should be available shortly, which is estrogen-progesterone for postmenopausal women in a single pill. so I do not think that is an unreasonable question at all.

The comments Anne made and other people made about fragmentation of care, I am not so sure I agree with. Very few dermatologists, internists or family physicians are going to be willing to give Depoprovera or Norplant or put in IUDs, particularly Depoprovera which is a non-approved indication as a contraceptive. I would be willing to do that as a gynecologist. I can defend myself. But I do not believe there is a family physician, internist or dermatologist who could possibly do that. So to demand a referral to a gynecologist seems reasonable, (a) for reinforcement and, (b) to make available to these patients options that might not be so available in the standard clinical armamentarium of a primary care physician.

I do have a wish list. My wish list is, number one, negative pregnancy test before starting and start on day two of the menstrual cycle. That gives you two days to make sure the period is there. You have a negative pregnancy test and your probability of starting a patient who is already pregnant will be very low. That is true of a variety of drugs we use in gynecology that are teratogenic.

Number two, I would recommend that the drug be limited to a monthly prescription. That demands return of the patient to the doctor every month. It is a good opportunity to get a pregnancy test. The physician certainly would not argue with that. These are motivated patients who

would not argue with that. So it seems to me, to get a good handle on monthly contraceptive effectiveness, that is a reasonable enterprise.

I think every identified failure, every identified pregnancy should be followed up to find out exactly why because there are several levels of responsibility -- patient, physician, pharmaceutical company and FDA. If we can identify where the failures in that responsibility occur, I think we will have a much easier time focusing on how to address those problems.

DR. BARBO: I agree that this drug should remain on the market. I would hate to have us in a position where patients would be going to black market sources. We would have absolutely no control at all or surveillance of the drug.

The responsibility is multiple. I believe the Company has done a great deal in their responsibility. My big concern for us is that physicians can give adequate contraceptive information and health. I just do not know how well dermatologists do that. If they do it, great. But I would hate to think that patients did not get adequate information and continuing information.

The patient does have responsibility. I do not know how to mandate that. I have never learned it in 30 years. It is a big continuing problem. In this country

nobody wants to take responsibility, it seems.

I believe that there ought to be a pre-start pregnancy test; a one-month prescription supply; a repeat discussion or evaluation before a second-month supply is given to women. I would like to add that I believe the obstetricians in this country need to be asking much more frequently if a patient is on Accutane or has taken it. I do not think that is very routine in obstetrical histories. We talk about DES, which is almost gone, but I do not think we are asking patients about Accutane these days.

DR. HULKA: Well, I will not repeat many of the things that have been said. But I would say that I believe that the prescribing of this drug should be left in the hands of the individual physician, and whether or not to use it or not then should be between the physician and the patient. These are the people who should be involved in the decision, not other organizations, committees or other institutions.

A specific point has been made about monthly visits to the doctor once the drug has been prescribed. That would be presumably for all women who are of reproductive age. I would think that might also be a matter of judgment because, certainly, many women in reproductive age are very able to control and manage their own fertility and their use of oral contraceptives or other forms of contraception. So I think that decision should also be an individual one between the

doctor and the patient.

I would like to very much commend the Company for the way they have so responsive in developing these pregnancy prevention materials and their entire program which has been described to us; also to the FDA and their work in the Accutane monitoring group; and I think most particularly to prescribing physicians because it is really quite a lot that is being asked of physicians which is out of the ordinary in terms of paperwork and the amount of responsibility and the time that that will require of physicians.

I think that one of the issues, as we look forward to monitoring and data collection of a variety of sorts, as has been requested -- it is going to be interesting to know what the monitoring of physicians will show. Do some physicians just stop prescribing the drug because it is too much of a problem and too much of a legal responsibility also to continue to do so? So I think there are still issues about how acceptable this packet of materials is going to be in practice.

I think there may be potential for other kinds of studies in the future, other than the follow-up study that has been proposed, which may have a greater level of potential validity. There is no doubt that voluntary reporting is rarely an accurate procedure.

The interesting thing about voluntary reports, as

it has been noted in many other circumstances, if you are reporting pregnancies and certainly if you are reporting congenital malformations, is that now that it is well-known to the public and to prescribing physicians about the teratogenic effects of Accutane, it is very likely that the bias in reporting will be toward reporting cases of these events that are associated with Accutane. In other words, the bias would move in the direction of showing an increased risk beyond that which may actually be there.

So I think there will be opportunities in the future for doing other kinds of studies to evaluate what is going on.

We are now going to reassemble the room for our next topic, which is the lactation suppression issue. We will continue on that before lunch but it will take us about five minutes to reorganize.

(Brief recess)

DR. HULKA: Could we reconvene, please? This is the section on prevention of postpartum breast engorgement with sex hormones and bromocriptine. Dr. Corfman has an announcement he wants to read before we start.

DR. CORFMAN: I am supposed to read this into the record. Based on the agenda for the meeting and all reported financial interests as of this date, it has been determined that all interests in firms regulated by the Center for Drug

Evaluation and Research which have been reported by the participating members present no potential for an appearance of conflict of interest at this meeting. However, in the event that the discussions involve these firms, all participants are aware of the need to exclude themselves from such participation and such exclusions will be noted in the record.

The other note I wish to make is that the subsequent meetings of the Committee will be February 27 and 28, as I noted. Anne Wentz has told me that the June meeting that we scheduled for next year conflicts with the Endocrine Society. So we will make it June 15 and 16.

DR. HULKA: Again the dates for our meetings for 1990 are February 27-28 and June 15-16.

I would like to mention just briefly before we go into the public open meeting, will you please pull out your questions that we are to address on postpartum lactation suppression. It was originally set in our agenda that we would go through all these questions late tomorrow afternoon. If you notice, there are 8 questions and several of them have subsidiary questions. I am suggesting that we take the first 5, plus question 6.1, 6.2 and 6.3 today, at the end of the day. These are the questions that deal more generally with lactation suppression and then specifically with the sex steroids, the hormones. That would mean we would be leaving

exclusively for tomorrow bromocriptine and the whole day would be devoted to bromocriptine.

But I believe the way these questions, depending on how we deal with question 1, which we actually answered at a prior meeting, and then questions 2, 3 and 4 go together -- I think these should be questions that we would be very prepared or just as well prepared to address today as tomorrow. So will you please keep those in mind, all the way down through 6.3, while you are hearing today's presentation and discussion? Then at the end of the day we will go through them. Thank you.

DR. WENTZ: I want clarification on those dates. We are meeting on a Tuesday and a Wednesday and a Saturday?

DR. HULKA: Let's hold on those dates for the moment until we can firm those up. I am not even sure about those dates and my availability. So hold on the dates.

Let's go ahead with our open public hearing. I understand we have two individuals who have requested to speak. First is Dr. Douglas Teich, representing the Public Citizen.

PRESENTATION BY DOUGLAS L. TEICH

DR. TEICH: My name is Dr. Douglas Teich and I am an internist and a research associate of Public Citizen Health Research Group, a consumer health advocacy group.

I want to thank the FDA for this opportunity to

state our views on this important issue of pharmacologic suppression of lactation and prevention of breast engorgement.

First some background -- a year ago our group addressed this Committee with data bearing on the lack of efficacy, minor and serious side effects and regulatory history of bromocriptine (Parlodel). Since there was no demonstrated need for this drug to suppress lactation in postpartum females, it lacked efficacy and it was associated with a wide range of side effects, we argued that this indication be removed from the new drug application approval for bromocriptine.

This Committee voted that there was no need to routinely use hormonal drugs to suppress lactation but that bromocriptine should be available to those with specific indications, such as stillbirth. In part, its unwillingness to remove the indication for bromocriptine related to fear that obstetricians would revert to the use of estrogens, widely regarded as more unsafe.

On November 29, 1988, we and the National Women's Health Network petitioned the FDA to amend the new drug application approvals for bromocriptine and estrogen and testosterone compounds to delete the indication for the indication for suppression of lactation and the prevention of postpartum breast engorgement.

In addition, we asked that the new drug application

approvals be removed from the estrogens Deladumone and Deladumone-OB, as well as TACE, for which this is the only indication.

We reviewed the available literature and concluded that there was no demonstrated need for any of these classes of drugs for this indication and that, as a group, they had proven only marginally effective and too unsafe to be used for such an equivocal purpose.

On March 15, 1989, having received no response to our petition, HRG wrote Commissioner Young, of the FDA, in support of our contention that postpartum lactation could be managed conservatively and that lactation suppressants should be used rarely or not at all.

We had contacted a number of leading obstetricians around the country and found that while bromocriptine was never or only seldom used, TACE and Deladumone were never used and, at some institutions, were felt to be contra-indicated.

We also reviewed the regulatory history of estrogens for lactation suppression, including this very Committee's recommendations, both in May, 1978 and again in april, 1984, to withdraw approval for estrogens for this purpose.

In fact, the FDA was poised to withdraw the drugs TACE and Deladumone from the market, having proposed a notice to withdraw the new drug application approvals for these

estrogen-containing drugs in October of 1978, when Parlodel arrived. Ten years later, remarkably, these drugs are still widely used for this highly questionable purpose.

On April 10, 1989, we received a response from Dr. Young, deferring a formal response to our petition until this Committee offered its advice. He posed the questions: "Are there certain circumstances, albeit rare, under which drug therapy is appropriate for lactation suppression? What drugs should be used and under what specified conditions might their effects on lactation outweigh their well-known risks?

We hope that with the information provided today snd tomorrow you will answer "no" and "none" to the Commissioner's questions and, thus, remove this risk to the health of more than 700,000 women each year.

I would like to very briefly review three aspects of this issue only: (a) the question of need for drugs to suppress lactation, (b) the use of estrogens and, (c) the use of androgens for this purpose. At tomorrow's open public hearing I will review our position on bromocriptine.

First the need for lactation suppressants: You will be hearing more about this question of need for prophylactic treatment for breast engorgement, in women electing not to breastfeed, from Dr. Lawrence.

In our survey of leading obstetricians with large university hospital-based practices, which formed the basis

of our March 15, 1989 letter to the FDA, we found that at Johns Hopkins, the University of North Carolina Chapel Hill, Yale, Iowa, UCLA and Brigham and Women's Hospital essentially no lactation suppressants are used. The practice at USC-LA County Hospital, where 16,000-18,000 babies are delivered each year, is representative. TACE and Deladumone are contraindicated and Parlodel is used only under the exceptional circumstance that a woman has had extreme discomfort due to breast engorgement during a previous pregnancy.

At other institutions, such as Michigan, University of Texas Southwestern, Mount Sinai, University of Pittsburgh and the UMDNJ New Jersey Medical School, Parlodel is occasionally, but not routinely, used and TACE and Deladumone are never used. Androgens are never used at any of these institutions.

The one dozen department chairmen polled felt that postpartum breast engorgement is a benign and self-limited condition that could be managed, almost universally, with breast support and analgesics. They felt that all of the medications used to suppress lactation have only marginal efficacy due to the high incidence of rebound lactation when they are stopped. They pointed to the known risk of thromboembolism with any high dose estrogen studied, the common side effects of bromocriptine, such as blood pressure swings, dizziness, nausea and vomiting, and the reports of life-

threatening or fatal events, such as seizure, stroke, psychotic reaction or myocardial infarction associated with bromocriptine. As Dr. Kenneth Ryan, Chairman of Obstetrics and Gynecology at the Brigham and Women's Hospital, put it, "who needs them?"

The use of estrogens: You will be hearing in greater detail from Drs. Wysowski and Stadel, of the FDA, on the risk of thromboembolism associated with estrogens, both generally and when used for lactation suppression.

I wish to call your attention to some of the information presented in our petition, in the context that, according to at least one recent paper, puerperal thrombo-embolism is the leading cause of maternal mortality in the U.S. today.

In 1978, Dr. Niebyl, now sitting on this Committee, reviewed evidence suggesting that only high doses of estrogen suppressed lactation at all. Given that prolactin levels continue to rise during estrogen treatment, it was not surprising that there was a substantial incidence of rebound lactation once the drug was stopped, if the patients were followed up to several weeks postpartum.

At that time, the Committee heard the evidence derived from three large retrospective studies from Great Britain, done in the 1960s, bearing on the risk of venous thromboembolism in postpartum women receiving estrogens for

lactation suppression.

The earliest study found an overall 4-fold increased risk of blood clots for those women receiving estrogens, which increased to lo-fold in women aged 25 and older. In this study, all 8 cases of pulmonary thromboembolism were in women who received estrogen to suppress lactation.

A second study showed a 3-fold increased risk overall, which increased to 6-fold for women having assisted delivery. A woman aged 35 or more, having had assisted delivery, had 10 times the risk of thromboembolism if she received estrogen to suppress lactation.

Finally, the third study again found an overall 3-fold increased risk of puerperal thromboembolism with estrogen inhibition of lactation. The relative risk increased further with increasing age and with assisted delivery, which are, themselves, known risk factors for venous thrombo-embolism.

These studies were flawed by the absence of an important placebo control arm of postpartum women not breast-feeding and managed conservatively. All the studies compared women receiving estrogens to women who breastfed. In addition, the British studies involved the estrogens DES (diethylstilbestrol) and ethinyl estradiol, rather than those being considered today. However, the Committee still found this data compelling in view of what is generally known about

the thrombotic risk of estrogens.

The 1978 Committee was persuaded by this data because it is completely in keeping with the strong epidemiologic evidence relating high dose estrogen use to increased risk of venous thromboembolism. The recommended dose of TACE is 48 mg a day for 7 days, for a total dose of 337 mg, or 200 mg over 1.5 days.

Compare this with the second generation of oral contraceptive pills, containing 50 ug or 0.05 mg of ethinyl estradiol every day, 3 weeks out of 4, which confers a significantly increased attributable risk of venous thromboembolism. According to the 7th edition of Goodman and Gilman, ethinyl estradiol is about 20 times as potent as DES, which itself is roughly 8 times as active as TACE. Thus, a course of c'hlorotrianisene for lactation suppression amounts to roughly 0.3 mg of ethinyl estradiol each day for a week, or 6 times the amount contained in a standard oral contraceptive, once standard, known to be associated with increased risk of thromboembolism.

Epidemiologic studies have shown that the risk of both clinical venous thromboembolism and subclinical thrombosis, detectable by plasma fibrinogen chromatography, increases during the first month of oral contraceptive use, remains constant regardless of duration of used, and declines to background within one month of cessation. Further

analysis of risk during the first week of use is beyond the resolving power of these studies.

However, laboratory studies of the impact of estrogens on the coagulation system do shed some light on this issue. Numerous clinical studies have suggested that deficiency of anti-thrombin III, a naturally occurring anticoagulant which inactivates thrombin, activated Factor X and other enzymes involved in clot formation, is accompanied by an increased risk of clinical venous thromboembolism. It is known that women using oral contraceptive pills have significantly decreased levels of functional anti-thrombin III and that the course of this effect parallels the time course of the risk of clinical events, mentioned above.

As Dr. Niebyl outlined in her remarks 11 years ago, pregnancy has long been considered a hypercoagulable state, though the mechanisms for this remain far from clear. However, studies have shown that postpartum women have lower anti-thrombin III levels than controls, which gradually return to baseline values.

One study comparing women receiving DES or quinestrol lactation suppression, with placebo controls, found lower levels as late as six weeks postpartum.

Finally, TACE itself has been shown in a randomized, prospective, placebo-controlled trial to prevent the normal rise of anti-thrombin III levels in postpartum

'omen, though the values in this study remained in the low onnal range, not as low as those reported in patients with ongenital anti-thrombin III deficiency and venous thromboses.

Therefore, it is biologically plausible that the se of high dose estrogens in the first week postpartum may ncrease the risk of thromboembolism. In fact, any other utcome would be surprising.

We would appeal to this Committee's good judgment n weighing a demonstrated absence of need and lack of fficacy against a known risk of uncertain dimension. We ould hope that the Committee will recommend, as it has twice n the past, that the FDA remove the indication for lactation uppression from the NDA approvals for these estrogens, and hat this third strike means that they are finally out.

(Laughter)

The use of Androgens: There are several formu- ations of androgen now approved for the indication of ostpartum breast engorgement and pain but not lactation uppression. These include methyltestosterone, fluoxy- esterone and testosterone enanthate.

As is stated in the labeling of Ora-Testryl, which s fluoxymesterone, and of Metandren, "there is no satis- actory evidence that this drug prevents or suppresses actation." These statements are based on the National cademy of Sciences National Research Council Drug Efficacy

Study, which cited only one paper supporting the use of these drugs for this indication.

We were able to turn up only three papers evaluating the use of androgen for lactation suppression. The first was a 1960 paper, involving only a small number of patients and poor measures of rebound, which found fluoxymesterone moderately effective when compared with placebo.

The second was an uncontrolled, non-blinded study of testosterone propionate in 21 patients, dating from 1938.

The last was a 1954 study, without controls, in which 125 women were injected with testosterone cyclopentyl-propionate during labor. Of note, 84/125 women (67 percent) continued to complain of breast discomfort. The only mention of methyltestosterone, the formulation currently labeled with this indication, is a statement alluding to sublingual administration of this agent.

The paper notes that breast congestion lasted 24-48 hours and occasionally longer, that aspirin and codeine were still required in some cases and that frequent administrations of testosterone were necessary.

No study addressed the phenomenon of rebound lactation, nor did any assess the well-known side effects of androgens, such as hirsutism, alteration in voice and other types of virilization.

We believe that there is no evidence of the

efficacy of androgens in this context, which justifies subjecting women to their serious risks, which include cholestatic jaundice, peliosis hepatis, or blood-filled cysts in the liver, and hepatocellular neoplasms. We believe that the indication for postpartum breast engorgement and pain should, therefore, be removed from these agents.

In summary, we urge the Committee to attend closely to these presentations which follow, always bearing in mind the question: Does the need for any of these drugs, with their very questionable efficacy, outweigh their certain risk of undetermined magnitude?

We ask the Committee to recommend the revocation of the new drug applications approval for Deladumone, Deladumone-OB and TACE, and the deletion of the indication for suppression of lactation from bromocriptine, and of the indication for prevention of postpartum breast engorgement and pain from the testosterone preparations. Thank you.

DR. HULKA: Thank you. We have someone from the Women's Health Network, if you would please introduce yourself?

PRESENTATION BY CYNTHIA PEARSON

MS. PEARSON: Cynthia Pearson, National Women's Health Network. I am the program director.

As you have heard in Dr. Teich's presentation, we joined with the Health Research Group last fall in the

petition to the FDA, asking for reconsideration of the approved indications of drugs presently being used for lactation suppression.

I am just going to comment briefly and not go over all the issues about safety that has been done by Dr. Teich, and will be done by the presenters in the future. There are two issues that are important to the Women's Health Network and that we would like the Committee to keep in mind as you listen today and tomorrow to the discussion about bromocriptine and the sex hormones. One is the rebound effect. What good are we doing women? If we are doing them some good by prescribing lactation suppressant drugs in certain situations, how much good is it if a significant percentage have a rebound later when they are home?

The other is need. I attended the Committee hearing last year when you discussed bromocriptine by itself. I heard comments from various Committee members that left me with the impression that many of the Committee felt that the average woman choosing not to breastfeed probably would do fine with support, information, some pain relief, but no lactation suppressant drugs, but there are certain women, in certain cases, where there was a specific need.

The things that were mentioned last year that have stuck in my mind ever since were stillbirths and women needing late abortions, possibly for genetic anomalies. Just

talking on a common sense level, as one person to another, I do not think women forget that they have lost a baby or lost the potential of a baby late in pregnancy if their breasts do not engorge with milk.

I do not think that the emotional issues of the unwanted end to desired pregnancy are resolved or even helped significantly by lactation suppressant drugs. There is a lot of evidence from other fields of research that grieving goes through the process most quickly and thoroughly if it is done without any drugs. And the kind of side effects that we look for in bromocriptine for their medical import have some other effects just on emotional stability.

So I just wanted to take a minute to put those two things out to the Committee. We will not testify again at the open hearing tomorrow. Our comments apply equally to the discussion today on the sex hormones and tomorrow on bromocriptine. But we would like to ask you to remember the issues of the rebound effect and whether or not the so-called hard cases really do create a special need for these drugs. Thank you.

DR. HULKA: Are there any other comments from the floor?

(No response)

We will then close comments form the floor and go on to our formal presentation. Our next presentation is a

review of the non-pharmacological suppression of postpartum breast engorgement. Dr. Ruth Lawrence, University of Rochester School of Medicine, is an invited speaker.

PRESENTATION BY RUTH LAWRENCE

DR. LAWRENCE: Thank you very much for this opportunity to appear before the Committee. I need to describe my orientation to the subject as a pediatrician and as someone who has spent much of one's life working toward lactation and as a student of the physiology of lactation.

As many of you know, I did prepare a brief statement on the physiology of lactation for the Committee last year in which I tried to point out what establishes lactation, and a good deal of what pertains to the establishment of lactation probably pertains to the physiologic adaptation to non-lactation since no matter when lactation ceases, whether it is immediately postpartum or days, weeks or months later, the same physiologic process pertains without benefit of medication or intervention. When women abruptly discontinue lactation for some other reason later, they find that the use of tight brassiere and not much else is quite adequate. Medications are very rarely indicated.

We were asked to do a brief study, in Rochester, to follow up on this topic and try and get an indication of what the incidence is of difficulties with women who were not choosing to lactate.

I did quote a study that we had conducted in Rochester two years ago. The primary investigator was one of our nursing graduate students, who was studying intervention for women who chose not to breastfeed and had a desire to test whether manual expression of the breast and hot compresses were an appropriate treatment for non-lactators who had trouble.

Because a number of points were brought up by this study, which was very thorough, complete and intense in a small group of patients, I wanted to first reveal the details of that study before reviewing the data collection which we made recently for this presentation.

I will repeat again that breastfeeding and human lactation is the physiologic completion of the reproductive cycle and is associated, at least temporarily, with ovulation suppression. So it is a physiologic process in which, rapidly after birth, the levels of estrogen and progesterone do drop and the levels of prolactin are sustained.

I would also point out that mothers who are lactating do experience a let down on hearing their infants cry or even seeing their infants. This has been shown to trigger release of oxytocin but not a release of prolactin. Prolactin is only released when the baby suckles. So women who are not breastfeeding must probably experience this same thing when they see, hold or hear their babies. So they may

have a little surge of oxytocin. This point has not been actually demonstrated by actual measurements of oxytocin levels but we know that at least seeing and handling one's baby does not increase prolactin levels unless the baby is actually put to breast or the breast is stimulated in some other manner.

The studies which have been done in the last two years really are on a very different population than the ones of ten years ago or more because many of the things have changed in postpartum care, probably the most significant of which is early discharge. What would have been called ten years ago early discharge is normal discharge. So women are leaving the hospital, if they have not had complications or an operative delivery, in 48 hours. So collecting data and making any comments about it is extremely difficult because the patient has gone home.

But in our in-depth study where the patients were followed at home, both by communication where they returned information and where the investigator telephoned them, it was very clear that returning home changed the perception of the problem; that women seemed to suffer less discomfort at home and, because they were ambulatory and up and about, the focus was less on their own personal concerns and more on concerns of their infant, their family and other things. So it became, if you will, a non-problem in this social circum-

stance of early discharge.

Now, to review some points about the original study, first of all, it was not a study of the incidence of pain when not lactating, but was intended to investigate a method of treating pain should it occur.

The study included a follow up of the first 14 days postpartum and included the perception of breast engorgement and the perception of pain. Then the patients were randomly assigned to the experimental group where the breast massage was used and to a control group of pain perceptions and then a total control group of women who had no complaints of pain.

A very significant part of this study was the difficulty in obtaining patients who had any complaints of pain. The investigator used our university postpartum service, where there are over 3000 deliveries a year, and in 4 months found a number of control patients who were not lactating but had no pain. But it became very difficult to find any experimental patients who were complaining of pain. So she also went to a second hospital in Rochester, a community hospital with an equal birth rate, however, a higher incidence of breastfeeding, and tried to identify patients who were experiencing pain.

She was ultimately able to identify 46 patients who were experiencing pain over a period of time when at least 3000 births had occurred and at least 800 women had been

identified as non-lactators. So it gives you a sense of the magnitude of the problem of finding women who were having significant pain.

She entered people into the study on the second postpartum day. One of the methods of assessing pain was actually asking the mother to grade the pain herself. She provided the mother with an index card with an analogue of pain description on it. There was a line from l-10 and 1 was no pain; 10 was pain as bad as one could perceive. The subject returned this card every day for the 14 days.

In addition, the investigator inspected the breasts and made her own judgment about the amount of engorgement, the amount of milk and any problems that might have been associated with that.

The following observations were made: Involution was considered to have occurred when the mother reported no pain and no milk visible for two consecutive days. She instructed mothers with pain on how to manually express their breasts and found no ill effects from that maneuver.

But she also asked another question, which seemed to have a correlation later in the perception of pain, how mothers felt about handling their breasts. Women who were uncomfortable about handling their breasts seemed to have a greater perception of pain.

Now, in the 46 women over the 4-month period, there

was no significant difference in cultural background of the patients. However, it was noted that married women who were well-educated, who were in a higher socioeconomic group and had private insurance, had considerably less pain and were not in the experimental group.

It was also noted that if one looked at the amount of drug that was required during labor, the women who had experienced breast pain had required more drugs during labor. So 57 percent of those experiencing the postpartum breast pain had also had multiple doses of drugs during their labor.

In addition, it was noted that mothers did not really note significant pain unless their breasts were hard to touch -- not just firm; not just full; and not soft.

On that lo-point scale that she provided for them, no mother, at any time, scored discomfort above a 6, barely above the mid-line. No pain was recorded after 2.5 days. If the mother was not uncomfortable in that period of time, she did not become uncomfortable at home later. The peak time for pain did appear to be at about 3 days.

The greatest length of time of engorgement and leaking varied between 3-17 days, with a mean of 9.9 days in the group that had massage and the group that received cold compresses experienced, on the average, some engorgement for 8.5 days, and those who had no pain at all had engorgement for 8.4 days. There is no significant difference between

these figures. It all tended to be the same. There was a very clear distinction, with the younger mother having a protracted problem.

One other change in the design of the study was that the original study included women who were 20 years old or older. Because of the inability to find women with significant pain, the investigator was granted permission to drop the age down to 18. So the majority of patients in this category who reported pain were between 18-20. Of course, it is a subjective impression and there seemed to be a difference in what different mothers perceived as being discomfort.

Based on this, we were attempted a prospective study within the hospital setting to see how many patients of ours today were having difficulty. Therefore, we made up a small sheet which we gave to the primary nurse that took care of the mother on the postpartum floor. Since no mother complained prior to two days, we asked the nurses to fill in this sheet at three days, or if the mother was discharged before three days by a few hours, she also completed this sheet. Again the difficult was that many of our mothers went home within 48 hours and so had no recordings made at all.

During the time that we conducted the study, there were only 42 mothers who were not breastfeeding and who remained for the 3 days in the hospital. Of these, 29 were vaginal deliveries. There were 11 primiparous and 17

multiparous. Only 8 had moderate tenderness; none had severe tenderness. That was 46 percent of the group. The only medication that they received was acetaminophen, and not all of them required that.

We tried to get some information on use of breast binders and found that the use of binders was actually a function of the nurse's conviction of their use and value, and not related to the mother's complaints. After we collected all the sheets I talked to several of the nurses involved, and it did depend on the time at which they had been trained and their own skill at putting on a binder as to how they effective they thought they were.

In addition, there were 13 mothers who had had C. sections, 6 primiparous and 7 multiparous. Of this group, actually only 1 was given suppressant medication and she had no pain. There were 7 of the remaining 12 who had not had suppressant medication who had moderate discomfort. However, as cesarean section patients, they were receiving some pain suppressant medication and this totally took care of any discomfort they might have felt. Their complaint was about engorgement and not about pain.

It was also noted, because a comment has been made about the effect of tea and coffee on postpartum engorgement, that one mother, for some reason or other, was noted to be drunk on the second postpartum day and the following day she

had significant engorgement and dripping of milk. So probably the association of alcohol was an important one in terms of management.

Because of the lack of number of patients, we went also to the second hospital that Miss Bowen had used in her study to try and collect some data. But the breastfeeding rate at that hospital is 75 percent and we did not find any mothers who had not been medicated as the non-breastfeeders belonged to the same obstetrical group who also happened to be ones who used suppressant medication.

So because of our lack of data for you, our lactation study center took on the responsibility of reviewing three months of charts, albeit retrospective, from our postpartum service, in January, February and March of 1989, during which time, because we have about 300 deliveries a month, we projected that there were about 900 deliveries.

The front sheets do not tell you whether a post-partum mother breastfed or not. So we had to pull all 900 chart. Then, having determined who the non-breastfeeders were, we had to review whether or not they were medicated because that too was not listed on the front sheet. So we finally arrived at 209 cases in this 3-month period that we reviewed carefully. Our staff at the lactation study center are experienced chart review individuals.

Our postpartum floor does use a very elaborate

nursing form that enumerates all of the possible things a woman could experience in the postpartum period and it has a check column. So it did not depend on the nursing staff remembering to record about pain, engorgement, milk, discomfort, medications, use of binder and things like that. So we felt that our retrospective review of charts was accurate.

We also reviewed the order sheets and the medication sheets and the day sheets, and we found a correlation between all of these. So we felt that what we had was reasonable.

We reviewed then the 209 charts. They were women who remained in the hospital beyond the second day since nobody reported pain under 2 days. So that is where the 209 patients came from. Of these, there were 50 who had vaginal deliveries. Only 50 women had stayed for the third day if they delivered vaginally and there were 159 cesarean section patients. In that group, 18 had received lactation suppressant drug, bromocriptine, and there were 187 who had received no medication at all.

In the group that received no medication, we had only 2 patients who complained of pain. There were 43 patients who experienced some engorgement and 28 patients who felt full but only 4 who experienced some dripping of milk in that time. So the incidence of symptoms was extremely low. A few of the patients were actually given acetaminophen for their discomfort. Among the cesarean section patients, as I

mentioned before, who were receiving postpartum codeine or Demerol or morphine, had no complaints of pain at all.

We noted that all the women who received bromocriptine took narcotic pain medications, whether they were vaginal or cesarean section patients. Only 91 percent of the women who had no suppressant medication required any narcotics. And 21 percent of those who had suppressant medication and 21 percent of the women who had no suppressant used a binder. So there was no difference in that group.

So to summarize this small collection of small observations, I would just like to point out again that early discharge from the hospital probably impacts a mother's perception of wellbeing and her perception of discomfort and pain, which seemed to be less at home. Pain medications which are given for other reasons are effective in relieving the discomfort of any postpartum engorgement. The only medications on which were discharged were either acetaminophen and, although it was not prescribed, ibuprofen has become such a common over-the-counter medication that they would have access to that. None of them were actually discharged on narcotic prescriptions.

As I mentioned, the binders seemed to be a function of the nurse's perception of their efficiency as to whether or not they were initiated, although patients found them comfortable.

Also it was noted that those women who had been prepared for non-lactation seemed to do better, those who had read about it and prepared themselves for their delivery. We noticed the same observation about successful lactation, knowing what to expect and being prepared, they did not seem to think the experience was very bad. As with other problems, the younger woman, the single woman, the unprepared woman, the woman from lower socioeconomic groups, with less education, experienced more discomfort and the ordering of suppressant medication was done by individual physicians and not by the indications of the patient or the socio-demographic background of the patient.

So we concluded in our multiple small observations that the incidence of discomfort, pain and symptoms occurred in only a small fraction of those women who did not choose to lactate.

DR. CORFMAN: Before you discuss Dr. Lawrence's paper, I would like to acknowledge the special efforts she undertook to have her group do this study that she reported to you. She did it really at our request and actually she and I worked it out on the phone as the only thing to do because the literature on this topic is negligible. The most recent thing we could find was Kokenauer's (phonetic) review that we sent you and it does not really speak to this need issue.

I would just like to thank her for the hard work of her group in undertaking this study.

DR. LAWRENCE: I apologize for any non-scientific aspects of it. We did not have an investigator to assign to this and did use our postpartum nurses with our clinician trying to proctor this. I feel very comfortable about the chart review because ***our*** investigators are experienced chart review people.

DR. HULKA: Are there questions for Dr. Lawrence? If not, thank you.

Is Dianne Kennedy here? Dianne, if we were to have lunch now, would you be able to speak after lunch?

MS. KENNEDY: Sure.

DR. HULKA: It is now 12:35. Could we start promptly at 1:35?

(Whereupon, at 12:35 p.m., the Committee adjourned for lunch, to reconvene at 1:50 p.m.)

AFTERNOON SESSION

DR. HULKA: Dianne Kennedy, of the FDA, will speak about extent of use of sex hormones and bromocriptine for prevention of postpartum breast engorgement.

PRESENTATION BY DIANNE KENNEDY

MS. KENNEDY: Thank you. I was up here a year ago talking to you about the use of bromocriptine. I have been asked to come up this year and expand on that, to include all drugs used in lactation suppression.

What I want to do first though is to remind you of what I was telling you last year that, because of the overlap between the hospitals and outpatient use with the lactation suppression drugs, it is very difficult for us to use the data sources that we have available to us to provide any quantitation on the use of the drugs. However, I think you will find with the data that I am going to show you that you will have a pretty good idea of the types of drugs that are being used and their relative use comparing one to the other.

I handed out a two-page list of products that are listed in the Pharmacy Reference (Facts and Comparison). These are the products that are listed there as being indicated for the use in lactation suppression and breast engorgement. They basically fall in one of four categories, bromocriptine, which is a semi-synthetic ergot alkaloid derivative; then you have estrogens, both oral and inject-

ables; the androgens, both oral and injectables; and then at the end of the list there are combination products of androgens plus an estrogen.

So with the list that you have in front of you, we will take a look at the data from several different data bases. It is actually a patchwork of data bases that looks at several different populations and several different points in the drug distribution pipeline, and we will see what we can find out about what drugs are being used.

(Slide)

The first data that I am going to show you comes from the National Disease Therapeutic Index. You already saw some data on Accutane use from this data base this morning. Just to remind you, it is based upon reports from a panel of 2000 office-based physicians who report on all the patients they see during their assigned 48-hour reporting period each quarter.

The thing to remember here is that these are office-based physicians. If they happen to see one of their patients in the hospital during the reporting time, they will report on that patient but this data base does not measure drugs used by hospital-based physicians or residents, who might be the ones that are more likely to be delivering babies in hospital and treating the women afterwards.

(Slide)

This table shows us the number of mentions for drugs where the physician is indicating that they are giving these drugs for lactation suppression. You can see along the top line that there seems to be a decrease in the times the physicians are indicating that they are using drugs for lactation suppression. These numbers are fairly small for this data base so that the standard error around them is fairly large. But it looks as if there probably is a decrease in the use of these.

Then you can see the specific drugs that the office-based physicians indicate that they are using for lactation suppression. Parlodel is by far the most frequently used product. But TACE and diethylstilbestrol do show up consistently. The three at the bottom, testosterone, Delestrogen and Deladumone are all injectable products. With this data base you do not see injectable products as frequently as the oral products because they basically are hospital drugs and these are office-based physicians where, most of the time, they are seeing the patients in an ambulatory setting.

(Slide)

Looking specifically at the three that are used the most frequently by this panel, bromocriptine, chlorotrianisene (TACE) and diethylstilbestrol, we see that when you are looking at the total use of the drug with bromocriptine, only about 30 percent of its use is for lactation suppression.

The majority of its use is as an anti-Parkinson drug. With chlorotrianisene, the majority of its use is for cancer and for something they call hormonal imbalance. With diethylstilbestrol, about 3 percent of its use is as a lactation suppressor, even though that is not labeled that way, and the majority of its use is for cancer.

(Slide)

The next data I am going to show you comes from Michigan Medicaid, which is based upon paid billing claims. Medicaid data, let me remind you, is for low income families and for aid to families with dependent children. With this data base we have information on outpatient diagnoses, inpatient diagnoses and outpatient drug use. There is no inpatient hospital drug use.

The data that we have available to us is from 1980 through mid-1988. We developed two cohorts of patients, /those that had a delivery in the hospital and those that had a diagnosis that was consistent with a stillbirth in the hospital. We took those two groups and we looked at prescriptions that they had filled at pharmacies within 30 days of having their delivery or their stillbirth. We ranked those and took a look at the drugs that could possibly be used for a lactation suppression. Again, we do not have any direct link between what it was actually used for. So we just went through and picked out those that could possibly have been

used as a lactation suppressor.

(Slide)

With the delivery file that we have there were 37,921 women who accounted for 49,836 deliveries. Bromocriptine was again the most frequently used drug in these women, 16 percent of the deliveries received a prescription for bromocriptine within 30 days. Diethylstilbestrol accounted for 1 percent of the deliveries. The other ones did show up but infrequently.

(Slide)

In switching to the stillbirth file, we only had 386 women in that file and they accounted for 407 stillbirths. Again bromocriptine was the most frequently dispensed drug after stillbirth, 19 percent of the stillbirths received a prescription for bromocriptine. TACE was 1 percent. Then the conjugated estrogens and DES shown up again.

I should say that with both of these, this table and the one I just showed you, bromocriptine was the number one product that was dispensed within 30 days of delivery.

(Slide)

The next data I am going to show you comes from a data base that is hospital data. It does have inpatient diagnoses and it does have inpatient drug use. So this is getting a little closer to what we really want to measure.

This data is 1987. It is based on 75 hospitals.

It is not projected. These 75 hospitals had 70,664 deliveries during 1987 and 15 percent of those deliveries received bromoc.riptine while they were in the hospital; 1 percent chlorotrianisene and 1 percent injectable testosterone. Deladumone and Deladumone-OB are categorized as injectable testosterone in this data base. You see that the other types of drugs are showing up but not as frequently as the top three.

Unfortunately, I do not have a slide to show you but yesterday I received some new data from this data base, for 1988. The panel of hospitals that they use now is up to 80 hospitals and they are projecting the data nationally. They projected that in 1988 there were 5.2 million deliveries in the United States and that 12 percent of those deliveries in 1988 received bromocriptine; 1 percent chlorotrianisene and 1 percent the testosterone category that includes Deladumone.

I also had them look at drugs that were being used in women who had had a stillbirth in these hospitals. They projected that in 1988 there was a little over 12,000 stillbirths nationally and that 39 percent of these women who had had a stillbirth received bromocriptine; 7 percent received Deladumone/Deladumone-OB and 2 percent received chlorotrianisene.

(Slide)

The next data come from the U.S. Pharmaceutical

Market-Hospitals, which is really quantitative information. The only reason I am showing you this is because it can give us a feel for trends in the purchases of these drugs by hospitals. This data base is based upon paid purchase invoices from wholesalers, private hospitals, city, county and state hospitals and psychiatric hospitals, with data projected to the national level.

(Slide)

This slide is kind of busy. I do not know whether you can see it in the back but the data are in thousands of tablets or in thousands of syringes, depending on the type of drug that we are looking at. The bromocriptine is at the very top. It is the 2.5 mg strength. It looks as if there has been an increasing trend in purchases for that particular strength. The rest of the drugs on the table all have been decreasing in use in varying degrees. The Deladumone on the table includes Deladumone-OB as well.

(Slide)

This table is from the National Prescription Audit. It shows prescriptions dispensed from retail pharmacies over time. This is a table that I showed you last year and I just updated it with 1988 data. 1978 was when bromocriptine first came on the market and it received the indication of lactation suppression in 1980. You can see that its use has continued to increase. There were somewhere around 1.3 million

prescriptions dispensed in 1988 for bromocriptine.

The orange bars on the table are that proportion of total prescriptions that were written by OB/GYNs and you can see that it stayed relatively flat over time. They accounted for about half a million prescriptions in 1988.

Just to quickly summarize the data that I have shown you, regardless of what type of population we are looking at or what data source we are looking at, probably somewhere between 15-20 percent of deliveries receive a drug for lactation suppression and bromocriptine is by far the most frequently used product. But the other ones are being used.

From hospital data it looks as if the women who are experiencing stillbirths are more likely to be given a drug for lactation suppression, maybe as many as half of them.

That is all that I have, if anybody has any questions.

DR. NIEBYL: Can you tell what percentage of the drug prescribed by OB/GYNs is for lactation suppression compared to, say, hyperprolactonemia or other indications?

MS. KENNEDY: No, not from any of the data bases that we have.

DR. NIEBYL: But a third are OB/GYN indications and the other two-thirds last year were for Parkinson's disease, presumably?

MS. KENNEDY: Yes.

DR. NIEBYL: I guess it must be a pretty large percentage, just thinking of the numbers of patients involved.

MS. KENNEDY: Probably. Thank you.

DR. CORFMAN: Thanks a lot.

DR. HULKA: We will go on and Dr. Lisa Rarick, of the Food and Drug Administration, will present. The topic is Committee recommendations and FDA actions concerning the use of sex hormones for the prevention of postpartum breast engorgement: a review of the efficacy of this treatment.

PRESENTATION BY LISA RARICK

DR. RARICK: I have the job of trying to update us on how these drugs have gotten where they are today.

(Slide)

We will begin right off with the androgens. Androgens, as a class, were originally approved after the 1938 Food, Drug and Cosmetic Act, most of them in the 1940s and the 1950s. The original Food, Drug and Cosmetic Act required evidence of safety for approval.

In 1962 there were drug amendments to the Act that also required evidence of efficacy for continued approval. Since there were many drugs between 1938 and 1962 to be reviewed, the FDA requested the National Academy of Sciences National Research Council to undertake an efficacy review study for all the drugs that had been approved between those

times. This Council was called the Drug Efficacy Study Implementation.

The DESI Committee, as I will call it from now on, reviewed the androgens in the late 1960s and early 1970s. The requirement was to come up with effectiveness categorizations for the drugs that they reviewed. Effectiveness could be considered effective, non-effective, possibly effective, probably effective, etc.

For the indication of postpartum breast engorgement, the androgens were given the evaluation "effective but . .." and that is exactly how it reads. The comments from the panel go on to state that the panel does not know of satisfactory evidence to support the efficacy for preventing lactation but at this time was in general use and had no imminent hazard to women and was continued to be placed on the effective list.

(Slide)

In terms of efficacy data, as Dr. Teich told you earlier today, to find studies on the efficacy of the androgens is quite difficult. Mechanism of actions is nice to postulate. There are theories discussed in the literature from the '30s to the '60s, some of them giving them the same ability as estrogens for the suppression of anterior pituitary hormones. There was thought that there was a direct effect to suppress the breast alveolar system. I like the last one,

most hormones, regardless of type, will give satisfactory esults --

(Laughter)

(Slide)

In terms of actual studies that I could find, we lid ask the sponsors, who market some of these products that .re currently available, to supply any efficacy reviews they ıay have but we received no response. I found a few in our wn files from the '30s to the '60s.

On the left, under author, you will see if they had comparison group. Most of these did not have a comparison r control study. The last one is a placebo study. You will lso note that there are small numbers of subjects. The umber of subjects are the actual subjects who were taking he androgen.

In the first study we see that they were given estosterone twice a day until they had relief. Interestingly tnough, these were patients that were begun anywhere between lay 3 and 10 postpartum; patients who were already lactating ınd then decided not to; stopped lactating and received estosterone twice a day. They report excellent efficacy in 0 percent but then again, as we have heard today, anybody who stops lactating between days 3-10 may have had relief without any therapeutic medication.

Lass' study, from 1942, was a methyltestosterone

study over 36 years. They gave results of 40 percent absence of pain and engorgement. Again, it is hard to know what that means. Garry, in 1956 -- methyltestosterone for 5 days, again, with 44 percent absence of engorgement.

The only placebo study here, in 1960, was a fluoxymesterone study, which was actually various dosing regimes, and they could show no statistical significance over placebo.

(Slide)

Our current labeling for the androgens: Androgens are considered as a class. They have a class labeling guideline for any of the marketed products, which reads: Androgens have been used for the management of postpartum breast pain engorgement. The class labeling guideline goes on to give dosage possibilities for the various androgens.

The individual products that contain the indication in the physician labeling also can sometimes add, or have sometimes added that there is no satisfactory evidence that this drug prevents or suppresses lactation, as we heard from Dr. Teich's report. That is all we really have on the androgens.

(Slide)

Let's go on to the estrogens. Estrogens in combinations -- combinations would include estrogens in combination with androgens. There are also some drugs on the

market which are estrogens in combination with other drugs.

These drugs, in general, had their original approval again based on the 1938 Act in the 1950s. Because of the drug amendments, during the 1970s the DESI Committee again was asked to review the efficacy of the drugs. The DESI Committee gave it an "effective but . .." evaluation and again states that the Panel does not know of satisfactory evidence to support the efficacy of these preparations to prevent lactation. Statements indicating this preparation prevents or suppresses lactation are too optimistic and should be modified.

(Slide)

You might ask what happened then. For the estrogens, in 1976, there were Federal Register notices and relabeling to discourage routine use and to include the potential risks of thromboembolism in the labeling.

In 1978, the Obstetrics and Gynecology Advisory Committee at the time reviewed the estrogens for the use of postpartum breast engorgement and recommended that it be removed from the labeling. That year, as Dr. Teich told you, there was a notice of opportunity for a hearing, proposing to withdraw approval of this indication for all estrogen-containing products.

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In 1979 and 1980, the FDA received multiple hearing

requests to continue marketing of these products from the sponsors of the products and from the American College of Obstetricians and Gynecologists.

Due to the weight of the sponsor's reply and the prospects of bromocriptine use, which was being approved in the late 1970s (1979), this led the Agency to postpone the hearings. In the 1980s, there were multiple meetings over this issue. There were many FDA statistical and medical officer reviews for the efficacy and safety data recommending simply more stringent product labeling at the time.

(Slide)

In 1985, the DESI Committee, which still exists, recommended that the safety of estrogens for postpartum breast engorgement be reviewed, with special consideration given to a comparison of benefits and risks of estrogens for this used versus Parlodel.

At this time, with the postponing of the hearing, it was most likely due to concerns over possible safety risks of Parlodel use and the Parlodel issue came up last year, in 1988, when this Committee met to review the use of bromocriptine for lactation suppression. At that time the risks and benefits were unresolved, which brings us to date.

(Slide)

When we look at the estrogens and their combinations, we should first understand why they would work

theoretically. As we know, during pregnancy estrogen and progesterone levels are quite high. At the time of delivery, with the decrease of estrogen and progesterone, the prolactin that is also high is allowed to work at the level of the breast. To give estrogens and their combinations would maintain a high level of estrogen after the delivery to continue to prohibit the prolactin at the level of the breast.

The androgens were added through various reasonings in the literature, mostly the theories were to decrease the possibility of estrogen-related adverse effects while contributing their own possible "efficacy" as they were used singly for this indication.

(Slide)

To look at some studies for the estrogens and their combinations, we will just quickly review various studies for chlorotrianisene, which is an estrogen, and some studies for Deladumone-OB and a few of the others.

This slide is on TACE, some studies from the 1950s. You see that the first three have no control groups and the fourth is a placebo study. The number of subjects on chlorotrianisene is given.

Nelson's report, in 1953, said that 97 percent were symptom free. This was a question and answer -- Are you symptom free? Yes/no. They showed a rebound of 3 percent.

This was a 2-week study.

Bennett, in 1954, showed 80 percent with none or mild symptoms. Interestingly enough, although this was not a controlled study, they mention 10 controls in their discussion who actually only had 70 percent of none to mild symptoms but they do not address the issue. Hendrick, in 1954, showed 75 percent symptom free and a rebound of only 3-4 percent.

Primrose, which was the placebo study, gave a 60 percent symptom free interval with 8-day treatment with TACE. Current TACE treatment is actually a 2-day treatment.

(Slide)

Further studies of TACE go into the 1970s. They would include 3 more placebo type studies. King showed 89 percent fair to excellent results with TACE versus 72 percent fair to excellent results on placebo. They do not actually address statistical significance, although I doubt that it is significant. They showed a rebound of 3 percent.

Binns' is a placebo study. Again 70 percent preferred TACE. That is all they say. They do not discuss significance or what the placebo group preferred or what they said.

Dr. Niebyl is here today and can clarify her study if questions arise. In 1979, she was actually doing a safety issue study but also included in her study some efficacy data on 99 patients, 53 of whom were on TACE. She showed no

difference in breast engorgement or need for analgesics between her groups on TACE and placebo.

(Slide)

This is a brief summary of her study. On day 3, you see 53 patients on chlorotrianisene. There is no difference between chlorotrianisene and placebo for breast engorgement or percent using analgesics. At day 8, you notice that there is some loss to follow up. Certainly half of the patients are not available. But again there is no difference between breast engorgement and percentage using analgesics and there is no statistically significant difference in patients satisfied with their drug.

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For Deladumone-OB we have similar types of problems with studies in terms of comparisons and no very good double-blind studies. Stein, in 1958, gives 31-71 percent effectiveness. This was 5 different dosage groups in 253 patients. Their rebound was 21 percent.

LoPresto had 4 differing groups in 197 patients in terms of doses, giving 60-90 percent "effectiveness rate". There is no comparison there.

Watrous did a comparison group but it is not a double-blinded study. He had 7 dosage groups in 132 patients and showed 70-80 percent effectiveness versus 40 percent for his patients on no medication.

Barns' is a placebo study with 12-16 percent rebound. As you can see, he had fair to good results in 54-96 percent, depending on which subjective finding you are looking at, or objective -- lactation, pain, tenderness and engorgement, versus 20-30 percent for placebo.

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To continue with Deladumone into the '60s, Jones did have a control group that did not receive a placebo and 54 percent of his Deladumone patients were symptom free versus 32 percent with no drug. He did have 6 different groups in 153 patients. No statistical significance is discussed.

Bare's is a placebo study, showing 79 percent effectiveness with Deladumone versus 30-60 percent in placebo. But they could find significance only on day 3 and 4 in their 7-day study.

Iliya's was a placebo study. They showed 90 percent effectiveness versus 30 percent effectiveness for pain.

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For the other drugs that were mentioned as possibly still being used, I just briefly mention diethylstilbestrol and can only find articles from quite a long time ago, showing, sort of on the category of the androgens, 26-46 percent absence of symptoms.

For ethinyl estradiol, an article in 1947, 58 percent absence of symptoms, with a rebound of 16 percent. Primrose, primorin-methyltestosterone combination, showed 48 percent absence of symptoms.

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Our current label of the estrogens and their combinations -- as you may know, the estrogens, the non-contraceptive type, have a class labeling, as do the androgens. It includes a labeling section entitled "information for the patient" which is also the patient information pamphlet given to each patient who takes the drug or is prescribed a drug containing any estrogen.

The information in the patient section has a section for "uses" and number 5 is to prevent pain and swelling. Then it goes on with a paragraph discussing the estrogens to prevent swelling of the breast after pregnancy, where the risk of thromboembolism is mentioned.

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The estrogens which actually choose to include this in their physician labeling also include the statement, "control studies have demonstrated the incidence of significant painful engorgement in patients not receiving such hormonal therapy low, usually responsible to appropriate analgesic or other sort of therapy. Consequently, the benefit to be derived from estrogen therapy for this indi-

cation must be carefully weighed against the potential risk of puerperal thromboembolism associated with the use of estrogens".

In conclusion, I think we have seen for the androgens, the estrogens and their combinations multiple studies. Few, if any, are double-blinded or have adequate follow up.

We can certainly understand the DESI Committee review and reservation at the time of their categorization of efficacy. At most, these drugs may be mildly effective, both theoretically on the basis of possible mechanism of actions, or by various analyses by different interpreters of these data.

But in light of our current question of need and possible safety questions with these drugs, we ask the Committee to advise us on further use and labeling of these products. Thank you.

DR. HULKA: Questions? Dr. Teich?

DR. TEICH: Dr. Teich, from Public Citizen. I just wanted to underscore that in addition to the multiple problems with these studies that you alluded to, there was no standard look at rebound effects. If you go across the whole range of studies of all the different compounds, it is not at all standard whether or not rebound lactation was even looked for, much less when it was looked for and how it was looked

for.

DR. RARICK: Right.

DR. TEICH: I just think that that also calls into question the efficacy of those drugs.

DR. RARICK: Exactly.

DR. HULKA: Dr. Diane Wysowski, from the FDA, will be speaking on safety of sex hormones for prevention of postpartum breast engorgement.

PRESENTATION BY DIANE WYSOWSKI

DR. WYSOWSKI: Sex hormones have long been used in this country for prevention of postpartum breast engorgement. But what do we know of their safety for this indication? Unfortunately, not very much.

I will review what we do know about the safety of the estrogens, the safety of the androgens and the safety of the androgen-estrogen combinations for the prevention of postpartum breast engorgement. I will be using data from the FDA's spontaneous reporting system and from epidemiological and clinical studies from the literature.

Before proceeding, I just want to say a few words about the FDA's spontaneous reporting system. It is a reporting mechanism for postmarketing surveillance of adverse drug reactions. It has been in operation since 1969, and this is relevant since most of the sex hormones that we are going to be discussing today were approved back in the '40s

and the '50s.

Spontaneous reports are primarily from physicians who report adverse reactions to pharmaceutical companies who, in turn, are required to report the information to the Food and Drug Administration. Because of problems with under-reporting and interpretations of causality, we have used spontaneous reports as possible signals of adverse drug reactions.

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With that as background information, let's turn to the safety of estrogens for lactation suppression. Let's begin with an old drug, Premarin, conjugated equine estrogens, marketed in 1942.

The 1988 PDR lists prevention of postpartum breast engorgement as the last-mentioned indication for this drug. Note that the daily dose for lactation suppression is much larger than that for menopausal symptoms but, of course, the duration of use is much shorter.

I reviewed spontaneous reports of adverse drug reactions for Premarin from the FDA's spontaneous reporting system. There were 160 reports in childbearing age females. Of these, there were 2 reports of thrombophlebitis; 1 report of puerpera; 2 reports of cerebrovascular accidents; 2 of pulmonary emboli; and 1 of cerebral infarction.

But a hands-on review of each of these reports

showed that none of the women had used Premarin for lactation suppression. There are no known epidemiological studies or clinical studies of Premarin concerning its safety for prevention of postpartum breast engorgement.

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Diethylstilbestrol is another old drug, a synthetic estrogen, approved in 1941. The indication for prevention of postpartum breast engorgement was removed by the Company in 1981. But, as Dianne Kennedy reported earlier, it is still used for that indication. The dose for lactation suppression is similar to that used for breast cancer.

There were 239 spontaneous adverse reaction reports in females of childbearing age, almost all of which were reproductive abnormalities in daughters of mothers who took DES during pregnancy. There was only 1 report of thrombophlebitis in a patient who took DES and concomitant TACE for prevention of postpartum breast engorgement. So she was getting a much larger than recommended dose of estrogen.

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There have been 2 epidemiologic studies concerning thromboembolism with DES for lactation suppression. One study was done by Daniel and others, in Cardiff, Wales, in 1965 and 1966. They compared the incidence rates of thromboembolism in lactating versus non-lactating women who presumably used DES for lactation suppression. But this was not

definitely known for each woman.

They found that the incidence of thromboembolism was 2.5 times greater in non-lactating versus lactating women and 10 times greater in non-lactating versus lactating women 25 years and older or low parity.

The primary problem with this study is that the dose of DES used for lactation suppression was 210-300 mg, which is 7-11 times the total recommended United States dose of 30 mg.

Another problem with this study was the failure to estimate the effect of DES independent of other risk factors, such as age and operative delivery. So it is not possible to determine the contribution of DES to the risk of thrombo-jjembolism from'this study.

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A second epidemiologic study, done in Scotland, ;/compared the incidence of thromboembolism in lactating versus non-lactating women, who also presumably received DES for lactation suppression.

The dose of DES was 80 mg, nearly 3 times higher than the recommended dose in the United States. The investi-gators found a statistically significant, 2-fold greater iincidence of thromboembolism in non-lactating versus lactating /{mothers. But when results were standardized for parity and method of delivery, the incidence of thromboembolism remained

higher in the non-lactating versus the lactating group but the difference was no longer statistically significant.

In addition to these epidemiologic studies, there have been 2 clinical coagulation studies in women receiving DES for lactation suppression.

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The first study was conducted by Daniel and others, of the Cardiff, Wales, group that I mentioned earlier. They found that the mean level of clotting Factor IX for the DES group was significantly different from the mean levels in women lactating or using natural suppression methods. The mean level for the DES group was above the range accepted as normal.

But, again, these findings relate to high dose DES, 7-11 times that recommended in the United States. So it is not possible to extrapolate these results to women who use DES in the United States for lactation suppression.

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The second clinical study tested clotting factors in 10 women breastfeeding, 11 given DES for lactation suppression and 25 normal, non-pregnant women. They found a delay of at least 3 weeks in the return to normal anti-thrombin III activity in the DES group compared to the breastfeeding group, whose anti-thrombin III activity reverted to normal 1 weeks postpartum.

But, again, the dose and duration of administration of DES in this study was greater than that for the United States. In any case, the biological significance of these findings is uncertain.

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Let's turn now to another estrogen for prevention of postpartum breast engorgement, Delestrogen. Dianne Kennedy informed us earlier that Delestrogen is being used a little for lactation suppression.

Here you see its profile. It is estradiol valerate injection, approved in 1954. Lactation suppression is the last indication of 7, in a dose comparable to that used for menopausal symptoms.

A review of the FDA's spontaneous reporting system showed 16 reports in females of childbearing age, including no reports of bleeding; 1 report of hypertension; 1 report of pseudotumor cerebri; and 1 report of hepatoma. But none of these reports had lactation suppression as the indication. There are no known epidemiological or clinical studies concerning the safety of Delestrogen for prevention of postpartum breast engorgement.

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However, there was 1 study of ethinyl estradiol, conducted by Jeffcoate and others, in Liverpool. The methods were very confusing but they claimed a 3-fold higher incidence

of thromboembolism in non-lactating versus lactating women, although the effect was seen primarily in older women with an operative delivery. So, again, we are left with the question of what is the independent effect of estradiol on thrombo-embolism.

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Chlorotrianisene (TACE) is currently the most frequently used estrogen drug for lactation suppression. You can see its profile. It too is a relatively old drug, having been approved in 1951, with prevention of postpartum breast engorgement as its number one indication.

The daily dose is at least twice that used for menopausal symptoms but, of course, it is taken for a much shorter duration.

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Because of the importance of this drug for lactation suppression, we wanted to show you all the reports in the FDA's spontaneous reporting system for females in the appropriate age groups.

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You can see the counts: No drug effect has the largest number, with 27 reports. There is 1 report of pulmonary embolus; 1 of intracranial hemorrhage; 2 of phlebitis; 1 of cerebral thrombosis; 2 of thrombophlebitis.

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Mostly there are just one of two reports for each reaction.

(Slide)

In addition to the 27 reports of no drug effect that I mentioned earlier, there were also 7 reports of breast engorgement for TACE and 3 reports of breast cancer in 2 individuals.

I reviewed many of these reports and several mentioned extenuating circumstances. The report of cerebral thrombosis involved an overdose of TACE. One of the two reports of thrombophlebitis involved a woman with a history of thrombophlebitis and pulmonary embolus. The second report of thrombophlebitis involved an obese woman, previously mentioned, who simultaneously was taking DES and TACE for lactation suppression. One of the reports of breast cancer was in a woman who reportedly took TACE for ten months for birth control. The other report of breast cancer just said "alleged breast cancer in a mother of four children" and gave no other information.

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There have been no known epidemiological studies of adverse reactions for TACE. However, there has been one double-blind, randomized, controlled clinical trial of TACE, conducted by Niebyl and others, in which coagulation measures were done in 24 women randomized to TACE and 26 randomized to

placebo.

Anti-thrombin III values were significantly lower in the TACE versus the placebo group on day 3 postpartum but, nonetheless, were within normal limits. So the biological and clinical significance of these findings is not known.

Now I would like to turn to a review of the androgens, methyltestosterone and fluoxymesterone, used for prevention of postpartum breast engorgement.

(Slide)

Here is Android, approved in 1981. Prevention of postpartum breast engorgement is the second indication of two for females. The doses are similar to those used for breast cancer.

There were no spontaneous reports of adverse reactions for this drug in the appropriate female age groups. There are no known epidemiological or clinical studies of Android concerning its safety for prevention of postpartum breast engorgement.

(Slide)

Metandren is another methyltestosterone drug, approved in 1940. It has prevention of postpartum breast engorgement as the second of two indications for females. Then the labeling makes a contradictory statement: There is no satisfactory evidence that this drug prevents or suppresses lactation. Note that the dose for lactation suppression is

less than that used for breast cancer.

There are no spontaneous reports for prevention of postpartum breast engorgement and no known epidemiological or clinical studies of Metandren concerning its safety for lactation suppression.

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The same holds true for Oreton Methyl --

(Slide)

-- and for Testred, two other methyltestosterone drugs. There are no spontaneous reports for prevention of postpartum breast engorgement and no known epidemiological or clinical studies concerning its safety for lactation suppression.

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This lack of information also holds true for fluoxymesterone. Here is Android-F, with no spontaneous reports; no epidemiological studies and no clinical studies concerning the safety for lactation suppression.

(Slide)

The same with Ora-Testryl. Again, the labeling gives prevention of postpartum breast engorgement as an indication, followed by the statement that there is no satisfactory evidence that this drug prevents or suppresses lactation.

(Slide)

I put Halotestin up here, just to show you that although it is a fluoxymesterone drug, it does not give prevention of postpartum of breast engorgement as an indication for its use.

(Slide)

Finally, I would like to turn to the androgen-estrogen combinations. Deladumone-OB is a testosterone-estradiol injectable, approved in 1955, with prevention of postpartum breast engorgement as its sole indication.

(Slide)

Here are all the spontaneous reports for Deladumone-OB for females for prevention of postpartum breast engorgement. There are 13 of no drug effect and several injection site reactions, as you can see.

(Slide)

There is 1 report of 3 individuals with pulmonary embolus; 1 report of thrombophlebitis.

(Slide)

There are 5 reports of virilism; 8 of voice alteration; and 21 of hirsutism. The report that says apnea of larynx was actually a report of cardiopulmonary arrest and it was coded here as apnea.

(Slide)

There are 3 reports of breast engorgement, in addition to the 13 that I mentioned previously of no drug

effect. There are several of vaginal bleeding.

As an aside, the report for the woman who arrested stated she had received spinal anesthesia and one hour later Deladumone-OB. Five minutes later she had a seizure followed by cardiopulmonary arrest. Resuscitation was successful.

There are no known epidemiological or clinical studies concerning the safety of Deladumone-OB for prevention of postpartum breast engorgement.

(Slide)

Next is Deladumone. It is similar in formulation to Deladumone-OB, with the same amount of testosterone but half the estradiol. Prevention of postpartum breast engorgement is the second indication of two.

(Slide)

Here are the spontaneous reports for Deladumone. The 3 reports of pulmonary emboli were all for the same patient.

(Slide)

There is 1 report of cholestatic jaundice; 3 reports of voice alteration; nothing much more.

(Slide)

There are 4 reports of hirsutism; 1 report of breast engorgement.

Again, there are no known epidemiological or clinical studies concerning the safety of Deladumone for

lactation suppression.

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There is only one study known to me concerning the long-term effects of any of these drugs. That is this one, by McTiernan and others. It is a case control study of thyroid cancer in which parous women who had ever used an estrogen-containing lactation suppressant were found to have 1.7-fold increased risk of thyroid cancer. These results have not been verified.

There are no other studies concerning associations of any of these sex hormone drugs when used for prevention of postpartum breast engorgement with breast cancer or with any other illnesses with long latency periods.

In summary, there is a paucity of good, definitive data on the acute and long-term effects of sex hormones used for prevention of postpartum breast engorgement. Consequently, we are left with mostly theoretical safety concerns, primarily about thromboembolism and coagulation problems with the estrogens, with little definitive data to either prove or to lay to rest these safety concerns.

DR. HULKA: Comments? Questions?

(No response)

Dr. Stadel will have some further comments on potential risks of this treatment.

PRESENTATION BY BRUCE STADEL

DR. STADEL: Those of you who know me, may appreciate that when I am not sure what to say I talk about oral contraceptives and vascular disease.

(Laughter)

(Slide)

So I am just going to comment on some perspectives because I think you have had an accurate description of what is available in the literature. There have not been the kinds of studies of these regimens, as they are presently used, which allow us to quantify risk.

On the other hand, we do know that at certain levels of exposure estrogens clearly do cause venous thromboembolism and I think it is worth considering the magnitude of that in relation to what the exposure is and then some other considerations, hoping that you can arrive at some intuitive feel for what you are dealing with in terms of risk because we are clearly not going to give you a quantitative figure.

For mostly 50 ug oral contraceptives, these are the incidence figures in current users for idiopathic venous thromboembolism, meaning when there is no evident predisposing condition; the incidence in non-users and the relative risk and the attributable risk, which is the more important figure.

Perhaps the most important column for what I want to say here is this one, postoperative venous thrombosis.

There are about 31 cases/10,000 surgical procedures evidently caused by having been on the pill at the time. So you are looking at 3/1000 women getting venous thromboembolism as a consequence of being on the pill at the time that they underwent surgery.

I use that as an example because it will at least allow some qualitative comparison perhaps to the state of the vasculature in the postpartum period where you do have known vascular changes; you have dynamic changes, which may produce some of the predisposing elements for thrombus formation. This is generally referring to deep vein thrombosis.

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So women taking 50 ug pills at about a 3/1000 risk -- I want to mention before I move on that the percentage of women on these types of pills who reach apparently critically low levels of anti-thrombin III activity, in the non-user it is about 2 percent of women who have borderline levels and that is increased to about 16 percent of women. So that is a perspective on the biochemical end of it. You have this in terms of the actual events and where the shift is in terms of the anti-thrombin system.

Then you go to the other extreme and that is women taking typical low dose hormone replacement therapy, estrogen alone in the amount of 0.625 mg or 1.25 mg of Premarin. The literature shows no increased risk venous thromboembolic

disease at that rate of daily ingestion. It has been studied in a number of studies and nothing has turned up.

Correspondingly, when you look at the impact on the anti-thrombin system, there is only a small decrease in mean anti-thrombin activity and there is a distribution change. It is not analogous to 50 ug of estrogen. It sort of appears that for most women that amount of estrogen is below the level which produces much of a problem, if they do not have predisposing factors because those studies, of course, are not in women who just underwent surgery or just underwent delivery.

So I am giving you two extremes. One is a known risk in a group with analogous predisposing conditions. The other extreme is that there does not appear to be a risk at the level of women on hormone replacement therapy.

The part that none of us can answer in any quantitative way is how do these two extremes of exposure that I have just described, oral contraceptives and hormone replacement therapy, relate to giving 72 mg of chlorotrianisene every 12 hours for 4 doses and how do they relate to giving DES 15 mg a day times 7 days? Those 2 dosage regimens have produced reductions in anti-thrombin III activity, which really delays more the return of the normal postpartum return. We normally have a return fairly rapidly. It appears that when the drug is given to suppress lactation, it

delays that. So there is a window of potential risk in someone with predisposing changes in the vasculature for putative disposing changes.

With that somewhat unsatisfactory statement, that is what I leave you with. I think what it says is that on the spectrum of risk here and no risk at the other extreme, you have a position which you can only arrive at by judgment. I cannot give you a firm quantitative figure. I cannot give you any quantitative figure of where it lies in there. You have to arrive at that in your perceptions of it.

I think that question then of uncertainty about what level of risk you are willing to talk about or tolerate, I can only see as being determined by your judgment as to the extent of any benefit that you perceive with regard to using these drugs to suppress lactation. Of course, if you perceive no benefit, then the ratio of risk to benefit is #infinity even if the risk is uncertain. If you perceive a benefit, then it entirely depends on what you perceive from what you have heard and what your experiences are.

I always like to ask what is the acceptable level of attributable risk? If these drugs were to cause venous thromboembolism in 1/1000 people, would you accept that in this indication? Or l/100,000? I think you really have to answer the questions on this issue. Thank you.

DR. HULKA: Was there a comment from the audience?

DR. TEICH: Yes. I just wanted to speak to one point that Dr. Wysowski alluded to, as did Dr. Stadel, namely, that the three British epidemiologic studies that involved DES and ethynil estradiol, done in the '60s, did show in all three that there was a synergistic risk of administering lactation suppression to women who were either older, had increased parity, or had had what they called assisted delivery, which was a very heterogeneous group, including forceps, cesarean section, low forceps, etc. I think that is not something to ignore since it is certainly consistent with what is known about oral contraceptives in terms of special risk in women who are predisposed.

In addition, it is clear that there are certainly significant numbers of older women delivering who may be preferentially given lactation suppressants. Or, certainly there are increased numbers of cesarean sections and it may very well be, since at least several years ago that was a group of women that were preferentially prescribed lactation suppressants, that it is exactly that group that may be getting these drugs preferentially and there may be some sort of synergy between those factors. I would just keep that in mind.

DR. MCKAY: Perhaps Dr. Lawrence could speak to this, we have looked at some of the physiologic side effects of various lactation suppressants. We have not talked at all

about the psychological issues and I would like some kind of commentary on whether there might be some benefit in a woman who has decided not to breastfeed to actually have the physiologic process begin that releases the oxytocin into the system. It seems that mothering behavior is increasingly being tied to the natural sequence of hormonal release after birth. Could you speak to that, please? Would there be benefit to a woman not to have any lactation suppressant even though she does not plan to breastfeed?

DR. LAWRENCE: Well, I think that is a very interesting comment because in the Bowen study, she had intended as her experimental design to encourage women to briefly manually express their breasts to relieve any pain they had. One of her ulterior motives, if you will, was to change their attitude towards their breasts and, hopefully, influence them for the next pregnancy to consider lactation. Therefore, she asked that question about how comfortable they were with their breasts before the study and before they were assigned to a research group.

A couple of women in the study did actually decide they had so much milk so why didn't they give breastfeeding a try? And that is also why I made the comment about let-down, that it is a physiologic response to hear your baby cry or see your baby and have let-down. But that is only in relationship to the flow of oxytocin. Prolactin is not

timulated to increase unless there is actually breast timulation.

Indeed, I think there is room for considering those ssues. I do not think we have the information, just as we o not have the information about the impact of breastfeeding n mothering. We, who work in the field, think that mothers 'ho breastfeed are not different but breastfeeding makes them .ifferent. But I have to confess that our data is lean and .hat needs to be studied.

But I think that is another issue in terms of how bothers feel about their babies if they are deprived, if you 'ill, of the natural hormonal flow.

DR. HULKA: We have two sponsors who would like to ıave a statement at this time. The first is Dr. Clyde Rolf, irom Merrell Dow.

PRESENTATION BY CLYDE N. ROLF

DR. ROLF: Madam Chairman, members of the Committee, thank you very much. Merrell Dow has conducted 3 placebo or, basically, no treatment, controlled studies, with a TACE 12 mg dose. As far as the 25 and 72 mg doses are concerned, there were 3 double-blind, placebo-controlled studies with the 25 mg dose and 6 with the 72 mg dose.

All of these studies showed significantly less breast engorgement, pain or swelling of the breast in the postpartum period compared to either the no treatment or

placebo group.

Patients were then followed at 14 days with a questionnaire and at a 6-week check up. At both times, the incidence of rebound breast engorgement or lactation has been equal or less than placebo in the 25 mg group. In the 72 mg dose, at 14 days, in 5/6 studies the incidence of rebound breast engorgement was less in the treated group and they were equal at 6 weeks.

Since TACE has been introduced, there have been 4 drug experience reports or thromboembolic phenomena. These were in patients that were treated for postpartum lactation. One of these reports was from the United Kingdom and it contained 6 patients from a single center where the investigator was reluctant to ascribe causality. There have been no reports of thromboembolic phenomena received by the sponsor since 1975.

Merrell Dow has submitted labeling to the Food and Drug Administration with a patient information pamphlet which lists the potential risks and, basically, exclusions for treatment with TACE, according to the guidelines of this Committee. This submission will basically put the use of TACE back in the patient-physician arena. Thank you.

DR. HULKA: Dr. David Winter, from Sandoz.

DR. WINTER: Thank you very much. As you know, we are on the schedule for some discussion tomorrow when the

issue of bromocriptine comes up. But since the Committee is going to discuss questions l-6.3, I believe, we felt it important to move one of our presentations to this afternoon. That presentation, which will be given by Dr. Bennett Walstatter, specifically deals with the need for treatment in the postpartum period. Since your discussions on risk-benefit clearly cover that point, we felt, with your concurrence, we would move that discussion up now.

If I may, I would like to introduce Dr. Bennett Walstatter, who will go through the rest of the introduction himself.

PRESENTATION BY BENNETT S. WALSTATTER

DR. WALSTATTER: I am Dr. Walstatter. I guess as time goes by, we get letters after our names -- M.D., Fellow of the American College of Obstetrics and Gynecology, Associate Professor of Obstetrics and Gynecology, Community Medicine, Family Practice, University of Missouri Kansas City -- out in the heartland but, more importantly, practitioner of obstetrics and gynecology.

First of all, I am pleased that I can be here today to share my experience in the treatment of postpartum lactation. I believe that we are here today to determine the need to medically suppress postpartum lactation. In order to do this, I think it is necessary to at least take a somewhat brief look at the recent history of lactation and breast-

feeding.

It was not that long ago, and do not be fooled by the bags under my eyes because I am not that old, that breastfeeding was not a terribly popular thing. It started back a long time ago and, yes, breastfeeding was very popular. It was the only choice.

Then technology stepped in. With technology came some interesting things. We had formula. The formula was expensive. So only the affluent could afford to not breast-feed. So the affluent switched away from breastfeeding and it became more popular among the affluent. It was a sign of accomplishment if you did not have to breastfeed.

But again technology intervened at this point and the price of formula went down and now formula became available to everyone and breastfeeding now became out. The pendulum swung away from breastfeeding and bottle feeding became more common.

Well, this went on for a while, until maybe 20-25 years ago, when all of a sudden the medical literature started showing some interesting things. Breastfeeding was good for the baby and all of these people who were now bottle feeding were now being informed that perhaps they were doing a disservice to their child by not breastfeeding.

The pendulum swung back. It now became very high tech to be low tech -- breastfeed. However, not all women

can or choose to breastfeed and it is incumbent upon us not to pressure them into feeling a failure for the inability to breastfeed or to make the choice not to breastfeed.

(Transparency)

Women choose not to breastfeed for a variety of reasons. Some of these reasons are physical; some are psychologic; some are social. I have taken an opportunity to list some here. You will probably all notice that there are some missing.

Under the physical, we see cracked nipples, mastitis, breast abscess -- 1 am just reading it off for you; you can all read it.

Under social, we list adoptions, stillbirth, premature birth. Missing from that probably would be congenital anomalies that make it not possible to breastfeed; also illness in the newborn.

The psychological, however, probably still remains the major source of why women choose not to breastfeed -- body image. Women deliver, many of them have gained weight; many of them feel uncomfortable with the way they look; they know that if they are going to continue to breastfeed their breasts are going to be enlarged and they have been "societized", if you will, into believing that this is not good. They see that and they decide that breastfeeding is not for them. They do not want it.

Others believe it is inconvenient. They have other responsibilities. They are going back to work. They happen to work in an office where they cannot pump their breasts. They go home to other children; they go home to other responsibilities and they choose not to breastfeed. Outside pressure -- probably the worst of all; probably it comes from their husbands or their male consorts. The last choice, personal feeling from previous experience, perhaps they had a poor experience breastfeeding the last time; they were just uncomfortable and they do not want to go through it again. So they choose not to breastfeed.

It is our responsibility as physicians to recognize our patients' needs and for us to respond to these needs with appropriate support.

Now, there are those who would argue that postpartum lactation is a physiologic event that is self-limiting with non-intervention. This may well be true. However, many areas of medicine would easily fit into that description. Much as we encourage our female patients -- the only ones, of course -- to have childbirth without intervention, without medication, we still stand by available, should they desire or need, to offer narcotics and anesthetics from the amide ester groups that will affect mother and baby.

It is not reasonable to deny the new mother medication that has been shown to be safe and effective to

accomplish her perceived need. Again, this is her perceived need. I am not advocating pan-usage of any medication. Routine usage should never occur. It is important for patients to be aware, however, of all of the options and to participate in the decision-making process.

Office and/or clinic counseling, as is done at my institution, gives patients valuable information. They are made aware of their choices and can participate in the final decision-making process.

Now a little bit about where I live. I live at a county facility -- well, not really; I go home sometimes, but it is in Kansas City. It is a county hospital. We have the third largest obstetrical service in the Kansas City area. Our patients are followed by nurse practitioners, residents and attending faculty members. Most of them are from a lower socioeconomic class. My department is responsible for over 1200 deliveries annually, again, mostly lower socioeconomics. Many of them are uneducated.

During the course of prenatal care, our patients are counseled about postpartum feeding alternatives, as well as methods of delivery. Breastfeeding and bottle feeding is discussed at antenatal classes and we firmly, strongly, without any question, encourage all of our patients to consider breastfeeding. That is not what this is all about. We want our patients to breastfeed. We believe that this is

what should be done.

Patients are also made aware of their choices in the same way as they are prepared for childbirth. Information takes a lot of fear away from situations; information allows the patients choices and options.

Well, what happens after childbirth? Well, our patients generally stay two nights, three days. Our pediatricians like to see the babies and like to take care of the babies before they go home. This gives us an opportunity to monitor them a little bit closer.

Approximately 35-40 percent of our patients choose to breastfeed. Of the rest, approximately 50 percent of our total deliveries, and some months greater than 60 percent of our total deliveries, choose to be medicated and that medication is Parlodel since it is the only medication that is currently available in treatment of postpartum lactation on my service.

Of these patients, approximately 10 percent will report some complaint or problem, mostly discomfort and a few will experience rebound. Patients, obviously, are excluded from the use of Parlodel if they have any contraindications. Of course, these patients are all started on the medication by prescribing directions. Unfortunately, our biggest problem is that we have no way to determine which patients are going to be symptomatic.

(Transparency)

Now I will show what we have, what was available, what we offer to our patients as far as education and what was initially available in our hospital. This is what the patients were told about -- and this will be updated -- the natural methods of suppression; use of nothing or use of a breast binder, with or without ice packs, with or without analgesics. Patients in our population do use more analgesics. Many of them are prescribed Motrin or ibuprofen. Some of them will get narcotics, Tylenol with codeine, Number 3; some Tylox.

The pharmacologic methods for suppression of lactation: Hormonal, Deladumone-OB injectable was available and TACE was available. These ar no longer available on our obstetrical service, and the non-hormonal choice of bromocriptine mesylate.

This is what our patients were given and this is the information. They were told risks and benefits, what the advantages are, what the perceived disadvantages were, what risks they might experience. However, the patients were given the opportunity to participate in the choice.

It has become obvious, at least in my institution and certainly in other places, that Parlodel is now the overwhelming choice of medications for the suppression of postpartum lactation.

(Transparency)

We have a study that was done using 204 total teaching hospitals and the availability of Parlodel was questioned. Parlodel was available in 201, or 99 percent; stocked on formulary, 96 percent; stocked but not on formulary, 3 percent. It was not available in 3 hospitals. It was unrestricted in all but 3 hospitals. The reason for restriction in those hospitals were contraindications of hypertension or cardiovascular disease; a postpartum mother who is 18 years old or less; and someone with undiagnosed amenorrhea or galactorrhea. Those were the indications that restricted use of the medication.

It seems quite clear, given this number of teaching hospitals and given the fact that it is prescribed, that there certainly must be a perceived need for the medication. But what is the need?

As I showed earlier, women desire suppression of lactation for many reasons. This need, as perceived by patients, I believe is incontrovertible. But why use Parlodel? Again, I would just like to point out that it is used immediately postpartum. We cannot prospectively decide which patients are going to be symptomatic with lactation.

After last year's meeting, Sandoz commissioned this study to answer some of the questions. The findings that I will present here, having reviewed the study, are very

interesting, certainly a little different from what we heard a little earlier.

(Transparency)

In this postpartum lactation study, non-breast-feeding women were identified and 62 hospitals were represented. Patients were divided into Parlodel and non-Parlodel usage. The screening was done by telephone, initially interviewing patients in the hospital, and 109 patients received Parlodel and 102 patients received no medication. A follow-up telephone interview was performed 19-20 days after beginning the use of Parlodel or 19-20 days postpartum. I think you will find the findings interesting.

(Transparency)

Interesting on this slide, at least to me -- this is a slide of patients who reported pain and 66 percent of Parlodel patients reported no pain versus 22 percent of //patients who took nothing reported no pain.

Significant also in this was the moderate to severe group , where a total of 16 percent of the patients reported moderate to severe pain, whereas, 54 percent of the patients who did not take Parlodel reported moderate to severe pain.

DR. CORFMAN: What is the mean?

DR. WALSTATTER: The mean was the amount of pain.

DR. CORFMAN: It should not be percent.

DR. WALSTATTER: It should not be percent. Thank

you. It is the mean amount of pain reported. It should not be a percentage, 1.7 was the mean amount of pain in the patient scale in Parlodel usage versus 4.4 as the mean amount of pain as perceived by the patients.

DR. CORFMAN: Was this a blinded study?

DR. WALSTATTER: This was a random study of patients who were not breastfeeding who were interviewed. Those who were not breastfeeding were divided into groups, one group receiving Parlodel and one group receiving nothing, no placebo. However, the interviewer did not know which group the patient was in. So it was done as a telephone interview.

(Transparency)

Also of interest, another key finding, if you will, is the patient's report of all symptoms. In the non-Parlodel group 81 percent of the patients reported pain, swelling and/or engorgement and leaking, whereas, of the Parlodel patients 38 percent reported any symptomatology. It seems that the patients who took part in this study must have been more susceptible to pain and effects of the lactation.

At this point I would also like to respond to our first consumer group -- I am sorry, I do not know your name. In your letter, you referred to two studies. In these two studies it showed that 8-33 percent of patients experienced moderate to severe pain. That does not seem like a lot of

people until you start considering that there are approximately 8.3 million births annually. That comes to almost three-quarters of a million women who are experiencing moderate to severe pain. Patients do experience that.

But in summary, what I would like to say, and I think it is important, probably the most important point is that patients should be encouraged to breastfeed. There is no question about that. However, not all mothers choose to breastfeed; not all mothers can.

It is important for patients to be aware of their options regarding suppression of postpartum lactation. Groups and subgroups will not be identifiable as to who is going to be most symptomatic. The patients have demonstrated a need and a choice for a safe and effective medication for the suppression of lactation. Parlodel, a non-hormonal agent, has been shown to be safe and effective for suppression of postpartum lactation in women who desire suppression.

Given the safety factor and the desires and needs of the patient, I think it is important for us to have that as a medication available for the treatment and suppression of postpartum lactation. Thank you.

DR. HULKA: Do we have questions?

DR. SCHLESSELMAN: In the clinical trial that you reported, could you please briefly describe how the trial was presented to the women with regard to encouraging them to

participate in the trial, a statement of the objectives of the trial?

DR. WALSTATTER: Patients were given a letter inviting them to participate in this trial, in this study. I have a copy of that letter with me, if you would like to see it. They were told of this study and asked if they would like to participate.

DR. WENTZ: Did you use a placebo or was it simply that the patients were untreated?

DR. WALSTATTER: No placebo was used.

DR. NIEBYL: I just wanted to make one comment and take issue with your list of contraindications to breast-feeding. I really think it is inappropriate to say that prematurity is a reason not to breastfeed. In fact, we encourage such patients to pump their breasts until such time as the infant can nurse. Similarly, some other things you mentioned, like mastitis which, again, does not necessitate stopping breastfeeding. In fact, we encourage patients to breastfeed while they are on antibiotics. That is not really pertinent and to the point --

DR. WALSTATTER: I would like to respond to that. The reason that I included prematurity is that a lot of premature babies are born at perinatal centers, to which parents travel hundreds of miles, and are not always there. While they would like to breastfeed, many of them choose, if

they are not going to be there, to try to resume a normal life. Again, we can debate --

DR. NIEBYL: It is not an indication for lactation suppression when the mother is 12 hours postpartum, the fact that the baby was born premature. They may later get discouraged and change their mind but that is certainly not the 'standard recommendation.

DR. WALSTATTER: Well, again, my stance is that a patient should be encouraged to consider breastfeeding.

DR. NIEBYL: Then you should argue that you should let them get engorged if they are going to get engorged because they might change their mind at that point.

DR. WALSTATTER: Well, that is fine.

DR. NIEBYL: So do not give them a drug to suppress lactation.

DR. WALSTATTER: Like I said earlier on, I do not advocate the pan-usage of any medication. It needs to be discussed with the patient and a decision needs to be made based on the patient's needs and desires, not on the physician's needs and desires.

DR. NIEBYL: We are really talking about the issue of whether a drug is necessary. There are certainly patients who make the decision not to breastfeed and they may get a little engorgement and most do not. But some will and that could be managed in that circumstance with non-pharma-

cologic things, such as binders, ice packs or whatever.

DR. BARBO: I would like to ask a question about body disfigurement with breastfeeding. Is that a perception of the women or is that a perception of their husbands since this is a physiological phenomenon?

DR. WALSTATTER: I would say that what I believe is that it is a perception of the environment that is laid on the woman. It does not necessarily come from her.

DR. BARBO: I hope not.

DR. MANGANIELLO: I have two comments. In one of the slides you were talking about the fact that Parlodel is on the formulary of teaching hospitals and that it if it is on the formulary there must be a reason for it, and one of the reasons is probably for lactation suppression. I know at our institution we also have a service similar to yours, about 1000 deliveries a year. It is a medical school, multi-specialty clinic setting. Although I am a reproductive endocrinologist, I am a practicing obstetrician and I have been there for ten years and I really cannot remember when the last time one of my partners or faculty members prescribed any medication for ovulation suppression. We do have Parlodel on the formulary but that is for other reasons, for hyperprolactonemia. So I think that your assumption is wrong about the fact that if it is on the formulary it is used exclusively for lactation suppression.

The other statement I want to make is that I do not think that is something which is necessarily, at least in the experience that I have had over the past 10 years, a treatment modality for a non-problem.

DR. NIEBYL: Certainly, there have been some surveys presented already earlier today that at many teaching institutions in the country this is not routinely used, which simply supports what you said. At the two institutions that I have been associated with, both of which are large teaching hospitals, in the last 15 years we did not use any lactation suppression pharmacology, no drug for lactation suppression routinely. We counsel our patients that in a small percentage of the cases they would get engorged and they dealt with this with ice packs or analgesics, if necessary -- similar to the group that Dr. Lawrence described. But it is on our formulary for other reasons, for Parkinson's or for hyperprolactonemia.

DR. WALSTATTER: Two points, one is that the medication is on the formulary unrestricted. That is first. Now, whether it is used -- that is correct, I cannot tell you that.

Secondly, I have been at both teaching institutions and community hospitals and in the community hospitals, I can tell you first-hand, the amount of Parlodel that is used in incredible. Patients are asking for it. Patients --

DR. NIEBYL: Patients ask for cocaine too, as I

recall.

DR. WALSTATTER: That is true. We have them at our hospital too and we do not give them that. However, we know that cocaine is not a particularly safe medication.

DR. NIEBYL: But just because a patient asks for it does not mean you should give it to her.

DR. WALSTATTER: No, but if she has a perceived need and we feel that she has a perceived need and we perceive that as well and we have something that is safe, I do not think she should be denied.

DR. WENTZ: I think it is perfectly clear that what we are hearing are the practices of a physician's patients clearly reflecting the physician's practice. We are certainly not going to convince you, particularly since there was not a placebo arm.

That is not really what we are here to hear about today and I think further going back here would be unproductive. I thank you for your presentation.

DR. HULKA: I wonder if we could have about a 15-minute break now and then come back and review these questions?

(Brief recess)

DR. HULKA: Would you please pull out your questions in front of you? We will take the questions in sequence. I would remind you that question number 1 is the reiteration of

a similar statement that we made last year.

I will read the question: Does the Committee reaffirm the recommendation made at its June 2-3, 1988 meeting that sex hormones and bromocriptine should not be used routinely for this indication -- this indication being postpartum breast engorgement?

Apparently we made the statement a year ago that sex hormones and bromocriptine should not be used routinely for postpartum breast engorgement. Do you want to discuss this question again or shall we just go right ahead with the question?

DR. NIEBYL: I think we just discussed bromocriptine, didn't we?

DR. CORFMAN: No.

DR. NIEBYL: We discussed both? Okay.

DR. HULKA: If you reaffirm then the statement, all those who reaffirm it, would you please raise your hands?

(Show of hands)

That looks unanimous. The Committee reaffirms the recommendation made a year ago that sex hormones and bromocriptine should not be used routinely for the indication of postpartum breast engorgement in women who do not nurse.

Then we go on to the next question: What is the Committee's estimate of the actual need of women who choose not to breastfeed, their need for prophylactic treatment for

postpartum breast engorgement other than analgesics and binders?

So what is the estimate of the need? That seems Like a qualitative response when you look at the next question, which says something about -- well, the next question relates to prophylaxis. Yes?

DR. NIEBYL: I just have one question about the term binders. I think the usual phrase is breast support rather than binders because we do not want to stimulate the breast by tight binding.

DR. CORFMAN: Okay.

DR. HULKA: Fine. We will just change that to support.

DR. WENTZ: And the wording looks as if we are recommending prophylactic analgesics and breast support and I do not know that we are using prophylactic analgesics.

DR. HULKA: I do not think that is really the intent of the question. It is a little awkwardly worded. It is really what is the estimate of the actual need for prophylactic treatment for postpartum breast engorgement --

DR. NIEBYL: With medication.

DR. HULKA: -- with medication. It seems to me that we have already said that we do not think there is a routine need for medical treatment for breast engorgement. So I am not sure then what it means by the estimate of the

actual need in question 2.

DR. NIEBYL: We will just say zero percentage require it.

DR. CORFMAN: But the form of the question is important and I think it is good for the Committee to change it. We did work hard on these questions. I would like to suggest that we just omit "other than analgesics and binders". Omit that because what we are after is the key issue that Dr. Lawrence was asked to address and that the sponsor addressed, and that is whether women -- aside from their perception, what is your perception for the need for these drugs for prophylactic use? If you cannot answer the question, say you do not know but at least try to answer it some way or other.

DR. MCDONOUGH: Phil, could we say the actual need of women who choose not to breastfeed for pharmacologic treatment for postpartum breast engorgement?

DR. CORFMAN: That would be all right but the point is that none of the labeling is other than prophylactic use. There is no indication for treatment of symptoms. So each time we have to repeat the fact that the indication is for prophylactic use.

DR. NIEBYL: We can just make a statement that the Committee does not perceive a need for a drug for women who choose not to breastfeed for prophylactic treatment.

DR. CORFMAN: If you agree with that --

DR. NIEBYL: Or something to that effect.

DR. MCANARNEY: This is a question more than anything else, and a comment. I was fascinated with Dr. Lawrence's data regarding women going home and the fact that they seem to be less symptomatic once they are home.

We have confined ourselves in this question to really two issues, that of analgesia and that of support. I do not know exactly where this would fit in but I find that fascinating. We talk all the time about the disadvantages of early discharge but here, for the first time, is one advantage. Is there any place for this? Will that be picked up from Dr. Lawrence's presentation? Because that was one of the very interesting new findings I think, that is that early discharge could be efficacious. I do not know exactly how to say it.

DR. HULKA: I hear your point but I do not know exactly where it fits in this.

The problem I am having with question 2 is that it looks very much like a different way of stating question 1. That is the trouble I am having -- or question 3.

DR. CORFMAN: I really think your comment, Madam Chair, is the critical issue here. It is a conundrum. Nobody proposes that this drug be used routinely. The sponsor and the expert clinician who spoke to us said it is never for routine use. On the other hand, the drug has to be

used prophylactically, before the woman may develop symptoms. So how do you know which woman is supposed to take it? For the, that goes down through a logical inconsistency that is very difficult for us to deal with. That is why we want some kind of statement from you that will help us when we deal with the sponsors.

Number 2 is a very simple question: Do you think such drugs are needed?

DR. HULKA: Let me state it again, changing the English just slightly: Among women who choose not to breastfeed, what is the Committee's estimate of the actual need for prophylactic treatment for postpartum breast engorgement?

DR. NIEBYL: None.

DR. WENTZ: Zero percent.

DR. HULKA: No need. All right, all those who think the answer should be "none"?

(Show of hands)

Is there anyone who disagrees with "none" as the answer to question 2?

(No show of hands)

I see that everybody says "none", including myself. So question 2 is among women who choose not to breastfeed, what is the Committee's estimate of the actual need for prophylactic treatment for postpartum breast engorgement?

The Committee's unanimous answer to this question is none.

Then question 3 is really not relevant because it says if such prophylaxis is deemed necessary for some women, and we have said that such prophylaxis is not necessary. So given the Committee's answer to question 2, question 3 is not relevant.

Question 4: How may these women be identified so that the physician will know which women may benefit from the treatment?

DR. NIEBYL: There are none. I think there aren't any but I think we should specify that we are addressing some of the special cases like stillbirth and I would like to specify that I do not think they are routinely indicated for women that have stillbirths either. If a woman has a stillbirth, a malformed baby or some other problem that contraindicates breastfeeding, that is the least of her problems, breast engorgement. She is going through a lot of hormonal and emotional changes that she needs help and support with. Adding a drug for lactation suppression is not going to make a significant difference in that patient, in my opinion.

DR. HULKA: Getting back to question 4 then, it is not relevant, just as question 3 was not relevant. Keep in mind, Jennifer, how we will get in the particular point you are making.

DR. NIEBYL: Right.

DR. HULKA: The answer to question 4 is not relevant, given our answer to question 2.

DR. MANGANIELLO: I really think it would be incumbent upon someone to prove that lactation in the situation of a stillbirth is harmful to the individual, rather than making the assumption that suppression of lactation is necessary in that clinical situation. I have not seen where people have come forward and shown me definite proof that lactation following a stillbirth is psychologically traumatizing the woman, needing to have lactation suppressed. I think lactation is a physiologic response and it is possibly part of the grieving process. Unless you allow that to occur, you may have some delayed psychologic trauma. No one has shown either way that it is beneficial or harmful. So if you have not shown that it is harmful, then there is no reason for treating it.

DR. HULKA: Paul, let me ask you something here, as I think of lactation, I cannot imagine why a woman who had had a stillbirth would want to lactate but she will have breast engorgement and she could be managed or handled in exactly the same way as a woman who had had a normal full-term live delivery.

DR. NIEBYL: Right. She might just have some milk leakage.

DR. HULKA: Right. Fine.

DR. MANGANIELLO: I stand corrected.

DR. HULKA: That was a very rapid movement through those 4 questions. I wonder if you would like to think a little bit about question 5 now. Question 5 is in a different vein. We are not talking about routine prophylactic use; we are talking about should these drugs be used to treat the symptoms of postpartum breast engorgement? So now we are presumably talking about a different indication or a different possible indication. But it is also noted here that no drug currently carries this indication -- this indication presumably meaning anything else, other than prophylaxis -- and proper studies would have to be submitted to the Agency before any other indication could be considered. Do you have comments about this?

DR. ROY: Do we have any information on that score? I mean, surely, people have used these compounds exactly in the setting of not treating and then whey they are symptomatic, then to treat. But do we have any compilation of that information?

DR. RARICK; The only information we have on treatment with a pharmacologic is with Parlodel and it is simple, anecdotal information. There are a few, scant studies that I will present tomorrow on treatment, for the estrogens and androgens.

DR. HULKA: So then we have nothing about treatment for the sex steroids. We are going to hear something about uses in treatment --

DR. BARBO: I think the one article that we were given on lactation suppression had some information and if you gave it later it did not do any good. So I think we have that.

DR. NIEBYL: You mean the sex steroids or the Parlodel?

DR. BARBO: On the sex steroids.

DR. NIEBYL: I think that is correct, they do not work. Lisa is going to present some of the small studies that maybe Parlodel works as a therapeutic agent after the patient has got engorged. So if you embarked on a policy of not treating and then the 10 percent or so of women who got engorgement and discomfort, you could potentially treat with those but still eliminate treating the other 90 percent unnecessarily. But I do not know the data on that.

DR. BARBO: But you would not be using the sex hormones.

DR. NIEBYL: No, that would not be with the estrogens. I am waiting to hear you present that tomorrow.

DR. CORFMAN: Question 5 is simply put in to be complete --

DR. NIEBYL: There are no data.

DR. CORFMAN: -- and to get the Committee opinion. There are no data to present. When Parlodel was first being considered by the Agency, there was data on symptomatic use but they withdrew that and only asked approval for prophylactic use. If you do not know the answer to 5, it is quite appropriate to say so but we wanted your views on record.

DR. NIEBYL: But should we hear some more information about bromocriptine before we answer question 5? Are there data about treatment?

DR. RARICK: Limited.

DR. NIEBYL: We are going to hear it tomorrow? I guess we should hear it before we answer the question.

DR. HULKA: Would you be willing to answer question 5 in terms of the sex steroid hormones?

DR. NIEBYL: Yes, we can answer that now.

DR. HULKA: Then is your answer that these drugs should not be used to treat the symptoms of postpartum breast engorgement?

DR. NIEBYL: Yes.

DR. HULKA: All those who would say that they should not be used -- the sex steroids?

(Show of hands)

Anyone who thinks they could be used or should be used, would you raise your hand?

(No show of hands)

The Committee will respond to question 5 in terms of the sex steroids. The question is, should these drugs be used to treat the symptoms of postpartum breast engorgement? The Committee feels that these drugs should not be used in such a way.

Do you want to speak to any other indications for the steroid hormones? I do not believe we have data on any other indications. Does anybody want to disagree with that statement, that we do not have data on other related indications? We said no. So shall we just quit at that?

Question 6: What are the Committee's recommendations concerning the following drugs currently in use for the prevention of postpartum breast engorgement?

It seems to me we are really reconsidering questions 1 and 2 but now with specific statements about each of the pharmacologic categories of estrogens, androgens, estrogen/androgen combinations. Then I guess we can hold on bromocriptine until tomorrow.

DR. BARBO: I would like to recommend that those indications be withdrawn for estrogens, androgens and estrogen/androgen combinations.

DR. HULKA: Okay. All those in favor of saying that they should not be used for prevention of postpartum breast engorgement? Would you raise your hands?

(Show of hands)

Anyone who disagrees, thinking that any one of those categories should be used?

(No show of hands)

Question 6: What are the Committee's recommendations concerning the following drugs currently in use for the prevention of postpartum breast engorgement? The three categories of drugs are estrogens, androgens and estrogen/androgen combinations. The Committee unanimously think that none of these drugs should be used for the prevention of postpartum breast engorgement.

Dr. Corfman is asking do we want to give any reasons why we are not recommending any of these agents for routine or preventive purposes. Anything on safety and efficacy, the usual things?

DR. MCDONOUGH: They are no more effective than breast binders or analgesics and might have some potential complications.

DR. HULKA: Estrogens, androgens or estrogen/androgen combinations are no more effective in the prevention of breast engorgement postpartum than are analgesics and breast support. They may also have some adverse effects.

DR. SCHLESSELMAN: Dr. Hulka, we voted on the second question a while back, which we rephrased, as I understood it, to read that among women who choose not to

breastfeed, what is the Committee's estimate of the actual need for prophylactic treatment for postpartum breast engorgement? The response was that there was no need.

That question having been answered as it was unanimously by the Committee, I would then ask why don't we take up bromocriptine as a drug to address the question that we have just addressed --

DR. CORFMAN: I can answer that. It is on the agenda for tomorrow. It has been posted in the Federal Register and we have to have an opportunity for a public hearing and have the sponsor have an opportunity to discuss the issues. So you cannot finish the meeting now. I am sorry, you have to come tomorrow.

DR. HULKA: Are there any other comments for today? If not, we will close shop. Thank you very much.

(Whereupon, at 4:05 p.m., the Committee adjourned, to reconvene at 9:00 a.m., Friday, June 2, 1988)

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FERTILITY AND MATERNAL HEALTH DRUGS

ADVISORY COMMITTEE

Bethesda, Maryland

June 1, 1989

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