FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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DERMATOLOGIC DRUGS ADVISORY COMMITTEE

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OPEN PUBLIC HEARING
NDA 18-662
ACCUTANE (isotretinoin) CAPSULES

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26 April 1988

Parklawn Office Building
Conference Rooms D & E
5600 Fishers Lane
Rockville, Maryland

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DR. DAVID GRAHAM

DR. JOEL KURITSKY

DR. EDWARD TABOR

DR. CARNOT EVANS

REQUESTS TO MAKE PRESENTATIONS:

THOMAS JANSEN, M.D

SIDNEY WOLFE, M.D.

CASIMER GRABOWSKI, Ph.D.

JAMES HANSON, M.D.

ROBERT L. BRENT, M.D.

C O N T E N T S

CONTENTS (Continued)

PROCEEDINGS

(8:07 a.m.)

DR. BERGFELD: Again I would like to call to order the Dermatologic Drugs Advisory Committee. We will be taking up two topics during the day: (1) the adverse effects of Accutane, which will take up the majority of the day; and (2) the status of the Patch Test Kits.

I would like to at this time introduce the new panel members. We have with us today Dr. Elizabeth Abel, a dermatologist from Stanford University, Stanford, California; Dr. David Stein, Director of Determatology, Children's Hospital of Buffalo, Buffalo, New York; Dr. Joseph Fleiss, Professor and Head, Division of Biostatistics, Columbia University School of Public Health, New York; Dr. Harold Minus, Associate Professor, Department of Dermatology, Howard University Hospital, Washington, D.C.; and Dr. David Woodley, Associate Professor, Department of Dermatology, and now the new head at Cornell University Department of Dermatology, New York.

They will be joining our other members who are Dr. Robert Stern, Dr. Lynn Drake, Dr. Shirley Osterhous, Dr. Neal Penneys, Dr. Paul Bergstresser.

So, thank you.

We now need to move on and to state that we have several guests that will be speaking today. We have a current list of approximately six guests. I would like to state at this moment, are there other guests that will wish to present a prepared statement during the day that we are not knowledgeable about?

[No response.]

DR. BERGFELD: No. I would like to also announce that the open comment period which is usually held in the first hour of such a committee meeting will be postponed and put on the agenda at the end of the discussion period, which will be in the mid-afternoon.

Dr. Tom Nightingale has a few remarks to make at this time.

DR. NIGHTINGALE: Thank you, Dr. Bergfeld.

As a matter of record we would like to note that in preparation for this meeting today the Agency reviewed the grants, contracts, and financial interests of the committee members and the invited guests. After this review, the Agency has determined that in order to avoid the appearance of a conflict of interest, Dr. Paul Bergstresser will not vote on the matter of Accutane today, and the Agency has granted a full waiver to allow the unlimited participation of Dr. Robert Stern.

Dr. Stern would like to make a comment now.

DR. STERN: Yes. Although I have been granted a full waiver, because of my continuing support for a research project from Hoffmann-La Roche Company and other consulting work I've done for them in the past, although never on Accutane, I would like to not vote on these proceedings, but I would like to, like Paul Bergstresser, be allowed to fully participate in the discussions and just not vote.

Thank you.

DR. BERGFELD: Okay. We are now moving on in our agenda, and Dr. Carl Peck, Director of the Center for Drug Evaluation Research, will make a few remarks.

Introductory Comments by Carl Peck, M.D.,
Director, Center for Drug Evaluation
and Research

DR. CARL PECK: Thank you, Dr. Bergfeld, for opening the session. I would like to give my welcome to the Advisory Committee and to the public at large, and to our colleagues in the press. May I ask the press to respect and assist our process by being as minimally disruptive as possible.

I would like to especially welcome the five new members of the Advisory Committee. I know what it is like to be new to this Agency. Having been here only six months, I have learned a few things about the Food

and Drug Administration, and I would like to take just a few minutes this morning to share a few things that I learned about the Center so that you can have some perspective of your role in the process of new drug development and drug regulation.

I am going to have to ask that the lights be turned off now so that we can turn some 2 x 2 slides on and some transparencies.

[Hereafter, vu-graphs are shown.]

DR. CARL PECK: I would like to explain a little bit to you about the place of the FDA and the Center for Drugs within the FDA, and a little bit about its mission and its organization.

As you can see from this organizational chart, the Food and Drug Administration is divided into roughly seven operational units. There are about 7000 scientists and support individuals that work at the Food and Drug Administration, and we are divided into a number of centers. For brevity, there is the Center for Foods, for Drugs, Biologics, Veterinary Medicine, Devices, and Radiological Health; a Center which concerns itself with developing toxicological data of use to the other centers; and a large network of regional, district, and resident posts--what we call "the field"--which allows us to stretch out and operate

across the country in satisfying our mandate in the regulation of foods, drugs and cosmetics.

So we will speak now mainly about the operation of the Center for Drug Evaluation and Research. The last time you met, which I believe was in November, we had recently split out from a conjoint organization that had been called the Center for Drugs and Biologics. May I have the next slide.

The Center for Drug Evaluation and Research is depicted here. There are roughly 1100 of us in this center, and we will be going over in a moment the general mission of our center. What I would like to point out to you at this point is a number of the operational units.

Apart from the head shed, which is meant to try to keep the place together, we are divided into roughly six operational units. There is an Office of Epidemiology and Biostatistics, which is headed by Dr. Gerry Faich. You will be hearing from a couple of the scientists that work within that section this morning, Dr. David Graham and Dr. Joel Kuritsky, who are pharmacoepidemiologists associated with the Epidemiology Branch, and they will be bringing to your attention certain investigations that they have undertaken on the usage of Accutane and estimates of some of its side

effects. There are roughly 100 individuals in this section.

In the Office of Compliance there are a couple of hundred individuals who focus on our law enforcement mission. In this section we have strong linkages with the field operation. We inspect manufacturing operations, clinical investigations, clinical investigators, and provide a compliance function.

The two offices of Drug Evaluation--Drug Evaluation I and Drug Evaluation II--are the heart of our new drug evaluation. Here Dr. Bob Temple heads the Office of Drug Evaluation I. There are a couple hundred individuals in there comprised of physicians, pharmacologists, toxicologists, chemists, who consider investigational new drug applications and new drug applications that are presented to the Center.

Just to give you an idea of the magnitude of the work underway within the Center, we are currently monitoring somewhere around 10,000 investigational new drug applications, of which 2500 or so are commercially sponsored; the remainder being sponsored by individual investigators.

The Office of Drug Evaluation II is headed by Dr. Jim Bilstad, who sits in the committee this morning. The Division of Anti-infectives is headed by Dr. Edward

Tabor, who will be speaking after me, and within that division is the Dermatology Drug Products Branch which is headed by Dr. Carnot Evans, who is also with us on the committee this morning.

So for the perspective of the committee, the epidemiological data that we will be discussing this morning has come from the Office of Epidemiology and Biostatistics. The primary responsibility for originally the I&D and then the new drug application for Accutane resided within the Anti-infectives Division, and jointly they have been monitoring the post-marketing experience.

Within the Office of Drug Standards we have a number of elements that focus on over-the-counter drugs and generic copies of originally patented drugs. There is an Office of Pharmaceutical Research Resources, and the Advisory Committee--unfortunately not appended onto this particular slide; this is an instance in which I have the wrong slide--actually reports directly to the Center Director to the Center Office.

If I can now have the transparencies, I would like to just review for the new members the main missions of the Center for Drug Evaluation and Research. This rather wordy first mission depicts our mandate to advise and regulate sponsors of new drugs by

establishing and setting medical, scientific, and legal standards.

These are meant to ensure that drugs which are efficacious enter the marketplace, and that we have sufficient information on the risk/benefit experience in advance of marketing that we can label the drugs properly.

The second transparency expresses our mandate to ensure that the drugs meet a high quality standard in terms of their manufacture, and that they are properly labeled.

The final mission which holds a co-equal place with our other missions is to gather information in the post-marketing phase so as to assure that the continuing marketing approval is consistent with everything that we learn new about risks and benefits of the drugs as they're actually used by physicians and by patients.

You can turn that off, now.

As you well know, the main business of the day is a discussion about Accutane, a drug known to be uniquely effective in the treatment of severe cystic acne, which is recalcitrant to standard therapies, and a drug with often tragic consequences to the fetus when inadvertently taken by pregnant women.

We are seeking your advice and counsel this

morning. As you know, our pharmacoepidemiological arm has undertaken epidemiological investigations on Accutane use in women of child-bearing age which call into question the effectiveness of the firms and the FDA's multiple efforts to restrict use of Accutane to patients with severe recalcitrant acne who are not pregnant before or during therapy.

Contrary to press reports, however, we at FDA have not reached a position on any particular regulatory action to take in this matter. Rather, we are counting upon you, along with several invited guests, to provide us with a reasoned, thoughtful, and balanced advice.

We ask you to dissect and discuss the various points of view, and to carefully advise us on the options. We will make no final decisions today. Rather, we will take your advice especially seriously in our consideration as we decide what actions are in the best interests of those who may potentially benefit, as well as those who may be harmed by the drug in the future.

I will turn the meeting back over to Dr. Bergfeld.

DR. BERGFELD: Thank you.

The committee will be taking up the questions that you received in your agenda program in the

afternoon session, but we will strictly abide by your request that we advise you, Dr. Peck.

Dr. Edward Tabor is now going to present.

Presentation of Edward Tabor, M.D., Director
Division of Anti-Infective Drug Products

DR. TABOR: Accutane was approved in 1982 prior to the time that I joined the Division of Anti-Infective Drug Products as Division Director. However, within a very short time after beginning as Division Director--in fact in two separate periods in 1983 and 1984--it was necessary for this Division to deal with birth defects caused by Accutane.

Enormous amounts of time were invested to try to find a mechanism to prevent women from taking this drug while pregnant. Some of those involved in this enormous effort were Dr. Carnot Evans, Dr. Phyllis Hewin, Mr. David Boswick, Dr. James Bilstad, and myself.

The steps taken were considered extreme at the time in the context of the way drugs are labeled in this country--and I think the U.S. probably has stricter labeling for prescription drugs than any other country in the world. In that context, the labeling and relabeling of Accutane was severe and radical.

The measures included--in addition to the box contraindication against use in pregnancy, and a

reduction in starting dosage for Accutane--they included a color brochure distributed by doctors and pharmacists; a patient leaflet, included with each bottle; and red warning stickers to be placed on each bottle by the pharmacist. All of these warned against becoming pregnant or against starting Accutane if there was a chance that the patient were pregnant.

Now data has become available from the Division of Epidemiology and Biostatistics which was formally circulated in recent weeks within the agency that these measures have not prevented two things: they have not prevented the widespread overprescribing of Accutane to men and women who do not meet the criteria on the current label for the use of Accutane.

The current label states that Accutane is indicated for "severe recalcitrant cystic acne." That is, acne that is cystic, severe, and that has failed to respond to other therapies. Secondly, these measures have not prevented the occurrence of pregnancies in patients who are using Accutane--including pregnancies that apparently were in progress in some cases at the time Accutane therapy was begun.

Extensive discussions have taken place within FDA over the past few weeks. These discussions were initiated in most cases by the Division of Anti-

Infective Drug Products, and have involved many people outside of the Division including Dr. James Bilstad, Dr. Gerald Faich, Dr. Carl Peck, Commissioner Young, and others.

Now we have brought the issue to you, the committee. We have brought you the data and a list of possible solutions, and the opportunity for discussions and presentation of yet other solutions. There are two reasons why we have brought this before you.

The first reason is that Accutane was presented to this DHHS chartered committee on three previous occasions. Although most of you were not on the committee at that time, there are plenty of us in this room who remember those meetings and the concern shown by this committee. Some of those who were here at that time and are here now include Dr. James Bilstad, Dr. Carnot Evans of FDA, and Dr. Sidney Wolfe from the Health Research Group.

The second reason why we have brought this before this committee is that this is an issue that is so important that it must be brought before the public and before a panel of experts from the medical community. We have also invited guests to participate in the discussion. These guests include experts on the toxicity of medications for the reproductive system,

experts on the rates of contraceptive failure, and experts on the care of pregnant women and the care of sick infants.

I want to thank all of you on the committee and all of the invited guests for your willingness to assist us on relatively short notice with this important problem.

Thank you.

DR. BERGFELD: That ends our introductory comments. We are now going to move on to the subject at hand. It is divided into two parts.

First is the data presentation, which is this morning; and the second, the options which will be taken up this afternoon.

It is my understanding at this time that Dr. David Graham, the group leader of the Epidemiology Branch Office of Epidemiology and Biostatistics of the FDA will now present.

Review of the Data by David Graham, M.D., Group Leader, Epidemiology Branch, Office of Epidemiology and Biostatistics

DR. GRAHAM: Good morning. I am pleased to have the opportunity this morning to present our data on the subject of maternal exposure to Accutane.

Shortly after the marketing of Accutane in

September 1982, the FDA began to receive reports of severe birth defects in the offspring of mothers who took the drug during pregnancy. These reports continued to the present signaling the existence of a major problem with Accutane.

As a pregnancy Category X classified drug, there is clear evidence of fetal risk. The risk of this drug in a pregnant woman clearly outweighs any benefit to that woman. Category X status is not focused on the avoidance of birth defects, per se, but rather is directed at pregnancy exposure itself. Pregnancy exposure is not an acceptable risk under any circumstance. Today I will review work done by Drs. Rosa, Baum, and myself on the subject of maternal exposure to this drug.

The work you will see this morning represents a more indepth analysis of data which was presented in our preliminary report two months ago. The analyses today incorporate many helpful suggestions from the manufacturer.

In the next few minutes we will discuss Accutane usage showing that the population with severe cystic acne for which Accutane is indicated is relatively small, and that Accutane use is extensive reaching far beyond its approved use.

We will next explore the issue of pregnancy exposure to Accutane, examining data from three different populations in the United States. Each of these data bases show that pregnancy exposure to Accutane occurs in between 1.5 and 6 percent of women exposed to the product. The majority of these exposures end with induced abortion, which has increased two-fold among Accutane-exposed women compared to women not taking Accutane.

Among the remaining pregnancies which come to term, severe birth defects and stillbirths occur.

In the third section we will show reports of birth defects continuing to be received by FDA. Under-reporting is extensive, and most pregnancy exposures are not reported.

In the last section we will discuss these data in light of the extraordinary labeling and educational efforts taken to prevent pregnancy exposure to Accutane.

The approach used in this section on Accutane usage will have two parts. In the first we will describe the size of the population which we believe fulfills the labeled indication for Accutane; in the second, we will assess actual drug use as measured by several data sources. Finally, Accutane use will be compared to the population of women who fulfill the

labeled indication to receive it.

As a starting point of our analysis, we begin with the labeled indication which Accutane currently has FDA approval for. Accutane is indicated for patients with severe cystic acne unresponsive to conventional therapy including systemic antibiotics. We used this approved indication as the template by which to estimate the number of women of child-bearing age for whom Accutane was intended.

No actual head count exists of how many women of child-bearing age have cystic acne fulfilling this labeled indication. To estimate its size we used results from three large population-based examination surveys. These are the only such studies providing sufficient detail from which to draw conclusions.

This slide summarizes the studies which we will discuss in more depth. Rea, et al., examined 1555 people aged 8 to 18 in the United Kingdom, classifying them according to a 5-grade scale for acne severity. Grade V, which most closely approximated the "severe cystic acne" we are concerned with today, had no patients found in that category for a prevalence estimate to 0 cases in over 1500 people examined.

In another study from the United Kingdom, Burton, et al., examined 614 adults. They used a three-

part grading system in which the definition for "severe" was, and I quote, "needing early medical attention because of severe symptoms or progressing disease." This category was much broader than just "severe cystic acne." Of the 614 patients examined, only 1 feel into the "severe" category for a population-based rate of 1.6 cases of severe acne per 1000 persons examined.

The final study which we examined was the National Health and Nutrition Examination and Survey, or NHANES. The study was designed and sponsored by the National Center for Health Statistics, and in it over 20,000 people chosen randomly from the population were examined by Board Certified dermatologists for the presence of various skin disorders. Cystic acne was one of the disorders specifically examined for. The study found an overall prevalence of cystic acne of 1.9 cases per 1000 people. Cystic acne was 5 times more common in males than in females, as shown by the prevalence ratios for males and females here. This excess of males was found in every age group between the ages of 12 and 44. Below the age of 12 and over the age of 44, cystic acne was not encountered in females, and was rarely encountered in males.

This study with a prevalence estimate of 1.9 per 1000 for cystic acne, and Burton's study with an

estimate of 1.6 per 1000 for all severe acne including cystic as well as noncystic, indicate the rarity of cystic acne in the total population.

Both Rea and Burton found that, while for any given grade of acne severity, women were more likely to seek medical attention than men, despite having lower proportions of severe disease. Because of this, and for other reasons as well, trying to estimate how many women have cystic acne based on who comes to the doctor for treatment is likely to cause large overestimations of the number of women with disease.

To avoid this bias, we derived an estimate of the number of women with severe cystic acne unresponsive to conventional therapy, including systemic antibiotics, on the basis of population-based references, and we chose to use NHANES because it was the largest study conducted in the United States and it dealt specifically with cystic acne.

This next slide outlines the approach taken to obtain an estimate of the number of women with severe cystic acne who had satisfied the indication for Accutane which is currently approved by the FDA. The total U.S. population in July 1984 was 237 million. We use this value because it is the mid-point of the period 1982 to 1986 which we studied in other data bases.

The NHANES prevalence for cystic acne of 1.9 per 1000 population was applied to the total U.S. population to come up with a national prevalence estimate of 450,000 cases. This is all degrees of cystic acne severity and includes both males and females. From NHANES we know that the sex ratio was 5.5 to 1 in favor of males. Only 15 percent of cystic acne occurred in females. Applying that 15 percent figure to the prevalence of 450,000, we arrive at a female prevalence estimate of 69,300.

The approved indication for Accutane clearly states that Accutane is for use only in cases of severe cystic acne, but what proportion of cystic acne is severe? The answer is difficult to obtain because no study has examined the distribution of severity among a randomly chosen group of cystic acne patients. Although NHANES determined the prevalence of all cystic acne, it did not publish data on the severity of cystic acne. So no estimate of what percentage is severe can be gotten from that source.

Also, there is apparently no universally accepted standard definition for "severe." However, from the original studies which formed the basis for the NDA approval of Accutane, "severe" was defined as 10 or more deep cystic inflammatory lesions, each of 4

millimeter or more in diameter.

In Peck's original pilot study published in 1979, the average number of cysts per patient was 26. In his larger placebo control trial published in 1982, the average number was 42 cysts per patient. These patients clearly had severe cystic acne. However, it is equally clear from the literature that there are patients with fewer than 10 cysts, fewer than 5 cysts, and even patients with only 1 cyst. A spectrum of disease severity exists, as it does for most other disorders including acne vulgaris. In acne vulgaris, a perimetal model for disease severity exists, with very few patients having severe disease relative to those with milder gradations of severity.

In the examination surveys performed by Rea and Burton referred to earlier, the distribution of acne severity was such that only a small proportion of all disease fell into the extreme category of truly severe. In Rea's study there was no cases in over 1500 patients.

Finally, the labeling for Accutane specifically uses the word "severe" in its description of when the drug is indicated, indicating that not all cystic acne is severe. So although no study has been published which describes the severity of cystic acne in

a large group of patients, we believe it is reasonable to assume that 50 percent of cystic acne might be severe. If the pattern with other diseases apply, this actual proportion may be much lower.

The resulting estimate for the number of women of child-bearing age with severe cystic acne comes to slightly under 35,000. This represents roughly the total number of women in the entire U.S. population who would have had severe cystic acne when Accutane came on the market in 1982.

"Prevalence" is the number of patients with disease present in the population at the time of a census or counting. "Incidence" on the other hand is the number of new cases developing in that population over the course of a period of time--generally, a year. "Prevalence" and "incidence" are directly related, according to this formula, prevalence equaling incidence times duration of disease.

From the pre-Accutane era the published literature suggests that cystic acne duration tends to be long. The mean duration of the disease published in two early studies was 8 to 9 years. We used 8 years in our calculation and obtained an annual incidence for severe cystic acne in women aged 15 to 44 of about 4300.

Given the nature of the disease, the incidence

rate for cystic acne is likely to remain stable over time. The duration of the disease could be shortened by the introduction of new therapy such as Accutane. However, this would only serve to reduce the prevalence without affecting disease incidence at all. As such, incidence is an intrinsic property of the disease and the population.

We now turn to estimating Accutane usage. There is no absolutely precise way to estimate the number of women of child-bearing age who have received Accutane. In Dr. Edward Lammer's 1985 article published in the New England Journal, a paper co-authored by employees from the manufacture of Accutane, it was estimated that 10,000 women per month were being newly started on Accutane, and that 160,000 had already received it by the time the article was submitted for publication in 1984.

This data was derived from a marketing survey commissioned by the firm. We extrapolated this number from 1984 exposures to obtain an estimate of 390,000 women of child-bearing age through the end of 1986. We also examined a drug-use data base called the National Disease and Therapeutic Index. This is a physician office-based survey which registers the number of time a drug is prescribed.

From this we obtained an estimate of 270,000 women of child-bearing age having been treated with the drug between 1982 and 1986. This is a somewhat lower estimate than that obtained by the manufacturer using a different commercial data base.

This slide shows the number of patient visits for Accutane between 1983 and 1986 based on data from the National Disease and Therapeutic Index. The shaded area represents women aged 15 to 44 who received prescriptions or had physician visits for Accutane in each of the years shown along the X axis. Over the years shown, slightly over 1.1 million prescriptions for Accutane went to the 270,000 women in this age group. One other feature to notice is that in each successive year the proportion of all Accutane use which went to women of child-bearing age remained relatively constant at about 40 percent of total Accutane use.

We may now compare the observed use of Accutane with what would be expected if every woman in the United States who satisfied the label indication of severe cystic acne had been treated with Accutane.

From the slides we showed earlier based on prevalence, we know that there are about--we believe that there are about 34,000 prevalent cases in 1982 when Accutane was approved. We estimate that the incidence

in each successive year was about 4300 cases. This would lead to a total number of cases at the end of 1986 of about 53,000 women aged 15 to 44 in the United States satisfying the labeled indication.

In that time period, from two different estimates, we have an estimate of 270,000 to 390,000 women getting the drug. Comparing the one to the other, we see that the excess of use of Accutane in the population amounted to a five- to six-fold excess.

If we, instead of looking at prevalence, assume that all prevalent cases were treated in the first few years after Accutane came on the market, we can then use current annual use as an estimate to compare against the incidence of new disease in the population.

The average annual use of Accutane in the population ranges from 63,000 to 92,000 new women aged 15 to 44. On an annual basis, we estimate about 4300 new cases of cystic acne in this population. If we compare the "incident exposure" to the incident cases we see that the excess of use in this population could be as high as 15-fold greater than the approved indication. In this analysis, only about 7 percent of current use may be used for the approved labeled indication in women aged 15 to 44 in the United States.

Our conclusion from Section I of our data is that Accutane is overused.

We will now shift gears and begin to look at pregnancy exposure to Accutane. Accutane carries a pregnancy Category X classification stating that this drug should never be used in a pregnant woman. Pregnancy exposure is potentially so severe, that benefit of the drug to the mother never outweighs the potential risks to the fetus.

In this section we describe the extent of pregnancy exposure to Accutane within the United States, relying upon three large population-based data sources. The most complete data with the largest number of Accutane users comes from Michigan Medicaid. Less complete data exists from Florida Medicaid and from Group Health Cooperative, an HMO in Seattle, Washington.

The Medicaid system provides health care to about 270,000 women aged 15 to 44 annually. Each time one of these women sees a physician, undergoes a procedure, or receives a medication prescription and submits it to a pharmacist, a billing claim is generated which is recorded in the Medicaid data base. The data recorded include the date of the transaction, the ICD-9 Code for the diagnosis, the name of the prescription drug, the prescription strength and number of pills or

tablets given, as well as the patient's age.

Each patient has a file in the computer to which billing transactions for medical care and services are added as they occur over calendar time. This slide provides background to the Michigan Medicaid system. Over the years 1979 to 1986, we have data available on nearly 500,000 women who at some time or other received medical care within the Medicaid system for the State of Michigan.

The average annual population of women of child-bearing age was approximately 270,000 per year. These women on average experienced slightly over 52,000 pregnancies, of which 29,000 were deliveries, 15,000 induced abortions, and 7000 other abortions labeled as spontaneous or not otherwise specified. Many of the "not otherwise specified" abortions are difficult to determine whether they are induced or spontaneous, and so they are lumped in the other category.

The study that we performed covered the period 1982 to 1986. This was because the computer tape for Michigan Medicaid transactions for 1987 was not available when we first began this investigation. Between 1982 and 1986 a billing claim for Accutane was processed on 928 women in this age group. In Michigan Medicaid approximately 90 percent of all Accutane use in

women is in this age range, with only 4 percent occurring in women over the age of 44.

Using a computer, we identified 55 women out of cohort of 928 recipients in whom an Accutane prescription fell within 270 days of a delivery ICD-9 diagnosis code, or 120 days of an abortion code. These 55 cases were considered suspected Accutane pregnancy exposures in our study. They represent 5.9 percent of all women in this age group who were treated with the drug; 50 of these cases appeared to involve first trimester exposure. Among the 5 other cases, 2 involved a second or third trimester exposure; 1 involved an induced abortion performed at 6 months' gestation for a suspected fetal abnormality; and 2 were late spontaneous abortions or premature stillbirths.

These latter three cases probably represent actual first trimester exposures but were excluded from our analysis because of their unusual presentation.

This busy slide shows pregnancy outcome among the 51st suspected first trimester Accutane exposures in Michigan Medicaid. We have the year of exposure, 1982 through 1986, across the top of the figure; and along the side we have the various pregnancy outcomes which we examined.

The bottom line here gives by year the total

number of suspected first trimester pregnancy exposures experienced in a given year. The fluctuations in numbers year to year are not statistically significant. Several points can be drawn from this slide.

First, pregnancy exposure to Accutane occurred in every year of marketing in this population. Also, the occurrence of pregnancy exposure has remained relatively constant over time. Third, induced abortion accounted for about 60 percent of all first trimester pregnancy exposure outcomes.

In the last year for which we have complete data, induced abortion accounted for 80 percent of pregnancy outcomes. This ratio of 60 percent compares to the national average of about 28 percent, which is very close to the Michigan Medicaid average of 29 percent.

Finally, 13 deliveries--26 percent of first trimester exposures in the Michigan Medicaid exposure reached delivery.

Regarding the exposed mothers in this slide, their median age was 25 to 29. They were not as young as previously reported in other retrospective type studies. For the 13 deliveries with first trimester exposures--that is this group here (indicating)--the computer records for the mothers were linked to those of

the offspring to further explore the impact of Accutane exposure during early gestation in this population-based prospective setting.

This slide provides details available at this time for the 13 children with suspected first trimester pregnancy exposures to Accutane: 1 was stillborn; 2 were listed with cranial facial birth defect ICD-9 codes; 2 others we suspect may have experienced perinatal death. This is because, although the computer linkage was possible, records were not found for the children. At the same time, their mothers remained in the Medicaid system, implying that these children had possibly died. Seven of the 13 were apparently normal, and in one we were unable to complete the linkage because of a confusion in the computer codes.

All told, there were 3 to 5 deliveries with evidence of Accutane-related problems. We are attempting to obtain the primary medical records for all these deliveries. It should be noted that the occurrence of the ICD-9 Code for cranial facial birth defects is extremely rare in Medicaid. Using a computer signaling module, the presence of two such ICD codes in 13 deliveries represents an extremely rare situation.

Among these 13 deliveries, 60 percent received only 1 prescription for Accutane. This is twice as

great as the percentage of the entire 928 women who received only 1 Accutane prescription. That is to say, of the 928 women who got Accutane, 30 percent of those women received one prescription and one prescription only for Accutane.

However, in this group of deliveries that proportion was doubled to 60 percent. This suggests that the pregnancy exposure event was recognized early in some of these cases because Accutane was not prescribed again. However, in 40 percent of these pregnancy exposure cases, patients did receive more than one Accutane prescription.

We will now shift our focus from a descriptive to an analytic exploration of these Medicaid data. We compared the pregnancy experience of the 928 women exposed to Accutane in Michigan Medicaid to the entire female population in the age group 15 to 44. In examining the data for possible confounding by age and race, we found that neither had a major effect on pregnancy, delivery, or induced abortion rates. The data presented today are adjusted for age. In performing the analysis, we assumed that a prescription for Accutane amounted to one month pregnancy exposure risk.

In Medicaid, drug prescriptions are generally

limited to one month's duration. In this slide, we show the pregnancy, delivery, and induced abortion rates per 1000 women per year in Accutane-exposed and nonexposed women from Michigan Medicaid.

When we compare the pregnancy rates among women exposed to Accutane with those not exposed to Accutane, we see that there is a slight difference in the rates amounting to about a 15 percent reduction in fertility. Also, there is a marked reduction in the number of deliveries per 1000 women among women exposed to Accutane and those not exposed to Accutane.

Finally, we see that there is over a 50 percent increase in the absolute rate of induced abortion among Accutane-exposed women in Michigan Medicaid compared to women not exposed to Accutane. These latter two differences were statistically significant.

A more important comparison to make, however, is what happens to pregnancy once it occurs. The data on this slide are rates per 1000 women per year. However, if a woman is not pregnant, she is not at risk, so to speak, for any of these outcomes. The more relevant comparison is one based on pregnancies, and that comparison is shown in the next slide.

The rates shown in this slide are based on

1000 pregnancies. Once again we compare our 51st trimester Accutane exposure group with all women delivering in the Medicaid system. As can be seen, the rates for delivery for 1000 pregnancies are reduced among Accutane-exposed women when compared to women not exposed to Accutane.

At the same time, the rate of induced abortion per 1000 pregnancies is increased from 293 to 594. The SMR over here is an estimate of the relative risk. It shows that delivery events among Accutane women occur about half as often among Accutane-exposed women as occur among women not exposed to Accutane. At the same time, induced abortion appears to occur about two times more often among women exposed to the drug compared to women not exposed to the drug. These differences were highly statistically significant.

This final slide shows pictorially the relative effect of Accutane exposure on delivery and induced abortion. It shows us that, relatively speaking, the drop in delivery rates experienced by women exposed to Accutane is explained almost entirely by the rise in induced abortion in this group.

While the pregnancy exposure rate for women taking Accutane is only slightly lower than the pregnancy rate for women not exposed, the number

reaching delivery is reduced in direct proportion to the rise in induced abortion.

We also examined pregnancy exposure to Accutane in Florida Medicaid. In this system, induced abortion is not paid for unless the mother's life is at risk from pregnancy. Therefore, we could not evaluate the total extent of pregnancy exposure to Accutane in the Florida Medicaid data base. However, if the proportions from Michigan Medicaid were applied to Florida for deliveries, one would expect about two exposed deliveries among the 134 women treated with this drug in Florida Medicaid.

When we examined the Florida data, we found two exposed deliveries, one with the first trimester and one with a later trimester exposure. We believe this finding supports the rates of pregnancy exposure and delivery observed in Michigan Medicaid.

The Medicaid system serves patients that are primarily poor, with minority groups over-represented. These systems may not therefore be totally representative of the Nation--although they are probably quite useful for considering the problem among the 21 million people enrolled in Medicaid programs nationwide.

Because of this possible

nonrepresentativeness, we also looked at pregnancy exposure to Accutane in a third population. Dr. Herschel Jick at the Boston Collaborative Drug Surveillance Program obtained and analyzed some data on Accutane exposure from the Group Health Cooperative HMO in the Seattle, Washington, area.

Group Health provides medical care to primarily white, middle class populations, a group very different from Medicaid. Annually, about 93,000 women of child-bearing age are covered by this program, with 3200 deliveries. Last year, Dr. Jick performed a study in 209 women aged 15 to 44 treated with Accutane and found four suspected pregnancy exposures for a rate of about 1.9 percent of all women treated.

Dr. Jick provided case synopses to FDA and, on review, 3 satisfied our definitional criteria for suspected pregnancy exposure. We should add, before presenting this data, that in Group Health Cooperative Accutane is available only from dermatologists, and that since 1983 women patients have had to sign an informed consent indicating that they have been told about and understand the risks of birth defects if pregnancy exposure occurs, and also that they agree to practice some form of contraception while on the drug.

This first slide demonstrates the incident

exposure for 1000 women per year. In the total U.S. based on NDTI data, Group Health Cooperative--the HMO from the Washington area, Seattle Washington area--and from Michigan Medicaid.

We can see that the annual incident exposure--and this is new therapy starts with Accutane in women 15 to 44 in Michigan--was about .8 per 1000 women per year, which is very close to the .6 per 1000 women per year from Group Health Cooperative, and which is in the ballpark of the 1.2 per 1000 women per year which is based on the total estimated new-patient starts applied to the total female population of the United States of 55 million.

I should add at this point that the data shown from Group Health Cooperative are preliminary, and that a full analyses have not yet been completed.

In this slide we compare pregnancy experience in Michigan Medicaid with Group Health Cooperative. The data from Group Health Cooperative once again are preliminary, but nonetheless are illuminating. The background pregnancy rate in this column among all women per 1000 per year is about 50 in Group Health Cooperative. Among women treated with Accutane, the rate is 39. This amounts to about a 22 percent decline in fertility among women exposed to Accutane compared to

women not so exposed.

This figure is derived once one adjusts for the fact that Accutane exposure does not occur over an entire year, but only encompasses a small proportion of a year. The important factors to note from this slide are two:

One, the national pregnancy rates are about 112 per 1000 women per year. The rates in Michigan Medicaid are about as far above that national rate as the rates for Group Health Cooperative are below that rate.

Secondly, the proportional decline in fertility among women exposed to Accutane is fairly comparable in both the Michigan and the Group Health Cooperative systems. According to Dr. Jick, the average number of prescriptions per patient is 4 in the Group Health system. Several other facts should be mentioned--we've covered those. Never mind.

In each population we examined, pregnancy exposure to Accutane was seen. This slide summarizes the knowledge that we have on those three systems. In Michigan, we had 928 women 15 to 44 exposed to Accutane. The crude pregnancy rate was 155 per 1000 women, with a delivery rate of 42 per 1000 women.

In Florida we had a delivery rate of 40 per

1000 women. We were unable to obtain a pregnancy rate because induced abortions are not performed routinely in that system.

Finally, in Group Health Cooperative out of 209 women we have a pregnancy rate of 39. In that system, no women reached delivery. I should point out that the three cases which satisfied our definitional criteria for Group Health, one ended in abortion, one ended in spontaneous abortion, and one patient was lost from the system.

We next wished to derive a range of estimates to define the potential magnitude of Accutane pregnancy exposure in the United States. The purpose of this was to establish the public health context of the problem.

To arrive at national estimates of pregnancy exposure and birth defects, we used a range of 270 to 390,000 women exposed discussed in Section I of this talk. We used the rates of 1.4 percent from Group Health Cooperative and 5.4 percent for first trimester pregnancy exposures in Michigan Medicaid to come up with a range of estimates of what proportion of women exposed to Accutane will experience pregnancy exposure. This is a wide range which we believe encompasses the entire gamut of experience going from HMO-style medicine to the public-sector type medicine.

We have assumed in our projections that 60 percent of these pregnancy exposures would end in induced abortion. This is a number derived from the Michigan Medicaid data and represents a two-fold increase above the national average.

We assumed that 26 percent would reach delivery, and that of those reaching delivery birth defects in 25 percent would be found. This last number is derived from studies published by Dr. Edward Lammer who will be speaking to us later today.

This first slide incorporates the lower bound analyses. The 270,000 exposure figure, the 1.4 percent pregnancy rate in that group, applying the assumptions we have stated previously, we estimate in a low-bound analysis that over 3800 exposed pregnancies may have occurred in the United States between 1982 and 1986. A majority of these ended in induced abortion, and there may have been 250 birth defects.

The upper bound analysis used the Michigan Medicaid numbers of 5.4 percent for first trimester pregnancy exposures, and the 390,000 population estimate. Applying those numbers, we come with an estimate of exposed pregnancies of 21,000 of which 12,000 ended in induced abortion, and of which 1300 would have terminated with a birth defect.

Because both group health and Medicaid differ sharply from the national average in fertility, we also chose a mid-point analysis of 3.4 percent as a reasonable approximation for the pregnancy rate for all women exposed to Accutane. In this analysis, assuming that 3.4 percent of the women exposed to the drug, and using as a denominator of exposure the lower-bound figure of 270,000, we would estimate that perhaps 9000 exposed pregnancies occurred, of which 5500 were induced abortions, and of which about 600 were birth defects.

We believe this midrange analysis may be the best approximation of what has occurred nationally. If this is so for the years 1982 to 1986, there would have been about 12 birth defects per month resulting from exposure to Accutane during pregnancy, with an additional 110 induced abortions in women so exposed. About half of these latter procedures are directly attributable to Accutane. They represent the excess number of abortions above the expected background and are a reaction to exposure to this drug.

From this data we conclude that pregnancy exposure to Accutane occurs in between 1.4 percent and 5.9 percent of women using the drug.

We will now shift gears and take a look at what has been the experience of reporting for adverse

reactions involving pregnancy exposure to Accutane.

This slide reviews the status of reports to FDA on adverse pregnancy outcomes received through about January of this year. In each year of marketing, the reports of exposure and birth defects has been received. These figures should not be viewed as reflecting incidence of pregnancy exposure to Accutane because there is much under-reporting.

For example, in the past six months FDA has received reports of previously unreported birth defects from each of the previous years. The most recent defect of which we were informed occurred more than nine months before it was reported to FDA. The time lag in reporting is extensive, and the further along we get from the time when the event occurred, the longer the lag becomes in terms of reporting.

It should be noted that induced abortion after Accutane is not routinely reported to FDA. The manufacturer has not officially submitted any reports of this outcome to the FDA. However, as shown a few minutes ago, most pregnancy exposures to Accutane end with abortion. The result is that not only are birth defect events under-reported, but all pregnancy exposure is greatly under-reported.

By way of illustration of this point, although

we have 55 suspected pregnancy exposures to Accutane from Michigan Medicaid, none of these appear in FDA's adverse drug reaction data base. Likewise, none of the three exposures from Group Health were reported to FDA. The point of this is to demonstrate that the tip of the iceberg has been reported to the manufacturer and FDA. There is a whole universe of pregnancy exposure about which we have no direct information.

When we talk about birth defects with Accutane, we are talking about severe, disfiguring, and frequently fatal deformities. We had originally intended to show a slide of a typical birth defect, but have elected not to do so. Among the 66 birth defect reports available for study, 44 had cranial-facial defects; 39 had major CNS defects; and 17 had major cardiac defects. Other defects affected the GU and GI tract, as well. The number of total defects was greater than the number of patients because a given patient may have experienced more than one defect.

Of the 66 reports we have shown here, 4 involve stillbirths, and 10 of these children died shortly after birth. Follow-up is lacking in many of these cases so that there may be additional deaths.

Under-reporting of adverse reactions is a well-described phenomenon, as this slide demonstrates.

Serious reactions such as a granular cyrtosis in Sweden, or death from serious adverse reactions in Sweden were reported only a fraction of the time they occurred. The adverse reaction reporting system in Sweden is one that is legally mandated, and physicians are required by law to report. There is no such law in the United States which requires physicians to report any adverse reaction.

In a study from the United Kingdom, looking at the reporting of thromboembolic death in women taking oral contraceptives, they discovered only about 15 percent of deaths in women who had taken oral contraceptives had been reported to the United Kingdom equivalent of the FDA.

Finally, from the CDC we have an example of reporting of sudden infant death in the 48-hour period following vaccination with DTP. The estimated number of deaths which should be seen following the 48-hour period of DTP vaccination is such that in terms of reports received by CDC they have received only 10 to 20 percent of the expected number. That expected number is not a number attributable to DPT itself, but is just the background rate.

In this situation, it is hard to imagine that the mother of a child who was so recently vaccinated

with this vaccine would not have told her physician that her child had died; so we must assume that the physicians are aware of these events when they occur, and that this 10 to 20 percent figure that we see represents the inertia of physician reporting in the United States.

With Accutane, the actual awareness of the physician that the drug is responsible for the event being noted may actually be lower than this 10 to 20 percent. This could occur if the woman gets her drug from the dermatologist and then becomes pregnant. She goes to the obstetrician who may be unaware of the exposure. If they are unaware of the exposure and a birth defect occurs, they are likely to attribute it to a chance event, and then reporting will probably not even reach this 10 to 20 percent figure for DPT.

Finally, we should note that reporting in Sweden and in the United Kingdom are on average about two times more complete than reporting in the United States. So that these under-reporting rates which we have shown here may actually be lower in this country.

We conclude from this that under-reporting of pregnancy exposure and birth defects is extensive.

Finally, over the years 1982 to 1987, a wide range of efforts have been taken by both the

manufacturer and FDA to deal with the risk to pregnancy posed by Accutane. Extensive labeling with Category X classification, contraindications, recommendations for pregnancy testing, counseling for contraception, numerous letters to physicians regarding these labeling events, and multiple articles in the literature have been instituted.

In addition to these, the professional literature has seen over 100 articles discussing the various aspects of teratogenesis with Accutane. Physician education has been intense. So has patient education. Counseling by her physician, distribution of patient information leaflets, pregnancy warning stickers on the bottle, all of these have been aimed at educating the woman when she takes the drug.

What has been the effect of these interventions? Well, from part one of this talk we have seen that severe cystic acne of the degree seen in the original I&D trials, and for which Accutane was approved, occurs in a relatively small number of women annually.

However, Accutane use in this age group exceeds this incidence rate perhaps as much as 15-fold. At the same time, Accutane over-use in this population has remained unchanged. Although cystic acne is five

times more common in men than women, the use of Accutane in women 15 to 44 is nearly equal to that of men. In studying pregnancy exposure to Accutane, we have seen that it occurs in the three different populations where it was searched for, and it occurred at a rate between 1.4 and 5.4 percent of women taking the drug. Although differing and socioeconomic and demographic factors, the overall incident exposure rate in these populations was comparable, and a reduction in pregnancy between Accutane exposed women was similar at about 20 percent.

Based on projections from this data to the nation, between 3800 and 21,000 first-trimester pregnancy exposures to Accutane are possible between the years 1982 and 1986. The mid-range estimate is 9000. The majority of these pregnancies ended with induced abortion, and between 250 and 1300 birth defects seem likely.

Finally, FDA has received and continues to receive reports of birth defects. For many reasons relating to dynamics of adverse reaction reporting, we are convinced that only a small proportion of such defects have been reported. Furthermore, because induced abortion accounts for most pregnancy exposures to Accutane, and because abortion is not reported routinely by physicians or the manufacturer, total

pregnancy exposure to Accutane--which is the focus of Category X classification--is likely to be even more under-reported than birth defects.

These data are only the tip of the pregnancy exposure iceberg. The data presented today I believe help to provide an answer posed by the question in number four.

Thank you for your courteous attention.

DR. BERGFELD: Dr. Graham, I wonder if you would stay there just a moment and see if the panel has any questions.

Dr. Stern.

DR. STERN: Yes.

DR. BERGFELD: Would you talk into the microphone, please.

DR. STERN: Sure. I found both your presentation and the materials you provided us earlier both interesting and very provocative. Perhaps I could go through and make some comments and ask questions in a little bit different order than the way you presented it.

I think what I would like to talk about first is pregnancy exposure, and then come back to incidence, prevalence of the disease, and your estimates of the degree of over-prescription compared to the package

insert.

First of all, I would like to ask one question that comes to me throughout the presentation about exposure and about your rates. My understanding, based on clinical experience, is that most people who get Accutane, most women who get Accutane, are likely to be 15 to 24 or at most 15 to 29; that of this 15 to 44 age group, the usage of Accutane in fact in the Medicaid population is probably even more concentrated in the 15 to 24 age group.

DR. GRAHAM: I have a slide on which I could show the age distribution of Accutane use in Medicaid, if that would be helpful.

DR. STERN: Or just give me a rough idea.

DR. GRAHAM: It is roughly comparable--it is slightly lower than the 15 to 19 year age group, about 17 percent; and rises to about 20 to 22 percent in each of the three next age groups; and then falls above age 35 out. So 35 to 39 and 40 to 44 falls.

I should add that the age distribution of Accutane use in Michigan Medicaid is very comparable to the age distribution of Accutane use in Group Health Cooperative.

DR. STERN: And what about pregnancy rates throughout this age group?

DR. GRAHAM: The age adjustment which we did and showed accounts for the differences in pregnancy rates among the different age groups of the population.

DR. STERN: I work with a COMPASS data base, and the numbers you give, as I understand how COMPASS works, unless you've done something else, are the numbers of women who had a claim for Medicaid that year. My understanding is that Michigan Medicaid doesn't really know how many people--or COMPASS doesn't really know how many people are eligible under Medicaid. If you have an iatrogenic encounter of any kind that results in a claim, then you are in the file for that year. So if you are perfectly healthy and have a Medicaid card, you wouldn't be considered in any of the denominator data here. Is that correct?

DR. GRAHAM: If you don't have a billing code in a particular year, then we wouldn't have access to that data.

DR. STERN: So all of your data will tend to substantially underestimate the group at risk if they obtain the drugs through any other method, or if they obtain any services through that method?

DR. GRAHAM: No. We're focusing on a population of women who received the drug, and that cohort of women is the 928 women that we have access to.

And in those 928 women, the experience that they have is a valid experience, and we have complete information on those people.

DR. STERN: Right. But when you use rates you are using rates with a very uncertain denominator.

DR. GRAHAM: No. The rates that we used were rates based on Medicaid usage.

DR. STERN: They are rates based on people who have used Medicaid claims, not the eligible population. People move in and out of Medicaid at all times. They not only move in and out in terms of eligibility, they also move in and out in terms of even if they are eligible, whether they had a claim during a given year period. So it is really not a very sure denominator.

The next question I--

DR. GRAHAM: The denominator is fairly stable year to year. There is a flux in the population in which there are some people who leave the system and other people who come in. However, the number remains relatively stable year to year.

Additionally, in terms of eligibility we don't know what the experience is of people who aren't using the system. We know that they are not having pregnancies. So if we were to include them in our denominator, the actual pregnancy rates in our system

would change mildly and would go down, but at the same time so would the rates in the Accutane group. Both groups would be affected, probably proportionately.

DR. GRAHAM: Let me ask you a couple of questions. Let me give you a scenario. You used 120 days within a therapeutic abortion for a scenario of being exposed. Let's take a very simple situation.

A woman comes in to a dermatologist, meets whatever the criteria is for that particular person to receive the prescription, at that time the prescription is given in good clinical practice, a number of tests including a pregnancy test are obtained. If that person goes downstairs during a clinic setting, they go downstairs and get that Accutane prescription and get a positive pregnancy test and decide they don't want to be pregnant at that time, how would they be counted in your data? They never took the pill.

DR. GRAHAM: In our data we had no cases where that occurred. In all of our cases, the Accutane prescription occurred prior to the induced abortion.

DR. STERN: But you don't get the abortion that same day. I'm saying I come in on Monday to my doctor's office. He says: Here's your CBC, your LFT, your cholesterol, triglycerides, pregnancy test; here is your prescription for Accutane. Call me and I'll tell

you the test results. And rather than coming in again, you stop downstairs and you get a prescription.

You've filled it. You now have a claim made on Friday. The next Monday you call up and say, I have some news for you. Don't start the Accutane because you're pregnant. And this, often young woman, says: Perhaps I don't want to keep that child. And three or four weeks later goes through the paperwork and has a therapeutic abortion. How would that person be counted?

DR. GRAHAM: That person would be counted as--

DR. STERN: --as an exposed person.

DR. GRAHAM: --an exposure. Let me explain, however, that epidemiologically that is the correct thing to do. There are two aspects to exposure which need to be considered, and the reaction to exposure.

One is the background rate. That is what is endemic in the population. It would be scientifically erroneous for us to throw those cases out which represent background cases in the population. They have to be included.

In addition to the background, you have added on top of that the attributable proportion, the attributable incidence, the attributable risk.

In the study we've done in Michigan Medicaid, we've found that there was a background rate in the

population of around 30 percent. In the Accutane-exposed group there was an exposure rate of about 60 percent. It is our belief that the difference in those two rates is the attributable proportion that is due directly to Accutane.

It includes also, and needs to include also, the background rates. That is the way epidemiology is done.

DR. STERN: But when you then get proportions, you are including both the rate of induced abortion attributable to Accutane, plus the background rate. Did you adjust for that in your projections?

DR. GRAHAM: The projections were for all abortions.

DR. STERN: Right. So they include the background rate.

DR. GRAHAM: And as I stated in the talk at the conclusion, half of those are attributable in accordance with our numbers to Accutane.

DR. STERN: Did you in fact ascertain--I've worked with this Medicaid data base. How many of the records did you review to make sure that the discharge diagnosis was correct and that an abortion was performed at that time? How many did you obtain?

DR. GRAHAM: Okay. For induced abortion, we

have not looked at any records. Let me explain what we have done, and what we are in the process of doing because this also applies to the deliveries, as well.

We have been trying now for about four months to obtain the primary medical records for the 13 exposed deliveries, and because of issues of confidentiality with the patients in the Medicaid system, and for a number of other reasons, we have not yet been successful in acquiring those records.

In trying to acquire records for induced abortion, I think we would meet with greater opposition than we are already meeting in trying to get the pregnancy records. To get around that, we have two approaches.

The first approach is to look at the context of the Medicaid profile. Since you are familiar with the COMPASS data base and you are familiar with the profiles of the--the Medicaid profiles, you are also aware that you have calendar time listed according to Julian dates. We'll start off in 1979, 1981, 1982, 1983, and on down the line. Then each time the woman has a procedure or diagnosis, it's recorded with the appropriate date.

When you look at large numbers of records for induced abortion, you most frequently find that there

are early indications, other codes, for pregnancy. You will see a code for pregnancy testing. You will see codes for absence of menstruation. You will then look down the record and soon thereafter you will see codes for induced abortion.

You look further down in the record and you see no evidence of a delivery. So you infer, but reasonably because you have multiple entries in the data base referring to a pregnancy event and the pregnancy event is apparently terminated with an induced abortion, and further on down there is no delivery to invalidate that. That is the first approach which we have used here and, for most of our cases, that kind of evidence is apparent from the record.

The second thing that we are trying to do, and which we had hoped to have by this Advisory Committee, was to obtain a procedure code tape from Michigan Medicaid. What this would represent would be an actual tape of a billing for the procedure itself, rather than for the office visit or the outpatient visit where the procedure occurred. So it is measuring something slightly different. It is a little closer to the event. Unfortunately, we've been unable to get--the contractor through whom we work to obtain our Medicaid data has had difficulty in compiling the procedure tape,

so we don't have that available. Our intention is to review that tape and to take our population and match it against that procedure tape when that procedure tape is available.

I have to add at this point, however, that at the time that we wrote our original preliminary study and brought it to the attention of other officials within FDA, it was deemed so important and of such an urgent nature that it was deemed inappropriate for us to wait for this other data to accrue. Had we done that rather than meeting now, we would probably be meeting a year from now.

DR. STERN: But at least in my experience in reviewing records from the Medicaid data base, there are, for example, miscodes, and there are a substantial number of miscodings in the ICDA diagnoses.

DR. GRAHAM: There are a substantial number of miscodings for diagnoses. There is not substantial miscoding for procedures.

DR. STERN: Because procedures initiate a bill. I understand that.

DR. GRAHAM: It is a different kettle of fish that we're dealing with. We have done validation studies for delivery in the past and have found a 100 percent sensitivity for the system. That is to say, all

records which list a delivery in fact had a delivery.

We believe that the data for induced abortion will probably be of similar quality--perhaps not as high, but of similar quality.

DR. STERN: Now did you in the study, since you do have apparently access to data on a longer history of medical events including prescriptions and procedures for these people who were exposed, did you look at them and take some controls and look at for example what their previous parity was based on this record at least within the Michigan Medicaid data base system?

DR. GRAHAM: We did not stratify for parity. We looked at age and race, which were the factors that could be most easily looked at in this setting, but we did not look at parity.

DR. STERN: In the 19 to 29 age group, which is the biggest group exposed to Accutane in your population, what is the number one reason for being on Medicaid in Michigan?

DR. GRAHAM: The number one reason for all women being on Michigan Medicaid is Aid to Families with Dependent Children.

DR. STERN: Right.

DR. GRAHAM: That applies not only to the

Accutane-exposed cohort, but also to the women who are in the control population. And by age-adjusting, we have accounted for the amount of confounding which parity might have as an effect of age. And most of the effect of parity, as you are well aware, is due to age itself. We have controlled for age, so we probably have a control for most of the effect of parity--not that I believe that it is a significant factor in this data.

DR. STERN: But you have not controlled for other factors? For example, if you take two different women, two different women may have different ideas about what they believe to be effective contraception, or preventing the birth of an affected child being not pregnant at the time they started, and two women may have very different ideas about how they wish to prevent having a child affected. And one way to look at that is to look at the experience of the people who went on to have induced abortions; and since one of the arguments you make is that this drug is inducing extra abortions, perhaps these women made the choice that there was a contraceptive failure and that that was a legitimate thing, and rather than changing their method of contraception to substantially decrease their baseline risk of pregnancy, they might have explicitly said, well, I hope I don't get pregnant, but made the explicit

decision "if I do, that is a legitimate decision, a medical decision for me, and that's how I'll deal with this problem."

DR. GRAHAM: To answer that question it would be necessary for us to be able to interview directly and personally the patients involved in the study, and that is something that is strictly prohibited both by OMB regulations, by Medicaid law, by State law, and we would not be able to do that.

However, in looking at the populations in the way we did the analysis, having a standard population and a background population and having a group of Medicaid women, differences in approach to contraception, differences in religious, moral, and ethical beliefs as to what one should do regarding the issue of an induced abortion and the like, are probably going to be randomly distributed in both populations--unless you can demonstrate with good data that there is a reason to believe that women who take Accutane may be more predisposed to do that. But we don't have the ability with our data to address that question.

DR. STERN: See, that is where I have to disagree with you. I think people who take Accutane for a whole variety of ways are different than people who don't take Accutane. I think they may well be different

in their attitudes about induced abortion. They may well be more medicalized. They may well be more medically sophisticated in certain ways. They are going to be different in age. They may be different in a whole variety of ways that are going to induce those rates, and I think these possible confounders are important enough that I find it very hard to know what your rates mean.

DR. GRAHAM: Well--

DR. STERN: And therefore, where it's usually the onus on the investigator to prove that he has taken into account possible confounders that would substantially affect your rates, and as I've heard it the only confounder you've really looked at--and it's still not clear to me how well you've looked at it--is age adjustment. Did you look at age adjustment for baseline pregnancy rates?

DR. GRAHAM: We looked at age adjustments. We looked at race adjustment. Neither of them had an effect on the--

DR. STERN: Those are the only two things.

DR. GRAHAM: Those are the only two that we have data to look at. We indirectly can assume that we have controlled for marital status because the entry criteria for Aid for Families with Dependent Children is

that you be a single parent head of household. So there is no associated man with the system.

And regarding whether or not women who get Accutane are very different from other women, they are different insofar as the disease that they have, but we have to deal with the population and what we see occurring. And what we see occurring is substantial amounts of pregnancy exposure.

DR. STERN: Let me then, as a last question in this area, let me ask you one question because I think it points out a lot of the potential problems of COMPASS data that has not gone through more rigorous analysis than an individual case-by-case basis. And that is in your report, your estimate of a two- to four-fold higher risk of spontaneous abortion in people who use the antibiotics commonly used for acne.

In my experience with the COMPASS data base, before you clean the data you tend to get an overestimate of almost every adverse effect associated with drugs, at least in the two or three times I've used it. And seeing that, let me just continue on that.

Let's take that as an equally valid data, and let us therefore assume as a point estimate that it is three times--which would be your middle case--and let's assume your prevalence of acne being eight years in

women, and we can come back and talk about why the inaccuracies, but let's use your data, the eight years.

That would mean a woman for an eight-year period of time would have a three-fold higher risk of spontaneous abortion using the other agents that are effective in this disease, the alternative therapy; whereas, we therefore, if we believed all these data, would then have to compare what the risk is for a five- or, to be fully comprehensive, a six-month exposure to this teratogen.

Did you do that simple calculation based on all your data what would happen for eight years of exposure to a three-fold increase?

DR. GRAHAM: The data that we analyzed was directed at Accutane, and we did not analyze data relating to antibiotic treatment. The reference in our preliminary memorandum, which you have read, was intended as a signal to let readers know that in one signaling module which we ran that there was the signal that this was a possible--that there was a possible increase in spontaneous abortion.

But it is very crude and unrefined and hasn't been subjected to analysis. We did analyze the data for spontaneous abortion with Accutane and, based on the crude data, we thought that there was from our data a

two-fold increase in spontaneous abortion.

But when we've done the more refined analysis, taking into account factors of age and race, we have found that at least in terms of billing codes for spontaneous abortion there is no difference between our Accutane group and the background population, and that the background population actually has a billing rate for spontaneous abortion of 14.7 per 1000, which is very comparable to the national rate of 14 per 1000. We didn't show that data, but that is what we found.

DR. STERN: But getting back to my point, at least as I understand what you have done, I am not sure why this two- to four-fold increase in risk that you project, or that you noted in your analysis for the alternative agents which are used for about 15 times as long a period and therefore during much of a woman's reproductive life are any less valid than the analysis you presented.

DR. GRAHAM: Well, for a couple of reasons. One, with the antibiotic data which was done from a signaling module, what that does is that looks for the first time the woman ever gets a particular drug--let's say tetracycline. She gets tetracycline in 1979. Maybe she gets it for bronchitis. She gets a 10-day supply, 250 milligrams 4 times a day.

In 1986, she has a spontaneous abortion. The signaling module will consider that woman as a tetracycline-exposed spontaneous abortion, even though there is no relationship. That is a very crude device which we used to help us pinpoint other areas for investigation down the line.

What we have done with Accutane is, we didn't rely on that crude analysis. We applied rigid, time-specific criteria between exposure and the outcome event that to us was the hallmark for a pregnancy--namely, delivery or abortion.

So the Accutane analysis is a very specific analysis that is honed in on a very focused period of time, and the other data that you have referred to is a signaling device with very crude, crude data that really shouldn't be emphasized. I think that you are overemphasizing it, perhaps.

DR. STERN: Well, but a signaling device, as I understand it, in fact relies on case control, looking at different exposures between cases and controls. And one of the things that surprises me, given the construct of the COMPASS data base, is I never thought it was really very much intended for looking at rates for some of the problems we've talked about, but as a way of ascertaining cases and controls, and then looking at

exposures. And I really wonder why you didn't do an appropriate case control study that, at least in the way most people have used the COMPASS study--

DR. GRAHAM: I can answer that question I think fairly easily. That is, you can talk to any epidemiologist and they will tell you that case control studies are much more subject to problems than are prospective cohort studies. That is because you run into problems with what is the appropriate control group to pick.

You pick one control group, you get one result; you pick another control group, you may get another result. When you deal with populations--when you get back to populations and deal with what is happening in the population, and you go on a prospective fashion, you are on much firmer ground. And that is what we chose to do because had large populations to look at.

DR. STERN: Tell me a little bit about the stability of estimates when in terms of a very bad outcome you're not even sure about the majority of the cases that you think might be very bad, and what would you think of a study that said--and it is completely related to this--that we might have had two deaths, or we might have had five deaths, starting with 50 exposed

people. What would be your general evaluation of the quality of the quality of follow-up.

DR. GRAHAM: I would say that if the researchers gave that qualification and then based their analysis on the more conservative estimate of which they were certain, that they were being scientifically responsible and that is what we have done.

DR. STERN: And what is the stability of a rate of 2 out of 50?

DR. GRAHAM: I wouldn't focus on the rate of 2 out of 50, or 2 out of 13, let's say, deliveries, because the point of this presentation is not to debate what is the rate of birth defects among women who get Accutane. There are other people who have done much more extensive work in that area, and we have relied on their figures to do that.

The fact that our number is in the ballpark of their number to us seems very confirmatory of the fact that we're dealing with a real problem.

In terms of stability of measures, I should point out that we are dealing with a cohort of 928 women exposed to Accutane. This is the largest single group of women of child-bearing age exposed to the drug presented in any form of which I am aware.

If we were to review the clinical trials which

formed the basis for Accutane's approval and studies which have been done on the drug subsequently, we will see that each of those studies had between 10 and 30 or 35 patients exposed to the drug. This is a very large study.

DR. STERN: But the next question, and which I will use to lead into the GHC data about which I have only two questions is, how typical do you think the Medicaid data base, the Medicaid individuals are with respect to child bearing patterns, contraceptive use, quality of medical care, adherence to medical care for this or any other condition such as say hypertension of that population? In other words, is this a population that represents in all likelihood the worst-case scenario applicable to certain people who often have not the same education, the same access to high-quality medical care as many of us are privileged to have? Or do you think that this population is in fact typical of what goes on in the world at large?

DR. GRAHAM: I think that the Medicaid population in general probably does differ from the Nation at large in some respects--and let me talk to you for a moment and show you what I am driving at.

We know that it has a higher pregnancy rate than the national average--193 versus about 112. But

when we look at how they deal with the pregnancies once they have them, they have the same rate of induced abortion that is national. They have the same 29 or 30 percent induced abortion rate on a per 1000 pregnancy basis. So they deal with pregnancies the same way that the rest of the Nation does.

When we compare them with Group Health Cooperative now in terms of how many women per 1000 in the population get Accutane on a yearly basis, we see that it is virtually the same--.6 versus .8. This is comparing what I suppose you would call very high-quality health care, the GHC-HMO compared to low-quality health care, the Medicaid system. And I am trying to put the construct the way you have phrased it to me.

We see that the exposure rates to the drug are very comparable in these two populations.

Third, we look at pregnancy again, and we saw that in Group Health Cooperative the fertility rate was as far below the national average as Medicaid is above it. Group Health Cooperative--the paragon of health; white, middle-class, HMO, high-quality medical care--is as far away from the national average as Medicaid is. And it likewise is not representative, and probably represents the best of all possible cases, just as in the same case I would probably agree that Medicaid tends

to be on the worst of possible cases.

It was for that reason that we presented our mid-range analysis which we think represents a reasonable synthesis of the two approaches.

A final point, though, I want to mention about Medicaid is that when we look at what is the pregnancy rates among women who got Accutane compared to women who didn't get Accutane in Medicaid and in GHC, we see that there is a small decline in pregnancy rates, but it is to a comparable degree. We're talking about a 15 or a 20 percent reduction in pregnancy rates in two different populations that by your question I infer we would expect maybe a very great difference, and we don't see it.

So I believe that the basic premises that you state in your question about Medicaid being so totally unrepresentative as to be useless is really off the mark.

As a final note on this, we can't forget that every State in the United States does have a Medicaid system; that this provides health care to 21 million Americans who cannot be ignored; that perhaps 15 percent of all deliveries in the country occur within this system. For any deliberative body to lose sight of that fact and get caught up in whether or not the data is 100

percent absolutely representative of everything in the Nation or not I think will miss the point of what our research has been intended to convey.

DR. BERGFELD: Rob, I need to constrict you a little bit.

DR. STERN: Let me make one question to just sort of respond to what you just said. Just tell me a little bit, was it 4 or 3 GHC exposed cases?

DR. GRAHAM: Herschel Jick sent us a list of five, actually. One was exposed a year before the pregnancy began, and he didn't really think it was a case, and we didn't. And of the remaining four, the second one had an induced abortion 123 days before their Accutane prescription ran out.

That didn't satisfy our 120-day definitional criteria, and so we excluded it. When Dr. Jick sent me the data, he considered--he had that labeled as a case. So he had four cases. We have used three cases.

DR. STERN: So the 1.4 percent was--

DR. GRAHAM: Based on 3 cases.

DR. STERN: Okay. And what years did they occur in?

DR. GRAHAM: They occurred in 1983, 1985, and the third one it is not clear whether it was late December 1984 or January-February 1985. It occurred in

that transitional period. This was after a time when women at GHC had signed informed consents fully apprising them of the risk of the drug, and agreeing to contraception and everything else.

DR. BERGFELD: Rob--

DR. STERN: I just need to make one quick statement.

DR. BERGFELD: One more point, right.

DR. STERN: I think you misrepresent my feelings about the importance of the problem. I think it is a very important problem. However, I do not think that the public health or a deliberative body is aided by estimates that tend to emphasize what are probably the upper bounds of the problem rather than concentrating on what are the most likely estimates of the problem, and talking about special populations which might need special interventions, perhaps, an identifying them.

So the problems I have with the report is so much emphasis on the upper bounds. I think we have a problem here. I think the problem is probably greater than the 60-some cases that have been reported. But the question is where it lies, and it really disturbed me for an investigator to take a little bit of a telemical position by so much emphasizing until the very end of

the report the upper bound, what is probably very near the upper 95 percent confidence interval of what the problem is for the Nation at large, rather than what is the problem for the Nation at large, and what are groups that might have a greater problem and need special intervention.

DR. GRAHAM: I appreciate your remarks--

DR. BERGFELD: Thank you.

DR. GRAHAM: I think that it was a balanced presentation.

DR. BERGFELD: Dr. Graham, we have another question from Dr. Fleiss.

DR. FLEISS: Well, first a comment because this issue of confounding will probably come up again and again.

It is important that we bear in mind a good working principle: epidemiological research. You control for the likelihood, for the reasonable confounders, and age certainly is one, and race was a reasonable one, but parity? That doesn't seem reasonable.

Remember, a confounding variable in this kind of research is one that is simultaneously associated with the outcome you're studying, and with exposure. Likely cystic acne is the variable that is most

associated with the use of Accutane, not parity.

DR. STERN: It is in this case for an important reason: it may have made people eligible for Medicaid so they can afford Accutane for a prior pregnancy out of wedlock. So therefore the fact that they've had a child now, and they might have had a prevalent case of acne, now for the first time they can go and get Accutane. So therefore a previous pregnancy experience is something that alters eligibility for the drug, and also alters the chance of subsequent pregnancy, and that is why it is a possible confounder.

DR. BERGFELD: Dr. Fleiss, do you have any other comments?

DR. FLEISS: Yes. With respect to the evaluation of the data from Michigan, the statistical precision of the result probably isn't all that great. Obviously, it can't be. But reproducibility across different data sets is important, and the estimated relative risk of two. Was that or wasn't that persistently found in the other data sets you looked at?

DR. GRAHAM: The problem with Florida is that they don't do induced abortions there unless the mother's life is endangered, and so we don't have induced abortions with Accutane because the woman's life isn't threatened by that pregnancy exposure.

In Group Health Cooperative we had only the three cases to deal with, so we don't have enough numbers to deal with, but we had no deliveries in that group.

DR. BERGFELD: Dr. Fleiss, do you have any other comments?

DR. FLEISS: No.

DR. BERGFELD: Do any of the panel members have a comment or a statement to make?

Yes, Dr. Minus.

DR. MINUS: I just want to make a clarification. Several times you and even Dr. Stern made mention of dermatologists giving medication and then going to the obstetrician. Do we in fact know that the majority of the cases of the patients who have birth defects were given medication by a dermatologist? If not, I think that we should just say "physician" rather than label dermatologists as the ones who are the primary offenders.

DR. GRAHAM: I think that in part that is a fair statement for many of the early adverse reaction reports which we received to the spontaneous reporting system. They were reported to us by dermatologists. So presumably the dermatologists had been the ones who had administered the drug. They are the ones reporting the

birth defect.

In more recent years, what we have discovered is that the majority of our adverse reaction reports of birth defect are reported by perinatologists, obstetricians, and the like, and that they are not being reported by the dermatologists. So I think that, whereas we don't know, and I agree with you that maybe it would be more appropriate to refer to when we talk about specific reports, to refer to physicians generically, so I apologize for any confusion over that because Accutane is given in 90 percent of the cases by dermatologists, but for these cases in all cases we don't know. So I stand corrected, and I apologize.

DR. BERGFELD: We have another question.

DR. BERGSTRESSER: I have a couple of very quick questions, Dr. Graham.

First of all, is your analysis of the information from Group Health continuing?

DR. GRAHAM: Yes. Our intention is to try to firm up the data. What we would like to do, one of the weaknesses with the Group Health data is that they don't have a good system to catalog induced abortions there. They only catalog ones that are performed in hospitals.

So the ones that are done on an out-patient basis, which is the majority, we don't have a clear

estimate of that. To get these figures we assumed that Group Health Cooperative would behave the way the rest of the Nation does in terms of 30 percent of pregnancies ending in induced abortion. So that is how we got the pregnancy rate of 50, which is an estimate.

I should point out, however, that in Group Health cooperative--it being primarily white, primarily middle and upper middle class--that that is a population which has a much lower induced abortion rate than the rest of the Nation. So it is quite possible that where we estimated the background pregnancy rate of 50 for Group Health, that it might be lower than 50, maybe 45, in which case the difference between 45 and 39, there would be even less than a 20 percent reduction in pregnancy rates among exposed women.

DR. BERGSTRESSER: The last question--well, first of all, I assume he is going to be available for comments after we've heard the comments from the company, so that if something new emerges we can ask him?

DR. BERGFELD: Is that true, Dr. Graham? You'll be here during the day?

DR. GRAHAM: I was planning to be here the entire day.

DR. BERGFELD: Thank you.

DR. BERGSTRESSER: And the final question has to do with another issue. That is, if we were dealing with anti-hypertensive drug we would be weighing two things. We would be weighing toxicity against benefit. Has your office considered at any time the issue of the benefit of Accutane to those who have received it?

DR. GRAHAM: I can answer that question I think this way. In the process of answering it, I'll actually ask a couple of questions.

Our primary responsibility is to deal with the risk side of products. Our job in adverse reaction monitoring is not one of assessing the benefits of the product. Our function is to highlight the risks and the dangers, and to bring these in a scientific fashion to the attention of others in the agency.

At the same time on a personal level, I can tell you that internally I and my co-authors and my deputy office director and branch chief and office director that we struggled, and I mean struggled over the implications of this data and what we believed should be the outcome of it.

For myself it boils down to a simple question which is: Pregnancy exposure is not acceptable under a Category X classification. So how many pregnancy exposures are acceptable? For myself, I am not able to

answer that question with anything other than zero. The acceptable number to me is zero, but others will have a different acceptable level.

I suppose that is why this group has been convened today.

DR. BERGFELD: Paul?

DR. BERGSTRESSER: During your thoughts on that issue, who serves as resources for information to you about the issues of the benefits of the drug?

DR. GRAHAM: Well, I have access to the published literature, of which I am not bragging when I say I have read most of it in the last five months. I have the benefit of interacting with Dr. Carnot Evans and Dr. Edward Tabor and in fact is the group leader for that group, and so I have lots of contact with them.

If the question is, have I ever treated patients walking into my office, the answer is, no. But I could ask you the question, have you dealt with children with birth defects?

DR. BERGSTRESSER: Well, I didn't ask the question so--I was asking who you dealt with who did know about it.

DR. GRAHAM: I've dealt with the resources within the agency and those available in the published literature.

DR. BERGFELD: Dr. Graham, I want to thank you for all of your thoughts, and especially your data for us to consider. What I would like to do now is to have an approximately ten-minute break for coffee, a quick break, at which time we will then reconvene to hear Hoffmann-La Roche's presentations, which will be 50 minutes.

[Whereupon, at 9:56 a.m., a break is taken until 10:11 a.m.]

DR. BERGFELD: As you are taking your seats, I would like to state that if any of the invited guests have questions to ask or prepared comments to make, these will be made on the agenda under "comments" and cited under "others."

We will proceed through our agenda so that we make sure everyone on the agenda speaks.

Our next speaker is a representative from Hoffmann-La Roche Company, Dr. Phil Del Vecchio, who will present his group of presenters to us. I understand this is a 50-minute presentation, Dr. Del Vecchio?

DR. DEL VECCHIO: [Nods in the affirmative.]

DR. BERGFELD: Fine, if you will proceed then.

<u>Introduction of Data on Accutane Capsules by Philip J. Del Vecchio, Jr., M.D.</u>

DR. DEL VECCHIO: Thank you, Dr. Bergfeld.

I am Dr. Phil Del Vecchio, Director of Drug Regulatory Affairs at Hoffmann-La Roche. We are very pleased to be here today to discuss Accutane and its benefits and its risks.

For the last five days we have all been exposed to a great deal of media attention, including today, and in some ways that's good because we believe this is in fact a public issue that deserves public discussion. At the same time, it may not be so good because in fact the media tends to concentrate on numbers, and in some ways forces us into discussing numbers rather than issues.

We hope to focus on the issues today. The discussion of the data is essential to understanding the problem and understanding the alternatives. I regret having to say that in the beginning that we at Roche totally reject the analysis and conclusions that were reached in the presentation by Dr. Graham, as well as in the memo that was written by Dr. Graham and his associates as being erroneous and without any scientific validity at all.

However, we do not disagree with Dr. Graham in terms of the problem. That is the problem of pregnancy exposures and general malformations. We have always

dealt with that in a very proactive and forward manner, and we plan to do that again today.

With me today to discuss this issue are Drs. William Cunningham who is an Assistant Vice President at Roche, as well as Director of Clinical Research for the Roche Dermatology Division; Dr. James LaBraico, a Senior Director of Drug Safety at Hoffmann-La Roche; our guest, Dr. Alan R. Shalita, Professor and Chairman of the Department of Dermatology at Downstate Medical Center in New York; Dr. John S. Strauss, Professor and Head of Dermatology at the University of Iowa in Iowa City; and others will be available from Roche as needed to answer questions or discuss this issue.

As I said before, we share the concern of the committee, the FDA, Dr. Graham, and the public regarding exposed pregnancies and congenital malformations. We will be presenting some data we will be refuting or attempting to refute some of the data presented by Dr. Graham, but we hope not to go into great detail on that.

In the simplest terms, we believe that we are dealing with a risk/benefit evaluation, as Dr. Graham stated. This, however, is a unique risk/benefit evaluation, because first of all the risk we are talking about cannot occur in 60 to 70 percent of the patients who receive Accutane. That is, the male patients as

well as female patients who are not fertile. It is restricted to approximately 30 to 40 percent of the Accutane audience.

Second, the event we're talking about is entirely preventable--again, a unique situation in a benefit/risk equation. Every one of these congenital malformations is a true human tragedy, and we share in that concern. On the other hand, the benefit of this drug has proven to be substantial not only to the 70 percent who cannot share that risk, but also to the 30 percent who in fact are at risk. The risk obviously must be reduced to an absolute minimum.

[Hereafter, slides are shown.]

You can put on the first slide, please. Just to briefly tell you what we will be presenting this afternoon so you will know what to look forward to, we will be presenting our proposal which consists of a radical change in the labeling for Accutane, a unique packaging configuration which is guaranteed to get the pregnancy warning to the patient, and a far-reaching peer professional program, including a unique contraception consultation program.

We will also discuss many of the other options that have been brought up at FDA and within our company and discuss the consequences and issues of those various

options.

Our goals in making these presentations, and our goals for this product are three:

That is, we wish to restrict the use of this drug to patients with severe recalcitrant cystic acne.

We wish to exclude pregnancy at the time the prescription is written for Accutane.

And we wish to ensure that the patient understands and is able to comply with the mandatory contraception warnings.

On this morning's program we will discuss the medical need for Accutane, some data on the patient prevalence and incidence measured by actual patient visits to the dermatologist's office, and our data on ADE's teratogenicity and our feelings about the adequacy of ADE reporting.

Our presentation should take approximately 50 minutes.

We would request that if you have any questions for clarification, certainly feel free to interrupt us, but otherwise we would request that we be allowed to finish the entire presentation.

And to address the benefit side of the equation, I would now like to introduce Dr. William Cunningham.

Presentation of William J. Cunningham, M.D.,
Senior Director, Clinical Investigation II
Department of Clinical Research and Development
Hoffman-La Roche Inc.

DR. CUNNINGHAM: Thank you, Dr. Del Vecchio.

I stand here today rather proud and pleased to be associated with Accutane since its initial clinical trials, and since its marketing in 1982. I think the members of the committee have seen my face a little too often, and in fact I have been here many times in the last two years to discuss the benefit/risk issues that we perceive to be the major issue with use of retinoid therapy.

The benefit/risk judgment is the single most important factor in using these drugs. This is as true today as it was in the past. Nothing has changed in that regard. We have always underscored the need to look at the risk side of these drugs. In fact, if you recall most of my presentations in the past have started with the risks of these retinoids, including its teratogenicity.

I have a unique situation that I stand both in the company and also at Columbia Presbyterian Medical Center in New York. I am a practicing dermatologist. I feel rather pleased to be that. I have an opportunity

in that forum to I think get to the heart of the problem--and that is, education of physicians and education of patients.

When the residents come to me and ask me if I think this patient is a suitable candidate for Accutane, I have a rather harsh judgment on that. I was raised with a certain ethical tradition, as well, and so I have some feelings of my own. I also have a very strong personal commitment to the proper use of this drug, and I insist with them that the teratogenicity issue be the number one that they consider.

The patient needs to have severe disease to start with. Whether female or male, in my opinion it doesn't matter, they must have severe disease.

The second thing they must have is the ability to understand and reliably comply with instructions. That is one of the single most important things in using this drug appropriately. The patient must not be pregnant at the time she initiates therapy. That is a given. We have underscored that with various options along the way.

Furthermore, the patient must be reliable and ensure that contraception is established, and that it will be maintained as one goes along in therapy. These four points I think are the single most important four

points to bear in mind when using this drug with female patients.

I think the medical need for this drug is quite clear, and Drs. Strauss and Shalita will be addressing that issue in a moment. When used appropriately in the proper doses and for the proper length of time, which is about four to five months' duration, this has a remarkable effect on the severe, debilitating disease. Remember this disease, as you will see in a moment by the pictures, is not minor acne that we're talking about. We are talking about severe disease with scars, and cysts, and terribly disfiguring physical and psychological consequences.

When used appropriately, the lesion count reduction is dramatic. In fact, we believe the drug has set the standard for severe acne treatment at the present time. It is 20th Century in every sense of the word. It produces a remission in the majority of patients, so the risk of all of the side effects, including teratogenicity, is a rather minimum time frame of approximately four to five months for most patients.

Rather than me speak about this, because again I stand in two places, I would like to ask two others that you know to speak in terms of the medical need for this drug.

The first is Dr. Alan Shalita. Dr. Shalita is currently Professor and Chair of the Department of Dermatology at Downstate Medical Center in Brooklyn. He is a past member of the Advisory Committee, a past member of the Board of Directors of the Academy, and is one of the world's leading experts on acne. I think you will recognize him from the literature and from personal appearances.

Dr. Strauss is a former President of the American Academy of Dermatology. In fact, he was president in the year that Accutane was marketed, and he is also Professor and Chairman of the Department at the University of Iowa.

Dr. Shalita.

Presentation of Alan R. Shalita, M.D.
Professor and Chairman, Department of
Dermatology, Downstate Medical Center
State University of New York

DR. SHALITA: Thank you, Dr. Cunningham.

It is a privilege for me to be here. I think that those of you who are familiar with my background know that despite the fact that I have been asked to speak here by the people at Roche Laboratories, that I also in large measure represent the dermatologic community, professional scientific community, and is

somebody who has devoted his professional life to the care of patients with acne, and particularly severe acne. I think I can qualify as a consumer advocate, as well.

I would like to briefly review for you the impact of the medical need for Accutane and its perspective, and why this is an essential drug in dermatology. And if we may have the lights down, because these are all clinical photographs, and the first slide, please.

[Hereafter, slides are shown.]

This is one of the earlier patients that we treated in the clinical investigations of oral isotretinoin. This young woman, as you can see, has severe cystic acne and was unresponsive to all prior therapy. I would like to give you some flavor of the impact of the disease in some of these patients.

This was a young woman who had training and who was aspiring to be a performer in the theater. She was unable to obtain gainful employment even as a waitress because of the disfiguring nature of her disease.

This is her after five months' treatment with oral isotretinoin in a milligram per kilogram per day. The last I have heard from her, she was touring with a

major Broadway stage company.

This young woman had, in addition to this Rosa type pustular acne of her face, severe acne of the chest and back, which is not an uncommon complication; was totally reclusive, would not go out of the house; literally had to be brought by her family to see us and, as you can see, had dramatic improvement after the disease.

This young man, in addition to the severe cystic acne of the back and chest and pustular lesions of the fact, the draining blood behind his ear and on his cheeks, had a condition known as gram negative folliculitis, which is only controllable by antibiotics, not curable by anything other than Accutane. He wore his hair long. It is pulled back here for the purposes of the photograph. He forever wore his hair long in order to cover the unsightly lesions on his face and, after treatment with Accutane, although he still has some scarring, for the first time in seven years he was able to feel comfortable with a haircut.

Acne is a multi-faceted disease, and I make no pretense to tell you that all patients with acne ought to be treated with Accutane. There has been some discussion on what is cystic acne today and the definition of incidence. This is ordinary, garden

variety teenage acne that does not require treatment with oral isotretinoin.

This is more severe inflammatory acne already with a few cystic lesions and some scarring. You can see significant scarring up here. The question of whether this would be a candidate for oral isotretinoin or not is a decision that needs to be made by the individual dermatologist, taking an accurate history of the patient in view of what their response to prior therapy was.

Here is obvious cystic acne of a most severe form. I should also interject, by the way, in order to clarify. Cystic acne by definition is "severe acne." There is no mild cystic acne. I think that definition ought to be put on the table fairly early.

Here is a patient again with severe inflammation, and this is what has been left from previous lesions and some cystic lesions. This is not only cystic acne, but the development of sinus tracks where two cysts merge one into the other. This becomes a very disfiguring disease because not only does one require oral isotretinoin or Accutane for this, but frequently one requires surgical intervention to clean out the sinus track.

Here is a quite extensive disease of the

chest, because this disease also occurs on the chest and back, with exuberant granulation tissue. You can see the scarring that has resulted from before. These are all candidates for oral isotretinoin. This shows you the extent of the diseases that can occur on the back.

What we are trying to prevent with good acne therapy, and particularly with oral isotretinoin because it is the only drug, as Dr. Cunningham said, that has set a new standard that provides this kind of prevention as well as curative therapy is this kind of scarring. This is a close-up photograph of a patient with significant acne scarring from previously destructive disease, and we certainly would like to prevent our female patients from getting to this stage of development--something that, had we had Accutane available for this patient 15 years ago when she was treated with tetracycline and everything else that is available and this was the end result--we would have not had this kind of severe destructive disease, had we had oral isotretinoin available at that time.

So in summary, I would tell you that there is a very significant medical need for Accutane. It is an essential drug for the patients with severe recalcitrant acne.

Thank you very much for your attention.

Presentation of John S. Strauss, M.D. Professor and Head, Department of Dermatology, University of Iowa

DR. STRAUSS: Dr. Cunningham, Dr. Bergfeld, I welcome the opportunity to be here. I too was here at one of the early Accutane hearings in a much smaller room and much more crowded.

While I have been invited to participate in this meeting by Hoffmann-La Roche, I feel that I am here representing the profession of dermatology, and had I not been invited by Roche, I would have requested time to make a presentation.

I am also here I feel as a patient-advocate for those with severe nodular cystic acne. I have, I am sorry to say, over 30 years of experience in treating severe cystic acne in a referral type practice that tends to draw a large number of patients at the severe end of the scale. I am also recognized as an expert in acne research.

As a dermatologist I feel that we have been indicted on the basis of evidence that can easily be challenged. Basic to the premise presented by Dr. Graham is that there are only about 4331 new cases per year of severe cystic acne in women who warrant treatment with the drug. This means that the average

dermatologist will see less than one eligible new patient once the pool has been exhausted per year. And I think all of the dermatologists on the panel, as well as those in the room, will agree that this is a very low figure.

Dr. Graham has also stated that 93 percent of the cases that have been treated with Accutane, female patients treated with Accutane, probably do not require the drug. I know our specialty particularly well, having served as the President of the American Academy of Dermatology and other organizations. We are responsible physicians. This is a gross misrepresentation of our therapeutic skills.

Likewise, I am confident that a statement that is contained in Dr. Graham's preliminary report that 85 percent of the female patients treated with Accutane have not been previously treated with antibiotics is not representative of the practice of our specialty. We are all aware that this is a drug that is to be used in recalcitrant treatment resistant disease.

My concern is very simple. Continued availability of the drug is of utmost importance to patients. Accutane is the singularly most important drug that we, the responsible dermatologic community, have for the management of severe disease. Not only

does it cause remissions, but the remissions are long-lasting and close to 90 percent of those treated.

I also appear to guarantee to you the cooperation of the specialty in eliminating the potential for women acquiring this drug during pregnancy. The value of the drug is just too great to do otherwise. The lack of its availability will set back the therapy of acne by 20 years.

What are the consequences? Can I have the slides, please.

[Hereafter, slides are shown.]

I want to show just a few brief slides which I will run over very quickly. The first of these two are patients who have scarring in the pre-Accutane days when we didn't have a drug as powerful as this to treat the patient. Those are all scars. They are not active lesion. You cut into them, they are fibrous tissue.

Another patient with severe scarring. What is our patient base that we should be treating? Very quickly, this young man has been resistant to all forms of therapy and is obviously a candidate for this drug.

Another man with very extensive nodular cystic acne.

Another person.

And still another one with very marked

scarring and a considerable activity on the chest. These are all male patients, but we're talking primarily today about female patients. I will show you some female patients who have this.

This woman needs Accutane. She has been treated with all antibiotics, and similar to the cases that Dr. Shalita showed you, she is treatment-resistant nodulo cystic disease.

Another patient with severe nodular cystic disease leading to scarring, an obvious candidate for this drug.

Another person similarly--now note there aren't the large number of lesions, so counts alone cannot give you the indication as to whether the drug should be used. The number of active lesions on this side of her face are only two, but they are leading to severe scarring.

What are our alternatives? We have lots of alternatives: tetracycline, dapsone, high- and low-dose corticosteriods, interlesional steroids, anti-androgens, spironolactone.

The patients who are being put on this drug are patients who have been treatment-resistant and at least have been through all of the antibiotics. The recommendation contained in the report, the preliminary

reports, talk about using sequential treatment with the various agents that we have.

I call to your attention the things like dapsone, high-dose corticosteriods, low-dose corticosteriods, interlesional steroids, and spironolactone using them for nonapproved usage. In the case of anti-androgens, they are not even available in the United States.

Are there any alternatives? I wish I could say that there were, but at least as far as I know at the present moment there are no alternatives in the pipeline of drugs that are coming to market or being tested that are going to be able to substitute for this particular drug.

We cannot go back to 1977. Our patients will not let us. They will either obtain Accutane through a black market with problems related not only to the purity of the drug, but dosage control; by purchasing it outside of this country; or by using a substitute such as ordinary retinol. They will take it without supervision in many cases, and without the necessary benefit of educational activity as to the dangers of the drug.

Furthermore, retinol is just as toxic and just as teratogenic--in fact, it is probably more toxic--than