DEPARTMENT OF HEALTH AND HUMAN SERVICES
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: DERMATOLOGIC DRUGS ADVISORY COMMITTEE :

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ORIGINAL

Friday, October 21, 1983

Conference Room M
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5600 Fishers Lane
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P A R T I C I P A N T S

COMMITTEE MEMBERS PRESENT:

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John R. Haserick, M.D.	Member
Marilyn C.P. Koehn, M.D.	Member
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James E. Rasmussen, M.D.	Member
Maria L. Chanco-Turner, M.D.	Member

FDA REPRESENTATIVES:

David C. Bostwick
C. Carnot Evans, M.D.
Edward Tabor, M.D.
Dr. Bilstad

C O N T E N T S

P R O C E E D I N G S

(9:00 a.m.)

DR. EAGLSTEIN: Let us get started.

There are several agenda items that could easily take a lot of time. We may have an abbreviated luncheon session as well.

So, the first thing I would like to do is welcome everybody and turn the meeting over to Dr. Evans, who is going to make a few opening remarks and announcements.

DR. EVANS: On behalf of the Agency, I would like to thank you for being present and we are appreciative of all the comments that many of you have submitted to the Committee beforehand.

I would like to acknowledge Dr. Edward Tabor, who is the acting director of of the Division of Anti-Infective Drug Products, who has taken Dr. Merle Gibson's place.

I would also like to acknowledge that we have a new Chair, Dr. Bill Eaglstein, who is chairman of the Department of Dermatology of the University of Pittsburgh.

We also have two new members of the Committee, Dr. Lowell Goldsmith of the University of Rochester Medical Center, who is not with us yet and also Dr. Marilyn Koehn of Mountain View, California.

I would also be remiss if I didn't publicly acknowledge the stalwart service given by other members of the Committee,

who finished their service last year, Dr. Faye Arundell, Alfred Allen, Henry Jones and Dr. Lee Lumpkin.

Those are the end of my comments, Mr. Chairman.

DR. EAGLSTEIN: Okay.

I think our first item is going to be Accutane and --

MR. BOSTWICK: We need to ask if there are any public discussion.

DR. EAGLSTEIN: -- right. But even before we have public discussion, I think for context for the Committee, and I am the one developing the context in that sense, my impression of what we have been given is information about a bunch of events. Some of them were predicted and some were expected more or less, and some, perhaps, were unexpected. And that in addition to information about these events associated with Accutane, we have got some reactions to the event and the reactions, at least that we have paper about, are in three categories. They are citizen's petition in reaction to these events and there are the sponsor's revised labeling in reaction to these events. And then this morning, we received -- I must say I received it last night after the subcommittee meeting, but most of you received it this morning, an FDA position or set of recommendations which would be a third reaction to these unexpected or expected events.

During the course of the first hour or two here, we

are going to have a time for open public discussion at which anybody else who wants to react can have the floor. And then we will have discussions by the sponsor and then discussions by the representative of the Public Citizen Health Resarch Group.

So, at this time, is there anybody who would like to speak in the time allotted to open public discussion?

(No response.)

DR. EAGLSTEIN: I think this is the time if anybody here wants to speak as a public citizen or --

(No response.)

DR. EAGLSTEIN: All right.

So, the next session will be initially devoted to presentation that will be spearheaded by Dr. Yard of Hoffman-La Roche, and he is the assistant director of Drug Regulatory Affairs and I am told that he is going to introduce several speakers and he has requested that the presentation, which is anticipated to last 45 minutes be uninterrupted by questions and that questions come at the end.

Does the Committee have any feeling as regards to this procedure? Would you like to interrupt during the course of the presentation, or would you rather comply with the request that the presentation be given in an uninterrupted fashion?

Mr. Kenney, any response?

DR. KENNEY: Let's comply, I think. Maybe we'll have an overview and maybe some of our questions would have been answered.

DR. EAGLSTEIN: Okay.

DR. KENNEY: If we listen to everything.

DR. EAGLSTEIN: Is that satisfactory to all of the members of the Committee?

(No response.)

DR. EAGLSTEIN: All right. If Dr. Yard wants to take the microphone at the podium.

(Slide.)

DR. YARD: Mr. Chairman, members of the Committee, members of the administration, ladies and gentlemen, my name is Dr. Allan Yard. I am the assistant director of Drug Regulatory Affairs at Hoffman-La Roche, Incorporated in Nutley, New Jersey.

On behalf of Roche, I wish to thank you for the opportunity to present this timely review of events that have occurred since Accutane was introduced in September of 1982, just a little over a year ago.

(Slide.)

DR. YARD: This morning, we shall first review for you the safety and efficacy of Accutane. This review will include a brief summary of the data in the NDA, as well as new findings that have become available to us during our continuing

research on Accutane since marketing.

Next, we will address new information and experiences that have come to us from health professionals during the past year. This part of our presentation will record the timing of these experiences and the steps that Roche has taken to communicate this new information to all health professionals and patients.

Lastly, we will invite your comments, your suggestions, your help on what Roche can do better to assure that this very effective drug is used properly by both physician and patient alike.

(Slide.)

DR. YARD: Speaking from Roche this morning will be Dr. William Cunningham and Dr. Philip Del Vecchio. Also, speaking to us will be Dr. John Strauss of the University of Iowa.

Our first speaker will be Dr. William Cunningham, who is director of clinical research of dermatology at Roche and he will discuss briefly the data in the NDA and also our continuing research efforts with Accutane.

Next will be Dr. John Strauss, who is professor of dermatology and chairman of the Department of Dermatology at the University of Iowa in Iowa City.

Dr. Strauss will share with us the results of a dose evaluation study with Accutane in which he was a principal

participant.

And the third speaker will be Dr. Philip Del Vecchio, who is director of Professional Services at Roche, and he will review for us the Roche communications effort during the past year.

Before presenting Dr. Cunningham, I wish to add also that we have with us this morning, Dr. James Corbett, Associate Professor of Neurology at the University of Iowa to assist us with any discussion on pseudotumor cerebri.

I wish now to present Dr. Cunningham.

DR. CUNNINGHAM: Thank you, Dr. Yard.

Mr. Chairman, we would like to thank you for this opportunity to address you this morning and to discuss with you some of the events that have occurred during the time of Accutane research.

I would like to start this morning by just giving you a brief overview because I know the members of the Committee are well familiar with the drug and you have all used it, but for those who haven't and who haven't heard some of the background, I will just start with a little bit of an overview and go into some of the history in regard to development of of the compound, some of the biological activities of the parent compound, Vitamin A. The clinical trials will be summarized just rather briefly in terms of efficacy and safety and then I will discuss a little bit the post-marketing

experience which we've had with Accutane since September of 1982.

I will summarize by drawing your attention to some of the continuing research that is ongoing in the area of Accutane.

(Slide.)

DR. CUNNINGHAM: Now, the retinoids as a class are a large group of compounds both naturally occurring and synthetic molecules that have been studied in the past, the vitamin alcohol is known as retinol, that is the standard Vitamin A molecule, if you will. All trans retinoic acid I'm sure you are familiar with as Retin-A, the anti-acne topical preparation. Vitamin A esters are the form that vitamin A is generally ingested in diet.

And then we get into the synthetic compounds, which are currently represented by 13-Cis retinoic acid or isotretinoin, the trade name is Accutane and the molecule, the aromatic retinoid, etretinate, which is currently in clinical trials in the United States.

It is a very large group of compounds. The parent compound, vitamin A, has several effects which are illustrated here.

(Slide.)

DR. CUNNINGHAM: Especially, one might note the effects of differentiation of epithelial tissue, effects on

growth. This parent compound action in a way predicts both the effects of the class of compounds in the biologic organism, as well as perhaps predicting some of the side effects which might see. Differentiation of epithelial tissue, for example, is one of the common effects of the drug and also one of the common side effects.

Similarly, growth and reproduction are intimately associated with vitamin A.

(Slide.)

DR. CUNNINGHAM: The historical background gives one a little bit of a perspective. The molecule was initially synthesized in the '30s, although it was known for many years before that. And therapy with vitamin A, I think some of you will be familiar with as it was instituted in the 1940s. The search for a better compound was ongoing at this time and in 1955 with a synthesis of 13-Cis retinoic acid, one had a molecule now which instead of an alcohol end group, had a carboxylic acid end group, and this changes quite dramatically the pharmacokinetics of the molecule.

The vitamin A compounds in general are stored in the liver and the carboxylic acid compound, 13-Cis is not stored in the liver. And this was the main area of interest in eliminating some of the potential side effects of vitamin A.

(Slide.)

DR. CUNNINGHAM: The history, I'll pick up again, with 1955 and a few years went by before it was introduced into human trials in Europe in 1971 in psoriasis and various other disorders of keratinization and clinical trials in the United States began in 1976 with cystic acne studies, and then in 1977 with disorders of keratinization.

And I might say that although the NDA, which was approved in 1982 contained 160 cystic acne patients at the time of approval, we have had experience up to date in our clinical trials with over 1200 patients. Although, as I said, they were not all part of the NDA originally.

(Slide.)

DR. CUNNINGHAM: The clinical trials in cystic acne, which were part of NDA consisted of 160 patients which were evaluable. The mean dose was 0.9 mg/kg/day, but there was a great range with dosing as high as 2.26 mg/kg/day. I might point out that the clinician experienced the phenomenon that the truncal acne patient did not respond as well, and these higher doses reflect to a large extent the treatment given to patients with severe involvement of the trunk.

The duration of dosing similarly varied according to the particular protocol. There were a number of different protocols. The mean duration was 16 weeks, which is about what our package insert currently recommends. The range,

however, was eight to 26 weeks. I might point out that the relapse rate at the lower range is rather significant and the 15 to 20 week period is the optimum treatment period at the present time.

(Slide.)

DR. CUNNINGHAM: I won't go into all of the efficacy details because you've had that presented to you in the past when you approved the drug for severe recalcitrant cystic acne. But with all these various parameters that I have just outlined, if one looks at those as an overview, one sees that one can achieve a 78 percent mean reduction in lesion count by the end of two months post-therapy.

Similarly, 80 percent of patients experience at least a 50 percent reduction of lesion count after a single course. If one retreats those that have failed, or those who have not received satisfactory improvement after the first course; that is, first and second course combined, one gets up to a 96 percent figure with patients showing at least a 50 percent improvement. So, I think although the figures here are rather simple, the efficacy is rather dramatic. And the pictures, of course, tell the story, and you've seen these; so, I won't belabor them.

(Slides.)

DR. CUNNINGHAM: But before and after treatment of severe recalcitrant cystic acne is a rather dramatic event.

This one doesn't project as well in the lighted room, but that is before and after.

(Slide.)

DR. CUNNINGHAM: Virtually no active lesions remaining, just scarring.

(Slide.)

DR. CUNNINGHAM: A woman with severe involvement of the face before therapy --

(Slide.)

DR. CUNNINGHAM: -- and after. And so, I think the efficacy of the drug is not at all in question.

Now, the safety of the drug is comprised of two phenomena, two parts. One is the NDA experience and this is out of standard side effect tables.

We have a very high incidence of clinical side effects with the drug. This was very clear from the beginning. Up to 100 percent of patients experience one or another of especially mucocutaneous side effects. It is very common. Generally rather mild to moderate. Occasionally, rather severe, but, in general, very treatable and very reversible.

I might point out that the musculoskeletal symptoms are seen in 16 percent of patients. In the NDA phase, all of those resolved rather promptly after discontinuation of drug and I'll talk a little bit more about this phenomenon

a little later.

The others, I won't go into specifically. I think you've seen these figures before and these are the figures that are in the package insert.

(Slide.)

DR. CUNNINGHAM: Laboratory side effects similarly are generally not a terrible problem. The elevated triglycerides in general, although they are frequent, are not reason for discontinuation of the drug unless they are very elevated. The short course of therapy here, I think, precludes a problem with elevated triglycerides.

Long-term therapy might be a little different, but here the short-term of four to five months, I think, one can tolerate even these modest elevations of triglycerides.

And Dr. Strauss will present some data on that in a few moments.

The other side effects, I think you are familiar with. I won't go into them in detail.

(Slide.)

DR. CUNNINGHAM: Now, the Accutane experience in the post-marketing period is much larger than that during the NDA period naturally. The drug was very well accepted. There were a large number of patients waiting for this drug. It was very effective. It was clear that it was. Up to 300,000 patients have been treated. This is an estimate.

It is not an exact figure. I think one could expect to have a broadening experience in the side effect realm with this kind of patient population. And, in fact, we do have that kind of experience.

I might point out that vitamin A is teratogenic in animals and in humans. It was known in the pre-marketing period that Accutane was teratogenic in animals. You see the data, for example, for the rabbit, the drug is clearly teratogenic at 10 mg/kg/day.

(Slide.)

DR. CUNNINGHAM: The original package insert contained the pregnancy warnings pretty much the same as they are at the present time. The use of this drug in pregnancy has always been contraindicated. Meticulous contraception has always been recommended.

And now we have human experience and that is that Accutane is clearly teratogenic at therapeutic doses.

(Slide.)

DR. CUNNINGHAM: The specifics of this, I think are again familiar to you. The current figures are that we have seven reports of fetal abnormalities in women who have taken Accutane during the first trimester of pregnancy. The congenital abnormalities, which I have listed, primarily, although there are a large number of others that are of less common appearance, the major one being the CNS malformations,

the ear and eye malformations. These are major fetal abnormalities and, again, underlie the necessity for very strict contraception. This is an absolute must with this drug.

(Slide.)

DR. CUNNINGHAM: Now, to digress a little bit to some of the other effects, pseudotumor cerebri or papilledema has been reported to us in a number of instances. We have the present time approximately 10 reports of either one or the other, with the majority being pseudotumor cerebri. We have a total of seven reports of that condition at the present time.

Now, I need to put this in some perspective although the epidemiology figures for this are not very good, one has to see that these are 10 reports out of about 300,000 patients who have taken the drug.

Six of them have resolved completely. Some of them had visual disturbances, which is a very common presentation of pseudotumor cerebri. The benign increased intercranial pressure causes papilledema, which has been seen in a number of these patients. One of the patients that was reported in retrospect probably had pseudopapilledema; that is the disks were -- the margins were blurred, but in retrospect it appeared that that had been the case before therapy and there were no sequelae from that.

Three cases, as you might expect, in this kind of

environment are still under investigation. There symptoms are resolving, but we do not have the last follow-up on those patients.

Now, five of the patients at least had concomitant tetracylcine or minocycline, and Dr. Del Vecchio will digress for a moment during his discussion about that experience. It is difficult to say at the present time whether there is an association or not. Certainly there is with the numbers, but whether there is, in fact, in terms of pathogenesis, that's not clear.

(Slide.)

DR. CUNNINGHAM: Now, the other eye related changes, of course, you are familiar with the high incidence of conjunctivitis with the drug. It is very common, and very treatable in general. We also had some experience with corneal opacities in the NDA period, the patients especially with disorders of keratinization had this as a result of the dryness of the eyes. Those were reversible on discontinuation of therapy. And in this post-NDA period now, we have had three reports of patients who have developed corneal opacities while on Accutane.

One of them resolved completely while on therapy after discontinuation of her contact lenses, so that was not a problem. One also were contact lenses, in general, but did not during the time of treatment and that at the present

time is nearly resolved. She has one small opacity remaining which has not interferred with vision. And one report was a nonconfirmed report that the patient was told they had opacities and there was apparently no vision problem, and the follow-up was not obtainable in that particular patient.

In general, I would say, this is not an unexpected event. The eyes are rather dry. Conjunctivitis is common. Meticulous eye care is necessary. I think you've all had that experience.

Now, the more disturbing question of visual loss has come up and I think that, again, as part of the pseudotumor cerebri and papilledema spectrum, one can expect that this is one of the most common presentations of pseudotumor cerebri in fact.

Other than that, however, we have had only one other report of visual loss, and that was in a patient that apparently had it as a result of encephalitis. The patient had a viral encephalitis. Had some decreased visual fields during that time. Upon recovery, the visual fields returned to normal and the patient has normal vision at the present time, although the patient did have a subsequent exacerbation of encephalitis. So, I would say that other than the pseudotumor cerebri, visual changes other than blurring -- other than blurring of vision from conjunctivitis, let's say, have not been observed to our knowledge.

(Slide.)

DR. CUNNINGHAM: Now, inflammatory bowel disease is a little bit of a different story, I think. Here you see the epidemiology figures. There are a total of nine reports to us out of this large population and it is hard to say whether there is over or under reporting, but we've had a large number of reports. I tend to think that the dermatologist has been very meticulous about reporting these patients, especially with disease of this sort.

Ileitis, in general, has an incidence of one to two cases per 100,000 per year, and to date we have four reports of ileitis. I might say that I see nothing other than a temporal relationship here. One patient in fact had a previous history of regional enteritis. One patient developed regional enteritis three weeks after discontinuation of the medication and did not develop an exacerbation after rechallenge with the medication. So, that one as well does not support the cause and effect relationship.

Similarly, with colitis, the figure for ulcerative colitis is 6.5 to 9.1 cases per 100,000 per year and to date we have five reports of colitis. Not all of them ulcerative colitis.

I might point out here as well that one patient had ulcerative colitis to begin with and exacerbated while on drugs. The relationship is not clear to that, but I can tell

you that it was on the second course of drugs. The first course was without incidence; so, again, I question whether there is anything more than a temporal sequence here. The two patients with ulcerative colitis, one was unexplained and at least temporally was related to drug. The other patient had a past history of megacolon and, interestingly enough, also had pseudotumor cerebri in the past from tetracycline, and developed ulcerative colitis while receiving Accutane.

Now, it is a difficult picture to sort out, but, again, I think what we are left with is a figure, at least a number figure which is well within the expected incidence from these diseases.

Furthermore, I might say that all of the other side effects which we have seen to date follow the vitamin A toxicity pattern very closely. The incidence of the side effects is different with Accutane versus vitamin A, but to a large extent many of the side effects follow that hypervitaminosis A pattern. And inflammatory bowel disease is not part of the hypervitaminosis A syndrome.

(Slide.)

DR. CUNNINGHAM: Now, I will digress from cystic acne patients, and I'd like to bring you up to date on the bone changes related to Accutane in patients with disorders of keratinization. We have a prospective study in place in

cystic acne patients looking for bone changes in that group, and to date we have had 30 patients complete that prospective study with baseline and follow-up X-rays, and, of course, X-rays showed no change in the cystic acne population. That's with package insert dosing and duration.

On the other hand, we have observed a rather high prevalence of skeletal hyperostosis with Accutane in patients treated for disorders of keratinization. These have been patients for the most part treated for long durations. Our oldest protocol, you will remember, goes back to 1977 and many patients have been on drug four and five years. The mean dose in that larger group is 2 mg/kg/day. The duration in that group is about two years duration, the mean duration. Many have received drug longer than that.

On the other hand, a smaller prospective study of patients with disorders of keratinization, again, at mean dosing higher than most of the patients are receiving for cystic acne; that is, about 2 mg/kg/day mean dose, and that small prospective study, five out of eight patients had X-ray changes consistent with skeletal hyperostosis at six and 12 month X-ray.

I might say that I have seen the 12 month X-rays. The changes are very minimal. The patients are asymptomatic for the most part. The progression of the disease is uncertain because most of the patients have such serious disease they

do not choose to come off therapy.

The six month X-rays, I might point out parenthetically were reinterpreted after the 12 month X-rays in the small study and when looked at with that careful scrutiny, small changes could be detected on that.

Now, the hypervitaminosis A syndrome includes hyperostosis in general. In the literature, that has been reversible upon discontinuation of drug.

I cannot say this at the present time for Accutane, but I would predict that that would be the case with these minimal changes.

So, I would like to just leave you with that in mind that there is no question that Accutane is related to bone effects, especially in long-term, high-dose therapy. In the cystic acne population to date, which we have looked at prospectively, there have been no changes of bone.

(Slide.)

DR. CUNNINGHAM: Other findings, I won't dwell on because our time is limited. Again, you are familiar with these, I believe. Many of you have experienced them. Rather more common side effects and less severe in general than the others we've been discussing.

(Slide.)

DR. CUNNINGHAM: Now, I would like to just in two minutes tell you what we are doing in the present and in the

future. First of all, our research effort in Accutane is rather extensive at the present time. It is ongoing. We are committed to a very prolonged period of follow-up with the drug.

Our epidemiology studies, for example, were initiated at launch. This is the first instance of such an event occurring in the industry that I am aware of. We have two major epidemiology studies in place in the Pacific West Coast. Both of those are looking at adverse reactions. To date, the experience is similar to the experience in the NDA period; that is, nothing outside of the NDA experience.

Those studies will continue, I presume, as long as we are using the drug and they are projected to go indefinitely. The musculoskeletal signs and symptoms, I discussed a little bit. That is ongoing as well and I've just expanded that study to 100 patients. I think we will have a very good prospective study that will very definitively answer the question which I believe has really been answered in the initial patients.

Lipid metabolism, as well, will be looked at in a large outpatient and inpatient rather detailed elaborate sophisticated lipid metabolism protocol.

Immunologic and androgen function, which many have requested be looked at is in place and is being examined. Semen analysis similarly is being looked at in cystic acne

patients.

And now I might say that at the time of approval, there was some discussion of dosing, and we had at that time in place a rather large, and, I think, rather definitive study which Dr. Strauss will address. This is a very nicely designed study, a triple dose study. Three investigators, Dr. Shalito, Strauss and Pochi and I believe probably the most definitive dosing study to date with Accutane.

And with that, I'd like to turn it over to Dr. Strauss to discuss that study.

DR. STRAUSS: Thank you.

Chairman Eaglstein, members of the panel, representatives of the government and interested parties. What I am about to describe to you is the results of a study, a double blind study involving dosing. Our question was addressed to try to determine whether there was any one dose that was superior to another in terms of clinical effect, at the same time trying to reduce the side effects, both clinical and laboratory that Dr. Cunningham has indicated.

And we looked at not only the clinical response in this group of patients, but the incidence of side effects, the incidence of laboratory side effects and the degree of these. And of greatest importance, as I'll emphasize, what happens in long-term follow-up in these patients because that is going to be a critical issue.

Dr. Cunningham has already pointed out to you this was a study that was done in three different centers. Dr. Pochi at Boston University; Dr. Shalito at Sunny downstate, and our group at the University of Iowa.

(Slide.)

DR. STRAUSS: The large study. We had at the end of the study a total of 141 patients who were analyzable, with at least 46 in each of the three treatment groups. Treatment was given for 16 to 20 weeks in these patients. If you look at this slide, you can see that the groups are roughly comparable in terms of age, in terms of duration of treatment and duration of acne. I want to emphasize that this was a fixed dose study. The same dose was used throughout in all of these patients.

(Slide.)

DR. STRAUSS: First of all, let's look at the clinical effects. If you can see this, this is a summary of the response of nodular cystic lesions 4 millimeters or greater in diameter on the face. At the end of the 20 week period, as you can see, there are roughly comparable decreases in the percent of lesions that we're seeing.

You will also notice that for the 12 weeks in the immediate post-treatment period that these patients were followed, there was a further decrease in the lesions. This is something that has been reported continuously in all of the

studies. And at the end of that 32 weeks, the 20 week treatment and 12 weeks of post-follow-up, you can see that the curves are roughly the same.

(Slide.)

DR. STRAUSS: Similarly, if we plot the lesions on the trunk, at the end of 20 weeks, the three groups are comparable. At the end of 12 weeks follow-up, the results are comparable.

So, from this, we would -- there seems to be an indication that all three dosages, a 0.1 of a milligram, 0.5 milligram and 1.0 mg/kg/day are roughly comparable. I should add that we did -- I did an earlier study -- it was one of the early studies that was done with the drug in which we investigated the three different dosages and this formed the basis for doing this study. And we had seen in that previous study roughly comparable results with the three doses.

However, in that previous study, the cell size was very small involving 4 or 5 per cell so that this study involving 141 patients does give us a comfirmation of the earlier study that we did.

(Slide.)

DR. STRAUSS: In terms of the clinical side effects, I plotted out here the clinical side effects that have been seen with greater than 30 percent incidence and with the three dosages. Of course, starting with chapped lips, as

Dr. Cunningham has already pointed out, this was the most common side effect. And you will see that there is a difference between 77 percent and 93 percent between the lowest dose and the highest dose.

If you look down the line, you will see that there is not any consistent change in relation to dose. And the difference to me between 77 percent and 93 percent is in line with what I'll discuss at the end of this is not anything that we have to be concerned with, and I think that it does not justify necessarily reducing the dose one milligram per kilogram per day to 0.1 milligram per kilogram per day.

(Slide.)

DR. STRAUSS: In terms of the laboratory side effects, I think there are two that there has been some concern, as Dr. Cunningham pointed out to you, were liver function and what happens to blood lipids. All of these patients had liver function studies done in each of the observation periods and I've plotted out here the results of 4, 8 and 20 weeks.

As you can see with 1 mg/kg/day at the 8 weeks and at the 20 weeks, there was a statistically significant increase in the SGOT aspartate transaminase.

However, even at the end of 20 weeks, the value of 32.4 is well within the normal limits. So, the elevation here, and these are group means, is not significant.

(Slide.)

DR. STRAUSS: When we look at the SGPT, or alanine transaminase you will see that once again there is a slight rise which was statistically significant at eight weeks, but still it is within the normal range.

(Slide.)

DR. STRAUSS: If we look at the LDH, there is no significant elevation all during the time that these patients were on treatment.

(Slide.)

DR. STRAUSS: And, finally, if we look at alkaline phosphatase, why there is a slight rise at four weeks, with 0.5 mg/kg/day and at 20 weeks with 1.0 mg/kg/day, these still are with normal limits.

In sum total for this particular -- these laboratory studies, while there has been a slight elevation in the mean values, they are still within normal limits.

(Slide.)

DR. STRAUSS: Turning to the blood lipids, triglycerides, of course, have been a major concern. We note that in this larage group, 141 patients, there were slight rises particularly with 1.0 mg/kg/day which were statistically significant as compared to baseline, but yet they still were within normal limits so that the elevation while there was a elevation, this was within normal limits. And I would like to reemphasize what Dr. Cunningham has already said that the

patients that we're treating with isotretinoin for acne, we are treating in general with lower dosages than the diseases of keratinization where some of the elevated triglycerides have been seen.

If we look at cholesterol levels,once again, a slight rise, but, once again, still within the limits of normal.

(Slide.)

DR. STRAUSS: And, finally, because the major concern is not with the triglycerides, but with the HDLs, high density lipoproteins, which, of course, has been tied to the possibility of increased risk of coronary artery disease with 1.0 mg/kg/day as well as with 0.5 mg/kg/day at eight weeks, there is a slight decrease in the high density lipoproteins.

Once again though, it has been the pattern that I've already talked about, the drop in high density lipoproteins, they still are within the limits of -- normal limits.

So, with these two laboratory parameters now, once again, there does not appear to be a clinical significant difference between the three dosages.

(Slide.)

DR. STRAUSS: One of the things that -- when Dr. Peck originally reported on isotretinoin, he elaborated on, and I think one of the things that is of greatest importance with this drug, is the length of remissions that occur with the drug and we did a survey of those patients who had been treated

with the drug, only one course of the drug, some 18 to 24 months later a survey was done as to what their status was, and I repeat that these are patients that had only one course of drug.

And as you can see, let's look at line "gone entirely," 0.1 percent, 23, roughly a quarter of the patients said that their disease was gone. With 1 mg/kg/day, half of the patients said that their disease was gone.

Going down to the bottom line here, those who were worse with 0.1 mg/kg/day, 30 percent reported they were worse, whereas only approximately 7 percent reported that they were wese with 1 mg/kg/day dose.

(Slide.)

DR. STRAUSS: We asked them the question: if acne is worse, is it as severe as it was before therapy? There's a clear cut difference between 0.1 mg/kg/day and 1.0 mg/kg/day. None reported that there were worse when they were on 1.0 mg/kg/day. 37.5 percent reporting that they were worse with 0.1 mg/kg/day.

Going down to if acne has recurred, have you begun any acne therapy? Once, again, the same type of difference between the two dosages. And so we think that this is a very interesting thing.

(Slide.)

DR. STRAUSS: But of more importance was what percent of the patients who were treated with isotretinoin

in the three different dosages in this particular study needed retreatment with isotretinoin, and there is a clear cut difference. With 0.1 mg/kg/day, over 40 percent of the patients required a second course of therapy, whereas with 1.0 mg/kg/day only 10 percent required retreatment. I think this is the most critical issue that this particular study has shown, because we are working with a drug that admittedly does have side effects. And it is my opinion; I think the opinion of my co-workers in this study that the ideal thing to do is to treat these patients as quick as possible and with just a single dose, a single course of therapy. And if that is one of our aims of therapy; then, there can be no question that the 1 mg/kg/day dose is more effective than the 0.1 mg/kg/day in terms of preventing the recurrences.

The summary of this data involving a large group of patients, 141 patients is that there is a clear cut difference in the remission rate between the three dosages, and it is our recommendation that the 1.0 mg/kg/day dose be the general starting and course dose when you are treating with isotretinoin.

I now turn the meeting over to Dr. Del Vecchio.

DR. DEL VECCHIO: Thank you, Dr. Strauss. Good morning. I am Dr. Philip Del Vecchio, I am director of Professional Services of Roche Laboratories and I here this morning to talk to you about Accutane communications.

What we have done to communicate that information that you have just heard over the past year, both the old information that we knew at the time of launch and the new information that has come out.

(Slide.)

DR. DEL VECCHIO: In order to do this, I am going to cover it in four different phases, four different time period, the first being the period of the approval and launching product back in fall of 1982; the second being the late winter and early spring of 1983 when the first indication came of the new adverse effects which were previously unrecognized; the third period being the summer of 1983 when we started teratogenicity data, the human fetal defects became know, and, finally, what we're doing at present and what we propose to do in the future.

(Slide.)

DR. DEL VECCHIO: And for each of those time periods, I'm going to go through the specific dates, the important dates taht things happened. What the things were that we needed to communicate and what our considerations were in making those communications, the actions that we took, and for the present and future time period what are future options might be, and in that regard, we would certainly like to ask the Committee for their input and information, their opinion as to which direction we might go.

(Slide.)

DR. DEL VECCHIO: The first time period is that of approval and launch. As most of you are aware, our NDA clinical program started in 1976 and in 1981, we submitted the Accutane NDA. Following two meetings of this particular committee, during which time the drug the drug was given an approvability status and the labeling was approved and the product was given final approval by the FDA, and the official launch of Accutane took place in September of 1982, just a little over a year ago.

(Slide.)

DR. DEL VECCHIO: And at that particular time the things that we needed to communicate were these: First, the indication, that is for severe recalcitrant cystic acne. We needed to communicate that very clearly. The dosing, 1.0 to 2.0 mg/kg/day in divided doses for 15 to 20 weeks. A very important consideration, teratogenicity in animals had very clearly been demonstrated. Obviously, we had no human data at that time, but based on that and animal data and human data for vitamin A, we certainly anticipated the possibility that there might be teratogenic effects in humans. And based on that information, obviously, we had to consider the problem of pregnancy, and, as Dr. Cunningham alluded to earlier, pregnancy was contraindicated from the start. This is a product, a category X compound from the very beginning.

We also needed to communicate the clinical side effects for Accutane. At that time, the only clinical side effects that were know were the mucocutaneous side effects and the muscoloskeletal side effects. And all of those were known to be both minor and reversible upon discontinuation of therapy.

In addition, we had to communicate the laboratory abnormalities, the most prominent one at the time being the lipid abnormalities.

(Slide.)

DR. DEL VECCHIO: There were some special considerations in regard to communicating these things. We did marketing research data which told us that there were a minimum of 360,000 severe cystic acne patients under the care of physicians at that time. About two-thirds of them were being treated by dermatologists and about one-third by non-dermatologists. We were told there was no effective therapy for those patients at that time. We have no idea of the number of patients who were not in the medical care system at that time who have come into the system since that time, since the coming of Accutane. This clearly is a minimum number.

The indication was very important. A drug that has a great number of side effects as this did needed to be used for the proper indication and that was severe cystic acne and we felt there was a very strong need to pinpoint that

indication, as well as, I mentioned, a very strong need to prevent pregnancy. Contraception was paramount. This was a drug that we knew that the possibility of teratogenicity was very possible and we did not want that to happen; therefore, we needed to warn patients and physicians about that.

Obviously, we needed to inform the physicians on the side effects profile, and the last point that we felt was very important and that was the need for patient information. In a drug that has up to 100 percent side effects, the possibility that a patient takes that drug might begin to experience side effects before they experience beneficial effects is very possible, and, I think, as most of you know, that is exactly what may happen with patients. There may be exacerbations of their acne. They may have other skin effects before they begin to feel better. We felt this could produce a very big problem with compliance. That patients may go on and off the drug. Might reduce the dosage themselves. Might not report back to their physicians, and, therefore, we felt that we had a very strong need to go ahead and issue patient information.

(Slide.)

DR. DEL VECCHIO: Well, what did we do. First of all, we decided which audience to go to. We went to all dermatologist with a very major emphasis on this product. We felt that the majority of patients should be treated by dermatologists with

this particular drug for this particular indication two reasons. Because it was a complicated drug in terms of the mucocutaneous side effects and also because of the pinpointing of the diagnosis.

And, in fact, as you will see later that is exactly what has happened. However, we also went to primary care physicians because we felt that they might see some of these patients who were being treated perhaps for side effects, perhaps for contraception, perhaps for the lipid problems. Also, some primary care physicians were going to treat patients with Accutane and for those physicians, we provided them with complete prescribing information, complete information. We did not go to the total medical universe with this particular product.

Obviously, we went to all pharmacists, all institutions in both the residence programs and the outpatient departments and, of course, we went to the patients, but only via the dermatologist and the physician in general.

(Slide.)

DR. DEL VECCHIO: I would like to show you some examples of the program, just a few examples of the programs that we've used for information to the physicians, to the pharmacists and to the patients.

(Slide.)

DR. DEL VECCHIO: This is an informational piece

that was used very early after the launch of Accutane.

(Slide.)

DR. DEL VECCHIO: That is the cover and what I would like you to see on this piece is the emphasis and the balance. You don't need to read all of this, but there are data here on efficacy and you see the pregnancy warning very prominentely displayed in bold type.

(Slide.)

DR. DEL VECCHIO: Another set of pages. I don't know who well that is in focus, but this particular area has to do with the pregnancy contraindication and data regarding work up and lipid abnormalities and side effects.

(Slide.)

DR. DEL VECCHIO: Another set of pages, the side effects profile, the same side effects profile chart that you saw from Dr. Cunningham.

Another piece, the cover of the piece, I think, is interesting. It is a very dramatic face of a patient with severe cystic acne. We felt that the photographs themselves helped to pinpoint the indication for which this drug is supposed to be used.

(Slide.)

DR. DEL VECCHIO: And following the page which shows the response to that drug.

(Slide.)

DR. DEL VECCHIO: The following pages have to do

with efficacy, reduction in sebum count, reduction in cyst count, reduction of sebum production.

(Slide.)

DR. DEL VECCHIO: And the following pages immediately after that are all basically what we call fair balance pages, teratogenicity and pregnancy problem in bold print. The work up for lipids, the side effects. I think what I am trying to point out from these is the emphasis that we have placed on not only the beneficial effects, but also the risks that we knew at that time with Accutane.

(Slide.)

DR. DEL VECCHIO: In addition to those pieces, these are three more informational pieces that were produced. The comprehensive product information, basically a monograph on Accutane. Everything you ever wanted to know about Accutane was contained in there.

The scientific summary on Accutane. We produce these for every one of our new products. It is a summary of all of the NDA information, a compiliation of all of the data that we have submitted to the FDA in support of the NDA application. In this particular case, it gave the resulsts of the trials for cystic acme as well as the safety profile on a total of 523 patients who were treated not only for acne, but also for other disorders. And because of the particular problem with the drug, we issued an additional scientific

summary at the time of launch which was this uninduced lipid changes, giving the physician some information on the triglycerides, the HDL levels and what to do about them and what they might mean.

(Slide.)

DR. DEL VECCHIO: This was a tear off from a patient chart. This was the patient's instruction sheet that the dermatologist was supplied with to give to his patients in regard to side effects. This is all the side effects. It talks about the drying of the skin, the pregnancy contraindication, and other warnings in regard to triglycerides and other things that may happen to the patient when they are taking Accutane.

(Slide.)

DR. DEL VECCHIO: And the back side lists the side effects, lists how frequently they occur for the patient's information. Gives them some hints about what to do about them. The ones that they can treat. They one they should see their doctor about.

We felt that the patient needed to get this information from the doctor. We are very concerned that we maintain the physician/patient relationship, the physician/patient communication and dialogue about this drug.

(Slide.)

DR. DEL VECCHIO: One final piece for patients,

a piece which we are very proud of and that is the patient information brochure, which we issued at the time of launch. This is the cover.

(Slide.)

DR. DEL VECCHIO: This is the back page. You will see on the back page a warning for female patients.

(Slide.)

DR. DEL VECCHIO: And just for your information, the warning itself specifically says that birth defects have been shown in animals. If you are pregnant or intend to become pregnant while undergoing treatment, you shouldn't be taking Accutane. Be sure to use an effective form of contraception and should you become pregnant, be sure to tell your doctor.

(Slide.)

DR. DEL VECCHIO: The inside of the brochure talked a little bit about cystic acne and a little bit about general guidelines in taking the medication.

(Slide.)

DR. DEL VECCHIO: And when you open it up all the way, it talked about what to be concerned about before treatment; things that might occur during treatment and what to expect after treatment.

(Slide.)

DR. DEL VECCHIO: You will notice again that on the inside of the brochure the same warning, which I have again

have blown up here just for you to see, the fact that we felt that these patients needed to have this information so that they knew what was happening. They knew how important it was not to become pregnant.

(Slide.)

DR. DEL VECCHIO: That brochure was made available in September of 1982. At that time, 500,000 of those brochures were made available through our sales force besides the ones that were mailed out to those people who requested them.

In 1983, up to about the summer of 1983, an additional 250,000 brochures have been requested and ordered by our sales force for distribution to physicians who wanted them.

I can assure you that sales representatives do not order unnecessary material to carry around in their trunks. The fact that 250,000 more brochures were ordered means that they were being distributed and they were being used.

This figure of 750,000 brochures that are out there does not include an additional 600,000 that went out by pregnancy warning letter. But they have been available over the entire year's period from the time the product was launched.

(Slide.)

DR. DEL VECCHIO: Accutane was obviously a very important drug. The FDA announced its approval. The media was interested in what was happending with this important new

drug. We received a large number of media inquiries. Our response to the media was exactly the way it was to the profession and that was we felt we had to give complete and important information. We wanted to be sure that the indication was highlighted. That it was for severe cystic acne. We wanted to be sure that the public knew about the fact that there were adverse reactions, and we wanted to sure that they knew about the need to prevent pregnancy. This is just one single example of an article that appeared in a New Jersey newspaper. You will notice the subheading mentions the fact that the drug causes some side effects.

(Slide.)

DR. DEL VECCHIO: And there is a blow up here of one of the paragraphs, one of the first paragraphs. It says, "Adverse effects from the drug make it unsuitable for treating milder cases and it should not be used by pregnant women according to information packaged with the drug."

Our finding was that the media in general was very responsible in reporting the things that we gave them. They did report the fact that the drug should not be used for mild forms of acne. It did report the need for contraception.

It was another sources of information that both the professions and the public had and we responded to it by giving them the most important information that we did have.

(Slide.)

DR. DEL VECCHIO: And one additional source of information was the FDA itself, the FDA Drug Bulletin, which was issued in August of 1982, and I believe appeared in September at the time of launch.

(Slide.)

DR. DEL VECCHIO: It contained an article on Accutane and all of its benefits and its risks.

(Slide.)

DR. DEL VECCHIO: I want to move on now to the spring of 1983. That was the approval and launch period. This is the period when be began to have reports of new side effects. As Dr. Cunningham has mentioned, the three major areas that we are concerned about for pseudotumor cerebri, and we had three cases reported to us in the spring. Since that time there have been four others and there were three additional cases of plain papilledema, as he mentioned.

Colitis, there were four cases during that period. And Ileitis, there were four cases also during that period.

There are a couple of very important points that need to made here, I think, in regard to pseudotumor cerebri. It is clearly a potentially serious illness. It is also not a medical emergency. Pseudotumor cerebri is a disease that is usually not drug-related. It is kind of unusual to have drug-related pseudotumor cerebri. There are the drugs that cause it.

The usual cause of pseudotumor cerebri is idiopathic,

it is unknown, and, as such, that can become a very serious illness, and in some cases may cause permanent visual loss.

There is no indication whatsoever that the earlier the diagnosis, the less likely there will be visual loss. As a matter of fact, patients who come in with visual loss may or may not have permanent visual loss, but I don't wish to minimize the importance of this illness because it is important. On the other hand, we don't wish to exaggerate the severity of the illness. I would encourage the Committee if you have any specific questions in regards to pseudotumor cerebri, I would encourage you to ask them of Dr. James Corbett, who is certainly an authority -- he probably has the largest collection of drug-induced pseudotumor cerebri patients in the country, and he is available for your questions later on.

The other point that I would like to make about pseudotumor cerebri is that there is no way this could have been picked up an earlier. The incidence is 10 in 300,000. An ADR that occurs in an incidence in one in 30,000 cannot be picked up in clinical trials. You would probably have to study 10,000 to 15,000 patients in order to pick up something like this. Yes,it had been known that it could occur from vitamin A toxicity. However, as Dr. Cunningham pointed out, this drug is not vitamin A. It is different than vitamin A. It has different characteristics, different pharmacokinetics, different metabolism. As such, you could not expect that

everything that happens with vitamin A is going to happen with Accutane.

The converse, however, seems to be true that just about everything that happens with Accutane may happen with vitamin A overdosage.

In regard to the ileitis, I would like to make a couple of points about this also. Dr. Cunningham mentiond the usual incidence,expected incidence of ileitis in this particular age group. It is considerably higher than the incidence of reports that we have. I know that there is a feeling that there is underreporting of adverse events to the extent of 1 to 10, and that may very well be true for an older more mature drug for minor side effects. We do not believe that is true for this drug. We do not believe it is anything near the 1 to 10 underreporting ratio that you see with other drugs.

As a matter of fact with a drug of this importance and this potency, with the amount of information that we have gotten out to dermatologists, our feeling is that this is fully reported. That dermatologists who don't normally deal with drugs that have serious systemic effects or potentially serious effects tend to let us know very early. They tend to ask information.

Just for your information, I just checked yesterday before we left. Our department is in the business of answering questions, of giving information to dermatologists about the

drug, side effects, efficacy, and everything else, and as of yesterday, we had received 6500 inquiries by phone and mail from dermatologists and other physicians involved in treating patients to which we responded by giving them information on a variety of things about Accutane. There were a number of places from which they could get this information.

To get back to ileitis, I think there is another important point that needs to be made and that is that the use of the term "Chron's disease," in conjunction with these particular cases is probably medically inappropriate. It could be that two of those patients, from the description given to you by Dr. Cunningham, may very well have Chron's disease or have had Chron's disease.

Chron's disease is a chronic granulomatos disease with remissions and exacerbations over a long period of time. It is idiopathic in terms in terms of its etiology being unknown. It is not specifically related to drugs. We have no evidence whatsoever that Accutane causes Chron's disease. We do know that these four cases did occur. Of these four cases, two of them could be considered ileitis, which was regional, but the mistake that we make, I think, in looking in the books and seeing that a synonym for regional ileitis is Chron's disease. That may be true, but this is not typical Chron's disease. Even if it is, as Dr. Cunningham has pointed out, the incidence of this particular side effect

is actually less than what is expected in this particular age group.

Our feeling is that the most that can be said about this is that inflammatory bowel disease has been associated with Accutane -- with patients receiving Accutane therapy, but there is no proven cause and effect.

And the final point on that, again, to repeat what Dr. Cunningham has said, this is not a vitamin A toxicity side effect.

(Slide.)

DR. DEL VECCHIO: What needed to be communicated at that time obviously the side effects, the new ones that we knew about, the infection, the prevention, and we needed to report to FDA, which we did.

(Slide.)

DR. DEL VECCHIO: And our action at that time was to request that the FDA give us a change in labeling. We sent a letter to them in May of 1983 requesting a change based on those particular side effects.

(Slide.)

DR. DEL VECCHIO: However, before anything could be done and that could be resolved, something new happened and that brings us to the summer of 1983 when the reports of teratogenicity came in. On June 15th, we received our first report. A week later, we received our second report. Those

were fully investigated; reported to the FDA and while they were being reported, a third report on a preliminary basis came in on July 5th. We contacted the FDA of July 11th and asked for a meeting to discuss new labeling and to discuss changes in the package insert. The FDA responded very promptly. We met with them on July 14th and very quickly thereafter the pregnancy warning letter was sent.

(Slide.)

DR. DEL VECCHIO: What needed to be communicated at that time? Obviously, one point. We now had human teratogenicity data. We had to reinforce the pregnancy contraindication one more time. I would like to emphasize that this is no different than it was in the beginning. The drug was and still is contraindicted to pregnancy, and in fact decided adding wording about the fact that we now had human data, there was no difference in what we had had before in regard to that warning. Nothing had changed except that what we anticipated might happen did happen.

Again, there is no way, of course, to determine this in clinical pre-NDA trials. You obviously cannot do studies on pregnant women. This is something that we did anticipate and, in fact, it did happen.

(Slide.)

DR. DEL VECCHIO: What were our actions at that time? Well, our first action was to send the pregnancy warning letter.

We notified our sales force, and I'll get to that in just a moment.

(Slide.)

DR. DEL VECCHIO: Let me just show you the letter. This is the pregnancy warning letter that was sent out.

(Slide.)

DR. DEL VECCHIO: It was sent out marked important Accutane pregnancy warning in bold red print on the envelope. It was sent out along with the patient brochure and the package insert, which had, of course, not yet been revised. This had all just started to occur, but we felt the warning had to be out there as quickly as possible.

We also asked dermatologists to let us know about their pregnant patients. To let us know about any pregnancies either with good results or bad results so that we could develop epidemiologic data.

(Slide.)

DR. DEL VECCHIO: That particular letter went to a total audience of almost 600,000 people as contrasted to our original material, we went to all physicians, osteopathic physicians, every pharmacy, all the Roche wholesalers, all physician assistants and, in fact, even a special list, a special AMA list that the mailing house obtained of physicians who don't wish to obtain milings. They don't wish to obtain a promotional mailing. The AMA agreed that this warning was

important enough that they allowed that list to be used for this particular mailing. 600,000 went out. We feel that this covered everything.

The reason we went to everyone was that we felt that everyone should know about it even those who were not known prescribers of Accutane. We felt they needed to know in the event they saw a patient or heard of a patient who was taking Accutane, someone in their family, some other patient, we wanted them to know about the change in the pregnancy information. Many of them might not have known about the pregnancy warning before, because we had not gone to them, but at this time we felt that everyone needed to know about it and, therefore, we went to the entire mailing list.

(Slide.)

DR. DEL VECCHIO: In addition to the warning letter, we notified our sales force immediately at that time. We asked them to visit all the known Accutane prescribers within the next two-week period to be sure they had received the letter. They knew about the pregnancy warning, this was indication that they knew about the new data.

We asked them to make presentations to pharmacists in regard to this new data when they entered the pharmacies. And we asked them to incorporate that warning in the new information in all of their future sales presentations.

We notified our clinical investigators who were

studying both the dermatologic use and the oncologic use of Accutane. We notified them both by personal telephone call and personal letter in addition to the letter that went to all physicians.

(Slide.)

DR. DEL VECCHIO: And, finally, we sent out warning sticker to pharmacists and wholesalers. This sticker was to be placed on every stock bottle of Accutane and it says, "Contraindicated in pregnancy. Label all prescriptions accordingly and inform patient."

(Slide.)

DR. DEL VECCHIO: In addition, we sent out these stickers which say, "Accutane avoid pregnancy during therapy." Those stickers are to be used by the pharmacist to put on the prescription bottle itself. In addition, those prescription -- those stickers were given to physicians, who when they wrote an Accutane prescription could put the sticker on the prescription to remind the pharmacist to put the sticker on the bottle.

As of this time, all of the new Accutane bottles already have that information on it. It doesn't require a sticker. The others are still available to the pharmacist. Again, we felt one more chance to get to the patient to remind her of the problems about pregnancy.

Before, I get to the present time period, I would

like to tell you where we stand in regard to what we know about the use of Accutance at this time. Approximately -- and this ia very approximate figure. Approximately 300,000 patients have been treated. About 5,000 dermatologists are prescribing Accutane and they are treating 85 percent of those patients at this time. About 12,000 nondermatologists are prescribing Accutane. About 15 percent of the Accutane prescriptions come from nondermatologists. If you divide that out, it means that the average dermatologist has treated 40 to 50 patients. The average nondermatologist probably three to four.

The important point in the slide is that at this point in time that there are approximately 17,000 physicians who are prescribing Accutane and probably account for 99 percent of the prescriptions. This is not a widely prescribed drug in terms of the number of physicians who are using it.

(Slide.)

DR. DEL VECCHIO: And let's come up to the last cuple of months and the present. You remember we left unresolved the adverse effects problem that came up in the spring because of the need to get the human teratogenicity data out. During this time period, of course, we were working on that, but additionally the new bone data that Dr. Cunningham alluded to also became apparent. The fact that the earlier section of bone changes in the EOK patients. And so on July 27th, we met with the FDA in regard to changes in

labeling for all of these things, the teratogenicity, and all the new side effects.

On August 9th, we received the FDA approval for current revised package insert, including the new paragraph on pseudotumor cerebri, as well as the other new ADRs.

A new labeling letter was sent in August, which I'll show you in just a moment. We have been in the process of revising the patient brochure. I'll show you that also in a moment. On the 20th, we met with the FDA to go over this new patient brochure, and it brings us up to the present time.

(Slide.)

DR. DEL VECCHIO: And what did or needs to be communicated at this time, the new side effects, the revision of labeling, the new patient information, revised patient information based on this new information. We need to distributed these brochures. We are looking at further information for patients. How far shall we go with information for patients.

(Slide.)

DR. DEL VECCHIO: What actions have we taken? First of all, we sent out in August, August 25th and 26th, a new letter to the same list of 600,000 regarding the new changes in the package insert.

(Slide.)

DR. DEL VECCHIO: This is a copy of that letter.

You will see that it clearly points out that there are three things included in the letter, Accutane and pregnancy in humans; Accutane and skeletal abnormalities and new clinical adverse reaction information. The pregnancy problems are again repeated and, again, in bold print both in contraindication and the warning section. In bold print again, another paragraph on the bony changes.

(Slide.)

DR. DEL VECCHIO: And the letter, of course, included the new package insert which is not shown here.

(Slide.)

DR. DEL VECCHIO: In addition to that, we are now in the process of completing our revised patient brochure. You, I believe, have this in your possession. I believe it was sent to you, and these are the proposed changes.

This is from the first page, that warning that you saw on the inside page. We have now expanded the warning to include human birth defects. We have strengthened it even further talking about discussing contraception with your doctor. Use during and for up to one month after Accutane therapy. That will be in bolder print than it was before and it will continue to be in this place in the patient brochure.

(Slide.)

DR. DEL VECCHIO: Again, before treatment an

additional paragraph has been added that now says, "Accutane should not be taken until you are sure you are not pregnant and you are using an effective form of contraception."

(Slide.)

DR. DEL VECCHIO: And, finally, the most important inside page, I believe, has to do with during treatment. We have added a section that has to do with the side effects that relate to the new ADRs that we have been discussing. That is this section here. I'll just briefly go over it with you. "You should be aware that Accutane may cause some less common, but more serious side effects. Be alert for any of the following early symptoms of these conditions."

We deal with the symptoms that have to do with pseudotumor cerbri, headache, blurred vision, nausea, vomiting, and so forth.

We deal with gastrointestinal symptoms, severe stomach pain, diarrhea, rectal bleeding and musculoskeletal, severe muscle aches and pains, stiffness of the joints. "These symptoms may be early signs of conditions which, if left untreated, could possibly result in permanent effects. If you experience any of these symptoms, or any other unusual or severe problem, discontinue taking Accutane. Check with your doctor as soon as possible."

This is our proposed revision of the patient review. As I said, you have that in your possession. We would certainly

like to have your comments in regard to that.

I would like to point out a couple of things about this. We continue to use wording which we feel the patient can understand. We don't feel it is appropriate to name diseases to give patients a scare word, or use medical jargon. Our objective is to get the patient to talk to the doctor about this particular drug. Our objective is to get the patient to know what symptoms should lead him or her to go see the physician and to ask him or her what they should do about it. We would like to encourage the patient/physician dialogue.

We don't want to have the patient making a decision themselves in reading a piece of paper. We want them talking with their physician and we feel this is the way to approach it.

(Slide.)

DR. DEL VECCHIO: The distribution that we suggest on this brochure, and we plan to go ahead with, would be all dermatologists. They will receive 10 copies of this brochure. In addition, they will receive a business reply card to order additional copies. We will go to all 12,000 identified nondermatologist users of Accutane. They will get the same.

All 60,000 retail pharmacies will receive three copies, plus a business reply card for each and the 700 Roche sales people will receive another very large quantity and they will be sure that this brochure is distributed to everyone

who may need it. Additional copies obviously will be available either through the sales people or directly from Roche.

(Slide.)

DR. DEL VECCHIO: I have shown you the labeling letter and the patient brochure. The sales force obviously has been informed to be sure that their presentation contains all this information. We are in the processing of revising our printed materials, our promotional materials to be sure everything is included.

We are also in the process of developing a booklet for females on contraception, a separate booklet to address the subject of contraception particularly aimed at the younger female patient, teenage patient who may not be appear of some of the problems of contraception and may have certain myths or fantasies in their mind about contraception, and we feel that that might be a useful adjunct to the patient brochure for that particular type of patient. That is in the process of being developed.

(Slide.)

DR. DEL VECCHIO: We feel that we have done, and we are doing everything that is necessary to get adequate information out to both physician and to the patient, to the medical profession, to everyone that needs to have it. We feel that what we are proposing is more than sufficient to make sure that gets out there adequately. However, there may be some

additional options which you may wish to consider. We would like to have your opinions in regard to those options.

First of all, in regard to the pregnancy warning itself. There has been a proposal to perhaps add a pregnancy test to the professional labeling and perhaps to the patient brochure. That is certainly something possible to think about it and it doesn't sound like there is very much wrong with that, and I don't think we would have any serious objection to that; however, I would just like to remind you that there is the possibility that a pregnancy test alone might lead to a false sense of security in either the patient and/or the physician. Our position has been to be sure that the patient is not pregnant. Only part of that is the pregnancy test. We feel that an adequate history and an adequate examination are also very important so that a pregnancy test alone is not sufficient. However, it certainly is a possibility.

Another possibility with regard to pregnancy is to make it a box warning. Put a box around the pregnancy warning and contraindication within the package insert to draw more prominence to it. We certainly would appreciate having your opinion in regard to that.

Another area we could go into is additional information on side effects, and our feeling is that that additional information is best given directly to the physician in separate pieces of material rather than in the official labeling itself.

I am concerned that putting a lot of information about pseudotumor cerebri in the package insert is not likely to have it read. We would propose a possibility of the option of developing additional information for the dermatologists, for the prescribing physician on pseudotumor cerebri. What is it all about. What to anticipate. How to handle patients who come in.

If you think about it for a while, you remember the headache incidence with Accutane. It ranges anywhere from 10 to about 20 percent of headaches with Accutane. 300,000 patients have been treated. If 60,000 of those patients showed up in your offices with headache, obviously there is a little bit of a problem screening the very small number who might have pseudotumor cerebri.

The physician needs to understand the complex of symptoms. The things that are important to look for, the important screeing areas that he might want to look for in order to screen these patients, and that is an additional area that might be used as an option.

And, finally, the possibility of putting in a warning in regard to tetracycline. Ad Dr. Cunningham said, we do not know the role of tetracycline in either the additive effect or the synergistic type of effect in causing pseudotumor cerebri. We also don't have very good efficacy data for concomitant use anyway. Certainly, many dermatologists

wish to use it for a period of time while they are treating with Accutane. The possibility of a warning to the effect that the combination of the two drugs may lead to an increased incidence of pseudotumor cerebri is certainly another option.

(Slide.)

DR. DEL VECCHIO: In summary, I have presented to you what we have done for both the health professionals and the patients over the past year. We feel that we've supplied current, reliable and timely information. We have supplied it in a way that was understandable and usable. The efficacy and importance of this drug are not in question. This is a drug that everyone accepts as being efficacious, as being very important. What has happened is that significant ADRs, teratogenicity have now been identified.

We have in the past, and we will continue, to inform both the medical profession, pharmacy profession, everyone that needs to know, including the patient, of all the information they need to have in a very responsible, informative and useful way. We will continue, obviously, to do that.

Our objective, as I mentioned before, is to maintain the patient/physician dialogues so that they can together use this drug appropriately. We feel that the responsibility for the use of this drug is a shared responsibility. It's shared by the corporation itself. We have a responsibility to provide information which is timely and accurate. By the

physician, who has a responsibility to get that information to the patient and by the patient who has the responsibility to look at that information; to use it appropriately; to respond appropriately.

In closing, I would like to say that when Accutane is used for the appropriate indication, with both the patient and the physician having adequate information on the benefits and the risks, and both of them engaging in an open dialogue on treatment that Accutane is a highly effective and safe drug.

Thank you. I would be pleased to entertain any questions on my presentation, or on anything that deals with the rest of our presentation.

DR. EAGLSTEIN: Thank you, Dr. Yard, Dr. Cunningham, Dr. Del Vecchio and Dr. Strauss.

Does the Committee want to ask questions now or go ahead to the next --

Ron, do you want to ask a question?

DR. GOLDNER: I would like to ask some questions. I have some burning questions.

DR. EAGLSTEIN: Burning questions.

DR. GOLDNER: Burning questions.

DR. EAGLSTEIN: For whom?

DR. GOLDNER: I guess Dr. Del Vecchio and/or Dr. Cunningham. Dr. Del Vecchio is going through, you know, an elaborate means to show us the communication that you have

done, and I'm sure we all know that and have received the communications.

I am a little concerned though about maybe the accuracy. I'm concerned because of a personal experience. Ten reports of pseudotumor rather than visual loss, I think, Dr. Cunningham, ten reports of -- you had ten pseudotumor rather than ten visual loss on your slide?

DR. CUNNINGHAM: Ten pseudotumor or papillidema.

DR. GOLDNER: Or papillidema.

DR. CUNNINGHAM: Some of them had visual loss as part of their pseudotumor cerebri complex.

DR. GOLDNER: Well, I am concerned about a personal report. I don't know -- I have some reason to suspect that a case that I reported is not really included in with that data because it was a little unique and I think you would have brought it out in some of the communications that you made about the uniqueness of the case that I reported to Roche. And I am concerned that when I called the company and reported an unusual possible reaction to the drug that I received very little follow-up and attempt to find out more about my patient.

I certainly gave adequate data and gave the patient's internist and whom else was treating her. I am concerned that if the company communicated only with the internist and did not get back in touch with me that there might be false data or false reporting. And I am wondering how vigorous the company

does go into reports of adverse reactions and how vigorous the company follows up on those reports to find out about the patient.

I called the company at my expense. Was given Dr. Rofsky's name. I tried to get in touch with him. When he was not available, someone else did speak to me from the company. Took my information and that was the last that I heard of it. This was a patient who had visual loss while the drug had been stopped. At the time of visual loss, she was not taking Accutane at the time we reported the visual loss. I certainly think that it was a close enough association for someone to have gotten back in touch with me and to further evaluated that report. And I wonder how vigorous you are in following up those reports and why a member of this Committee who reported an adverse reaction received no follow-up?

Are those ten just documented, or are they just reports, and how vigorous do you determine to find out about the reactions to this drug?

DR. DEL VECCHIO: Dr. Goldner, those ten cases are very meticulously documented and investigated as are all of those, particularly the more serious ones. I cannot respond specifically to your particular case. I am not aware of that. You did mention one possibility. Reports frequently come in from several sources on the same case. It may very well be that communication went on with the person who did the report-

ing, who was following the patient for the pseudotumor or the visual loss, and for some reason that information did not get back to you.

It doesn't matter whether it is a Committee member or a dermatologist, or a nondermatologist, they are followed meticulously.

Dr. John Pepper, who is chief of our Medical Services Department is with us today. I don't know whether he can comment specifically on your case, but I can only tell you that we have an obligation. In fact, under law, we have an obligation to be very meticulous in that investigation and to present them to the FDA.

DR. GOLDNER: That is exactly my point. It you have a meticulous -- if you are meticulous in that, it would seem that you would follow all leads on this.

DR. DEL VECCHIO: We do. And I have to presume it was done, but I have to presume from what you are telling me that you did not receive that information back. That being the case, I have to apologize to you for that, but I can assure you that any case that was reported was fully investigated and included in our reports to the FDA. I don't know whether Dr. Pepper has that case available. Perhaps we can look it up and get back to you in a little while.

I, personally, cannot respond directly to that.

DR. GOLDNER: I am concerned, of course, not with the

fact that it is my personal case, but I am concerned with the fact that I had a case that I don't think is in that data and I wonder how many more are that way?

DR. DEL VECCHIO: It has to be in that data. If your case was reported, it has to be in there somewhere. We report all cases to the FDA even if we feel there is no -- even if you said that you felt there was no significant association, we would still be under an obligation to develop the information and to report it. And I can only say to you, again, if you did not get that information back, that was inappropriate. You should have gotten.

DR. GOLDNER: I agree.

DR. DEL VECCHIO: But I would stake my standing here on the fact that that case has been investigated and is somewhere in those files and included in the data that we presented.

DR. EAGLSTEIN: Did you report a pseudotumor or a visual loss?

DR. GOLDNER: I reported a visual loss.

DR. DEL VECCHIO: Well, it may be in the group that has the report as visual losses, but,again, I would have to bow to Dr. Pepper on that. I do not have those in my head. I cannot respond to that.

John, are you aware of that particular case?

DR. PEPPER: I'm trying to look it up.

MR. BOSTWICK: Let me ask that if you do make a

response and if you haven't had your name read into the record yet, please come up here and tell us who you are so we can get everyone's name right.

DR. DEL VECCHIO: Could we please give Dr. Pepper a few moments to look that up and perhaps respond to you later?

DR. EAGLSTEIN: Absolutely.

What other questions, Dr. Goldner?

DR. GOLDNER: Well, maybe you can go around. I have some other comments that I can make, but you can go to anyone else. I'm wondering about -- nothing was mentioned about the possible recommendations of pretreatment evaluation of the retinal disk. I mean, should we not consider some things about looking at the retina. I mean, now that we know that there is such a problem, should there not be a recommendation of pretreatment evaluation. If a dermatologist doesn't feel comfortable in using an ophthalmascope, maybe that patient should be properly evaluated. That hasn't been brought up. I think it can be discussed.

DR. DEL VECCHIO: I recognize that that is one of the recommendations that the FDA has made in that material that you have received. I would prefer to defer that question to Dr. James Corbett, if it is the pleasure of the Committee, because I think that he could give us a little bit more definitive information on what an appropriate screening

mechanism may or may not be. If that's all right with the Chairman, I would like to ask Dr. Corbett to respond to that.

DR. EAGLSTEIN: Did you mean, Dr. Goldner, the prescribing dermatologist check to see if the disk is normal?

DR. GOLDNER: Right.

DR. EAGLSTEIN: Before treatment?

DR. GOLDNER: Right. That's exactly what I meant.

DR. EAGLSTEIN: Is that what you want to address by --

DR. DEL VECCHIO: Well, I believe that's the question a routine screening before, a baseline and then following the patient routinely --

DR. GOLDNER: Oh, yes.

DR. DEL VECCHIO: -- without symptoms?

DR. GOLDNER: Yes.

DR. DEL VECCHIO: I would prefer that Dr. Corbett address that question.

DR. CORBETT: I think that a pre-treatment situation examination of the optic disk is a pretty straightforward sort of thing and if there is any question in your minds as to whether or not the disk is swollen -- if there is any question about what the appearance is, I think it is reasonable to refer the patient to somebody who has more expertise than you and that may be an internist, that may be an ophthalmologist, whoever you like, but I think to recommend that everybody has a pretreatment examination, and then what are you going to

require, are you going to require that the patient have a pre-treatment examination and photographs taken, or drawings be made? I think that it would add considerably to the expense and may not be a very high yield situation.

DR. RASMUSSEN: Does visible papilledema appear or precede symptoms, or is there any association whatsoever?

DR. CORBETT: Yes. There is an association. I would say that at least an idiopathic pseudotumor, which is what the vast majority of cases of pseudotumors that are available to look at, that depending on the study, somewhere between 75 percent and 100 percent of the patients have symptoms as well as signs; that is, they have symptoms of headache and transient visual blurring, as well as papilledema.

In some studies where the patients have come in through an ophthamologist's office, patients will be discovered to have papilledema without headache or without any other symptoms, but I would think that if you review the drug-related cases, vitamin A-related cases, all of those patients were symptomatic, save one that I am aware of. They had headache as a warning that something was going on.

DR. RASMUSSEN: Well, given the time frame in which we see patients, which is not once a week with this type of drug, do you think there is a value to looking at someone's optic disks? It would seem to me that if there is a close association between symptoms and papilledema, that you would get much more

out of relying on symptoms than looking at somebody's eye brows, because it is a means of picking up the developing pseudotumor cerebri.

DR. CORBETT: I don't think you do one exclusively.

DR. EAGLSTEIN: Dr. Pomerantz?

DR. POMERANZ: Yes. I would like to see a more detailed analysis of what went wrong with the patients that have gotten pregnant. Is it the failure of patient communication? I would like to know what percentage of those patients were being seen by dermatologists, what percentage were being treated by other physicians, and also is it conceivable that this drug interferes -- were any on contraception at the time that they got pregnant and is it conceiveable that this drug interferes with contraception in a similar manner to tetracycline?

DR. EAGLSTEIN: Can you address that? I think there are two questions. How many of these people who got pregnant were treated by dermatologists compared to other physicians? And were any of them on presumed adequate contraception?

DR. DEL VECCHIO: I cannot answer the first question specifically. There were patients being treated by both dermatologists and nondermatologists. In some cases, we don't know. It is not always possible to get that information. The reports on these came to us from such places as OG/GYN physicians, pediatricians, geneticists. We were not always able to get information directly from the physician who treated

the patient. In fact, it was very difficult at times to do that. However, it was both categories. I can't give you the breakdown. I don't know that. In fact, there are enough missing among the seven cases that I can't tell you that. There are many others, of course, who underwent either an elective or spontaneous abortion after becoming pregnant while on Accutane. And those patients, we have very little information on most of those particular patients.

Most of them, as far as we know, were on contraception, but there are some exceptions. There are some things you can't get around. One of the first patients reported was a 16 year old young lady who denied being pregnant at the time she was put on Accutane therapy. She claimed she did not know she was pregnant until she was 6-1/2 months along by which time she had already completed her Accutane therapy and was one of the first reports of having a major birth defect. There are those kinds of things that happen.

Obviously, that particular case would have been an ideal case to have a pretreatment pregnancy test. It probably would have picked it up. Most all of them have been on one form of contraception or another. We have to rememeber that every form of contraception has a failure rate and there are going to be pregnancies in patients who are taking Accutane on the usual contraceptive methods if they are of child bearing potential.

Now, again, if you would like the specifics on all of the cases, we do have that available, but that would take a little time to compile. Dr. Pepper also has that available.

DR. EAGLSTEIN: Are you saying that you could not find out what doctor prescribed Accutane?

DR. DEL VECCHIO: Not always.

DR. CHANCO-TURNER: Eight cases, seven cases?

DR. DEL VECCHIO: John, am I incorrect on that. Do we have information on all of the prescribers on the seven cases of birth defects?

DR. PEPPER: We have some data.

We have fairly adequate data on drug usage in the majority of the pregnancies. There is a little variation in the picture we get from the obstetrician who is treating the case in the terms of a pregnancy and the dermatologist report on the use of the drug.

DR. EAGLSTEIN: The question is: did a dermatologist prescribe the Accutane or did a nondermatologist? And if a nondermatologist, what --

DR. PEPPER: As far as my recollection goes, all of the patients were dermatological medications.

DR. EAGLSTEIN: That was the question, wasn't it? All of the cases were given the Accutane by dermatologist?

DR. PEPPER: To my recollection.

DR. DEL VECCHIO: That is not true of all the patients

who become pregnant. Those are all of the seven who have had birth defects. There are others among the other group who were treated by nondermatologists.

DR. EAGLSTEIN: Okay.

Is this related to this same issue?

DR. KOEHN: I wonder if there were any more results on the 13 other pregnancies that are coming to term between September of '83 and January of '84, according to the August 17th ADR highlights? Have any more of the 13 people delivered?

DR. DEL VECCHIO: I don't know. If you are asking if we have had normal deliveries other than the ones that we've reported, we haven't had any additional deliveries that I know of that have been -- there was one patient who did have a normal delivery. I'm not sure if it is in that group that you are referring to. That particular patient apparently did not take Accutane during the critical period of organogenesis. She probably started shortly thereafter the first trimester.

The others are yet to come. We have seven that we know of are all that we have and there are additional ones that were are waiting for.

DR. POMERANZ: I have one other question which you may consider as a when did you stop beating your wife kind of question. But at least there is anecdotal evidence in northeast Ohio that there is considerable detailing by the Hoffman-LaRoche people of this drug to nondermatologists. That's what

I've heard, and I wonder if you have any programs in place to restrain the enthusiasm of your marketing people?

DR. DEL VECCHIO: The sales representatives were given very specific directions to promote the drug, as far as the total promotional approach, only to dermatologists. However, where a nondermatologist wants the information, we have an obligation to give it to him and we are doing that. Where a nondermatologist is already prescribing the drug, we are obviously giving him all the information that he needs to have. I don't think we have an alternative. If a nondermatologist wishes to prescribe the drug, we want him to have all the information available. I personally do not believe that that is happening in large degree, Dr. Pomeranz, but I cannot account for any individual area or any individual person.

There is not a great deal to be gained from indiscriminate promotion to a large number of physicians who might not write very many prescriptions for Accutane. It's not really a very economical use of a sales representative's time, and I frankly doubt if that would be done on a very large scale except to those who are writing fro the drug at the present time. Certainly, that is our policy and the sales representatives are given very specific direction as to what their objectives should be and whom they should be visiting and whom they should not be visiting.

DR. EAGLSTEIN: I think we will go ahead. Thank you,

and we will ask Dr. Sidney Wolfe of the Public Citizen Health Research Group to address us and then we can get back to questioning both these presenters and Dr. Wolfe.

DR. WOLFE: Thank you. I am just going to take a few minutes here to talk, first of all, about the adverse reactions to the drug, particularly ones that have come to light since the drug was marketed. And, secondly, something that wasn't discussed by the company for some curious reason, namely an alternative dosing that involves starting at one dose and reducing it such as advocated by Dr. Peck, one of the original investigators, who is now at NIH. And, third, what we believe the best remedies are for the problem of best and most completely informing both doctors and patients about the proper indications for and proper use for the drug.

I will start out by first by saying at least in the modified way the same thing Dr. Del Vecchio said that the drug is an important and useful drug and the better we all can do at arriving at the safest use in those people for whom it is indicated, the better will all be. It is not a drug that should be taken off the market at all. On the other hand, a number of people think it came on the market a little too quickly, this country being the first in the world as opposed to the second or third, or worse, if that's the way you look at it in the case of other drugs. So, the goal of all of us is really to make sure that if the drug is used everyone from

on both sides, documentation -- are adequately informed and pick out those side effects that may occur as soon as possible.

As far as the adverse reactions are concerned, it was just stated that pseudotumor is not a medical emergency. I think that's not true on one hand, and on the other hand, there are several reasons why our consultants, Dr. Morris Victor (phonetic), who is chairman of the Department of Neurology at Case Western and Metropolitan General and Dr. Melvin Greer, who has, as Dr. Corbett has, written and studied pseudotumor extensively wide, they believe it is an emergency. First of all, any patient who presents with symptoms, signs of increased intercranail pressure has the possibility of not only having pseudotumor, but also having the result of trauma or having a brain tumor, and so that the immediate evaluation of someone with headache, papilledema, and so forth clearly is an emergency situation.

Secondly, the discontinuing of the drug in this case, a possible cause of the pseudotumor is something that has to happen right away and, therefore, the advice to immediately discontinue the drug upon findings that may relate to pseudotumor is obviously a good idea, but it is again part what I and, I think, others would describe as a medical emergency.

And, third, even though there have been no control studies because they would be unethical on taking a bunch of patients with pseudotumor and not doing anything in a well

designed, randomized control study as opposed to doing an initial or repeat spinal taps. It is certainly suggestive at the least that in the cases where the increased intercranial pressure is particularly high that it is a good idea once, obviously, you've ruled out other causes of intercranial pressure to do repeat taps.

Dr. Victor has looked at a series of patients with this, and so forth. So, I think that just for the standpoint of placing the proper perspective on the finding of pseudo-tumor and treating it, diagnosing it and treating it as rapidly and effectively as possible that I think it is reasonable and, I think, necessary to describe it as a medical emergency.

The other point I'd like to just mention for a minute has to do with these figures you saw concerning the expected incidence of various side effects as judged from whatever best judgments one can make as opposed to the actual number of cases that have been reported.

Now, to be sure, once a drug has been on the market for a long time, the likelihood of reporting various side effects is diminished, although some would argue that as papers appear in the literature, there are more waves of reporting, but whereas I would agree with the statement that long after marketing there are fewer and a smaller and smaller fraction of actual reports coming in to the FDA or company, I

certainly disagree with the notion that the reporting is near or close to complete at the present time. It would not fit in with anything that is known, to my knowledge, about any drug. The estimates of 1 in 10 are the high end of the range that people say are being reported. Others have estimated that it is as few as one in 100 adverse events that occur in conjunction with the use of the drug are reported to the FDA.

One of the big problems is the accessibility to practicing physicians of the reporting forms. Just last week we requested and got from the FDA for the last two years, the month by month analyses of how many total adverse reactions are being reported to the FDA either from the companies or from doctors directly, the ones coming from doctors directly are about fifth or so of the ones, total ones coming in. And what is interesting is that there appears to be a significant wave of reports following each of the instances in which a FDA drug bulletin which contains a report on the back page comes out. This only happens three times a year and the fact that there is this wave after to me indicates, amongst other things, that at all times physicians who are practicing medicine in this country do not easily have accessible a report to send in even if they see something that they believe may be drug-related. So, I think that it is not possible to make any kind of statement that side effect X, whether it be ileitis or

colitis, or whatever is occurring at about or less than the expected instance based on the spontaneous reports that come in to this country.

In Britain, a health system with many flaws, from my viewpoint, there appears to be probably between one-half or two times more reporting based on the amount of a given drug that is used here overall. So, I think that we are getting a small fraction, perhaps it is higher -- and I wouldn't dispute that -- the possibility that it is higher than 1 in 10, but that it is close to complete is not something that is very likely, I would say. And it certainly is unprecedented as far as anyone I've ever talked to about adverse reactions.

Just for a few minutes on the question of dosing. I was glad to see the very nicely done study by Dr. Strauss and his colleagues in the other medical centers which, as he said, enlarged upon, but came up with pretty much the same kinds of findings on the much smaller study where there were only four or five patients in each of the three dose groups.

The thing that I don't know and perhaps if I see more of the data that was presented, could answer the question as to how many of the people who went back on the drug went back on what dose and for how long, because one of trade offs, particularly since a significant number of people at the even lowest dose did not need further treatment is the decision as to whether the total amount of drug that is going to be

given out to everybody in such a study is going to be more or less or the same if you go back to a second dose, assuming that you've started out at a lower dose with everyone. So, I'm sure there are some data on that. I'd like to see them to answer that question.

But what was not mentioned at all is something that has been, to the say the least, a tug of war between NIH, Dr. Peck, and Hoffman-La Roche over the issue of their having patened a dosage schedule. I don't know what it is in the briefing package that was sent to the members of the Committee, because unfortunately I didn't get one. I would have at least liked to have had a chance to look at the proposed labeling for the doctors and patients so that we could comment on it. I caught at least some of it on the slide, but I don't know whether, for instance, the issue of this starting out at one dose and then systematically reducing it as posed by and studied by Dr. Peck was in the brochure of information you got. Certainly, I'm sure you have seen Dr. Peck's studies, the ones that have been published and the issue really has to do with another way of reducing the total amount of isotretinoin that people get, which to the extent that something, whose side effects are similar, not always identical with vitamin A toxicity, has to be described as a dose-related kind of group of side effects.

Anything that can be done to treat people effectively

and at the same time reduce in one way or another the total amount of drug that is given is likely, even though the laboratory values are less than 100 percent convincing, they certainly -- the trends with all the laboratory values are towards larger abnormalities even though the average within the normal range at the higher doses.

Certainly, the occurrence of things such as pseudotumor or the gastrointestinal problems are likely to be less with a lower dose. I don't think that there should be much dispute on that despite whatever one has seen with the lab values.

And given that, the second approach to making sure that people are getting the lowest dose beyond the starting out at 0.1, 0.5, or 1.0 is Dr. Peck's approach. As I said, it wasn't mentioned at all this moring. What has happened is that the company has now paid NIH $50,000 and has signed an agreement whereby if the reduced dosage is adopted as the labeling way for the drug, they will get a very small percentage of the increment, the increase in the amount of the drug that is sold.

DR. EAGLSTEIN: Could you explain that more fully?

DR. WOLFE: Well, I mean, I can explain only to the extent that I understand it because we have gotten some documents concerning this whole tug of war and a lot of legal briefs, and so forth. I understand some of them, and it really has to do with the NIH, Dr. Peck, having obtained a patent

on the dosing regime that would have you start, for instance, at 1.0 for two to four weeks, then drop to 0.5 mg/kg. Because they have a patent, if this is adopted, as I understand it, as the preferred treatment for people getting Accutane for cystic acne, and it is thereby incorporated in the labeling, according to the agreement signed a few months ago between NIH and the company, the company would have to give a percentage, I think it was 3 percent of the increase in sales above the time when the agreement hadn't been reached to the NIH for the right to use this patented dose reduction schedule.

But without going into any more of the details, the point that I am raising is here is yet another possible way which is said to be effective in one of the company brochures describing Dr. Peck's experiment. It does say that this was an effective treatment for acne, cystic acne. As I said, I am disappointed not to have heard a discussion of it and since one of the conditions for the approval of the drug, the so-called Phase IV studies, post-marketing studies was the consideration -- and this is a recommendation of your Committee at approval -- was the requirement to do some post-marketing surveillance on the question of different dosing. We heard that one study, a very nicely done study as far as I can see, on the -- starting out with 1.51 has been. I wonder whether or not a study,any more are necessary using the Dr. Peck approach has been done. If it hasn't, I don't understand why,

because it certainly is a dosing method that appears to work (a), and (b) would reduce the total amount of the drug that people would get and would, therefore, as far as I'm concerned, reduced the likelihood of side effects by getting the markedly lower dosage of the drug.

The last point, as I said, I want to mention is what are the best remedies to the question of maximizing the information flow to both doctors and patients.

There has been a lot of debate and dispute over the last six or seven years on the topic of mandatory patient package insert. The Food and Drug Administration reviewed all of the studies published and unpublished on the topic. Had hearings, meetings with the drug industry, everybody, and concluded that it was important to begin an experimental mandatory patient package insert program which was to have begun after the final regulation was finalized in early 1981 for just ten classes of drugs, such as the benzodiazepams, Valium, Librium, and others and Darvon, and eight other classes of drugs.

This program was cancelled due to pressure on this Administration from the pharmacists, doctors, and so forth. And, therefore, it is not in place. But the information upon which it was based is still valid. If anything, more examples of why such programs are necessary and have come to light since the cancelling of the program. And the two kinds of

considerations are, one, are for certain drug patients usually, if not always, getting full accurate information on both proper indications and side effects from physicians and, two, if not, do voluntary approaches work. One the first question, there are a number of studies on a number of different drugs that suggest that -- they don't suggest, that show that patients are not adequately informed even much, let alone most of the time about proper use and side effects to look for with certain prescribed drugs.

And, secondly, on the question of is the voluntary approach for providing such information adequate, most of the studies that have been done prior to the time that the regulation was finalized showed that some are between 5 and 10 percent of the patients got patient information, brochures on a voluntary basis, that's including the inclusion of them in the pharmacy and, in some cases, in the doctor's office. It was because of the answers to those two questions that a mandatory program was started.

Now, it may be that a volunatary program such as has occurred thus far and is clearly desired by Hoffman-La Roche for this drug will do better than 10 percent. Maybe it will do 40 or 50 or 60 percent, but given the importance of the information, both on the proper prescribing and on the variety of side effects that can occur, which,amongst other things, may affect the decision of the patient who doesn't

have cystic acne, for instance, to subject themselves to the drug, I think that we need to do something more than a voluntary kind of approach, namely, mandatory patient package inserts, which is what we have proposed in our petition that I hope will be adopted here.

In terms of the notification of doctors, I did an informal survey, and it was a small informal survey on the question of how many of the people who received that second letter that you saw, the envelope for which you didn't see, because unlike the first which had a very adequate warning on the envelope concerning birth defects, the second one really did not have what I would call an adequate warning and might not have even been opened by a number of people. But I spoke to people who had opened it and some who hadn't. Those who had opened it -- and this is the letter where,again, there is a reminder of the birth defect, plus there is the information, secondly,on the hyperostosis, and, third, the new kinds of information such as the pseudotumor. I spoke to,I think, five or six dermatologists and I talked to someone yesterday who is in internal medicine residency rotating to dermatology at University Hospital, and he had spoken, at my request, to another six. None of these people, having looked at the letter, had noticed that pseudotumor is a new problem. It is sort of buried in the last part of the letter.

Of the people I spoke to, one of them was a clinical investigator, had been and is still a clinical investigator for

the drug and certainly is as aware or more so because of that of some of the problems associated with the use of the drug. So, what I am saying essentially is that not only from the patient standpoint is the lack of mandatory patient package inserts acceptable in terms of reaching most people in the most effective way. But from the doctor's standpoint, sending things out like that letter in the way in which the pseudotumor was downplayed, it said, "Usually associated with monicycline, tetracycline" which at least in terms of the ten cases is not true. I believe it is five with and five without. It is somewhat misleading and, of course, if one took a look, as we did, took a day or so or actually a few hours or so to get the information, the relative occurrence, as best as one can judge, of pseudotumor cerebri as associated with monicycline and tetracycline as opposed to pseudotumor cerebri as associated with isotretinon, it is much rarer with monicycline and tetracycline despite the fact that there are millions, conservatively, of people getting tetracycline or monicycline for acne and other problems every year over the last decade or so that FDA has been collecting adverse reaction information, fewer than one case per year on the average of pseudotumor in people using tetracycline or monicycline has been reported whereas in less than a year, we have these ten cases in people using Accutane. The fact that half of them had been using monicycline or tetracycline means likely that it is not caused by the

monicycline, tetracycline alone. It may, as was just suggested, be a combination effect, but certainly one of the responsibile parties statistically is likely to be Accutane in most, if not all, of those cases. And I discussed this with Dr. Greer. He agreed that what looks like is being seen here with Accutane is something that is higher in terms of occurrence than has been seen with tetracycline.

So, in summary, there have been some very serious side effects reported. Some predictable. I would say all predictable as far as the pseudotumor or birth defects. And as far as the some of the intestinal problems, they may or may not have been predictable. They certainly are occurring. We don't know whether these people will continue to have regional ileitis for a long period of time and thereby the technical definition of Chron's disease, but certainly from what little we have been able to see, these people are seriously ill with their intestinal problem.

The dosing question, I think, needs to be addressed in terms of the regime that Dr. Peck has studied which would result in a much lower total dose to people. I think serious consideration should be given despite the fact that the company would have to pay the NIH for adopting that kind of dosage recommendation.

And, finally, on the remedies, I think that we really do need to have mandatory patient package inserts to reach

everybody. Another, I think, important spin off of mandatory patient package inserts is that it increases, not interferes with the doctor/patient relationship. One of the curious and steady complaints offered during the years when various parts of the drug industry, doctors and pharmacists and others, were objecting to patient package inserts is that patient package inserts on a mandatory basis interfere with the doctor/patient relationship. That statement is present in an affidavit from the American Society of Internal Medicine and other groups who said that if -- and this is in the context of efforts to try to block mandatory patient package inserts for estrogens, menopausal estrogens. I think that what has happened in talking to a large number of practicing physicians, they agree that when the doctor knows that on a routine required basis every patient is going to get -- every patient, not 10 percent or 50 percent, or 60 percent -- is going to get a brochure, they are much more likely out of their desire to preserve the doctor/patient relationship to add a discussion between himself and the patient to this more formal written kind of information that is going to come out at the pharmacy in the case of the three patient package inserts that are now required. I think that that kind of spin off to encourage most, if not all, doctors to make sure that the patient is not surprised when they learn that Accutane is not approved for acne other than severe cystic acne, or when they learn

that you shouldn't be pregnant with the drug or when you learn that it can cause pseudotumor or whatever else. That should not be a surprise, and I think that is one of the more important side effects of mandatory patient package inserts is greatly increasing the likelihood that doctors and patients will talk to one another.

Thank you. I'd be glad to try and answer any of your questions.

DR. EAGLSTEIN: Before I ask the Committee, I would like to ask for a little clarification of one point. With regard to doses, will lower doses lower the incidence of the serious side effects, the birth defects, pseudotumor?

DR. WOLFE: Well, these do not appear to be "allergic idiosyncratic reactions." And the reason I say that is because they have been previously described in either animal studies or in association with hypervitaminosis A, and I think that one can at least reasonably accurately assume that the more drug there is, the more likely they are to occur and the less drug there is, the less likely they are to occur. I mean, there are obviously aren't any studies on that, nor, hopefully, will there ever be. But I think that given that as presenters from the company that said that at least many, if not all, of these adverse effects that are being seen were previously known to occur with hypervitaminosis A, and I don't believe that they have occurred with lower or "normal" doses

of vitamin A. I think that they can be described as dose-related and, therefore, every effort to lower the dose should be made.

DR. EAGLSTEIN: And it just occurred to me that in the course of discussing lower doses, we would be discussing them to avoid the more minor side effects, such as chapping and eye dryness as compared to the major?

DR. WOLFE: Well, I think the main concern is reducing the major ones. I mean, if you also wind up reducing the amount of epistaxis, which was one of the "more minor effects," it was significantly different between 1.5 and 0.1, that's fine also, but both are likely to occur.

DR. EAGLSTEIN: So, it is your feeling that that we would reduce major?

DR. WOLFE: I believe that that would occur, yes.

DR. EAGLSTEIN: Questions from the Committee?

Ron?

DR. GOLDNER: Is it possible to have a brief presentation of Dr. Wolfe's credentials as to who he is and what his training has been?

DR. WOLFE: I am a physician. My training is in internal medicine. I started this group 12 years ago. Prior to that time, I was on the staff of the NIH in -- arthritis in those offices for five years doing clinical and laboratory research.

DR. HASERICK: Do you have your boards in internal medicine?

DR. WOLFE: No, I don't.

DR. HASERICK: Where do you have your boards?

DR. WOLFE: At Cleveland Metropolitan General Hospital.

DR. EAGLSTEIN: Further questions about this presentation? Especially, I think, you discussed the dosing and you also discussed the fact the pseudotumor cerebri probably is, in some people's opinion, a medical emergency? And that you pointed out the desire -- and you did petition for a mandatory patient package insert. Are there any questions on these areas for Dr. Wolfe?

Yes?

DR. CHANCO-TURNER: Would it be ethical at this time to ask for a presentation from the three neurologists who are here as to the significance of headaches? The evaluation of headaches as a symptom of papilledema? It was presented earlier that quite a few of the patients that we give Accutane to develop headaches at some point or another and it would really be very useful for most of us, and we can tell our colleagues later on, just how excited should we get about a headache or two?

DR. EAGLSTEIN: You would like the neurologists to discuss what, the significance of headaches?

DR. CHANCO-TURNER: The significance of headaches

or what signs, you know, what symptomatolgoy we should really look for before suspecting papilledema prior to visual loss, hopefully? You catch it before that happens because I really also don't think that it is practical to require an ophthalmologic exam of every patient before we put them on Accutane.

DR. EAGLSTEIN: Also, there were corneal opacities, which would be part of it, I guess.

DR. CHANCO-TURNER: That's right.

DR. EAGLSTEIN: There is only Dr. Corbett, is that right?

DR. WOLFE: Well, if I could just comment briefly on it. Certainly -- I mean, the figures that were given there were the average number of patients being treated with Accutane per dermatologist were 40 to 50, something like that? Is that what the figures showed, 40 to 50? And the incidents of headache was somewhere between 10 and 25 percent, I think, in a different series; so, this would mean that on an average a given dermatologist, who I would agree with Dr. Pomeranz, should be the main, if not the exclusive people using the drug, might have a dozen or more, somewhere in that range, of people who took the drug and developed the headaches.

Certainly the idea of discontinuing the drug immediately, as apparently has been proposed, is a good idea. I think also certainly having the person come in and do a

fundoscopic examination to see whether attendant to headaches are any changes of the papilledema. That is not a terribly complicated thing to do. If dermatologists for some reason or other don't feel they would like to do that, certainly, someone else could see these patients, but I don't think that is a difficult thing to do and given at least what is described as the average number of patients being seen by a dermatologist that would not close down their offices. This is, of course, over a long period of time -- I mean, I suppose 50 since the drug has been introduced in the market. It may increase and so forth.

DR. EAGLSTEIN: I think Dr. Turner was concerned, or wanted more information as to the need to examine every patient ophthamologically before they start Accutane. You are answering that if they have a headache, then you should look?

DR. WOLFE: Well, at the very least, and as far as whether every patient should have an ophthamologic exam before they start, I suppose from the standpoint of product liability and/or malpractice, it might be important to see whether someone has either a corneal opacity -- I think in some of the animal experiments, there have been lenticular opacities also. Or whether they have -- this is rarely the case -- some congenital problem that may blur the disk. And there was one patient who was said to previously had papilledema before in retrospect. Is that right?

DR. CORBETT: Pseudopapilledema.

DR. WOLFE: Pseudopapilledema, okay, fine.

I can't answer the question right on the spot. This may make sense, again, given that we're not talking about huge numbers of patients per doctor over any period of time. It isn't that difficult to do a fundoscopic examination of the patient.

DR. EAGLSTEIN: Dr. Tabor?

DR. TABOR: We are fortunate in having in the audience today Dr. David Harper, who is an neuro-ophthamologist, who has just joined the Division of Anti-Infective Drug Products and I wonder if perhaps Dr. Harper could just make a few brief comments on some of the questions that have just been raised?

DR. EAGLSTEIN: And does he want to come to the microphone?

MR. BOSTWICK: We need you up here, Dr. Harper.

DR. HARPER: I agree with Dr. Corbett that the performance of an ophthalmologic examination on every patient prior to the institution of the drug therapy would be difficult and probably lead to confusion and ultimately medical records on that are difficult to interpret without fundus photographs. However, since headache is such a prominent part of the pseudo-tumor cerebri, and at that point the examination of the optic nerve head is usually changed adequately to be readily visible, it does seem to me that it is reasonable to have an

ophthalmoscopic examination on anybody who does develop headaches. Whether or not that leads ultimately to a diagnosis of pseudotumor cerebri or not, it would help to rule it out or in in, and it would be quite useful.

DR. HASERICK: What do you think of Dr. Wolfe's suggestion of doing a spinal tap on patients with papilledema?

DR. WOLFE: My suggestion was doing a spinal tap in people with papilledema who have already been diagnosed as not having other causes of increasing intercranial pressure but on whom a diagnosis of pseudotumor had been made, and, again, that suggestion of a number of people such as Dr. Morris Victor, who has treated a number of people with pseudotumor that way.

DR. HARPER: Well, the diagnosis of pseudotumor cerebri essentially requires a spinal tap. Now, inasmuch as just reliance of the CT scan could be misleading, there are other conditions that can cause increased intercranial pressure that do not show up well on the CT scan, and so part of the criterion for the diagnosis of pseudotumor cerebri in most people's hands is a spinal tap showing essentially normal spinal fluid examination along with these days, a CT scan.

DR. WOLFE: So, in terms of the chemical composition it is cellular, but it is showing increased pressure?

DR. HARPER: Right.

DR. WOLFE: Well, I think that is technically

correct, but at least in terms of the data that is presented, some of the patients that make up the ten with pseudotumore that have been associated with Accutane did not have LPs, or at least they weren't reported. I was speaking now only of the initial one which should be, but isn't always done to make the diagnosis, but also the possibility of repeat ones for therapeutic purposes.

DR. HARPER: The question to me was what do I think of the spinal tap, and I agree with Dr. Wolfe that this really is part of the work up of pseudotumor cerebri. I presume in a somewhat conservative setting, one could discontinue a drug and if the condition resolved rapidly that perhaps it wouldn't be necessary, but normally it is considered part of the overall work up.

DR. HASERICK: There is a lot of risk to that procedure, is there not?

DR. HARPER: One normally does it after other studies which show that the absence of any large mass intercranially, a CT scan is done and then a spinal tap.

Would Dr. Corbett like to address that point?

DR. CORBETT: Yes. There is a great deal of risk in not doing it. And the lumbar puncture is performed after the CT scan is done and prior to the time that we had CT scans available, we had to do arteriograms and if those were negative, then numoencephalograms, and things of that sort. Today, we can do a CT scan. It is very fast. It tells us

that there is no mass lesion in the brain. Once we've done that; then, doing a lumbar punction is mandatory because there are a lot of conditions that can masquerade as pseudotumors, including sarcoidosis, neurosyphillis, septicemic meningitis, we have seen a number of different conditions. The commonest problem that we see is the patient who comes in with headaches from whatever cause and pseudopapilledema, and I think in any neuro-ophthalmologist's practice, this is something that we're asked to see eight, ten, twelve times a year. I would say that one patient in five or six that we see who is sent in on a diagnosis of pseudotumor turns out to have pseudo pseudotumor.

DR. HASERICK: But you do the spinal tap after the CT scan?

DR. CORBETT: Sir?

DR. HASERICK: You do do the spinal tap after the Cat scan?

DR. CORBETT: Yes.

DR. CASTIELLO: What I am asking is if a person has a headache and the consideration of pseudotumor is made, is the lack of papilledema then enough to rule pseudotumor out, or must you do all these other things to be absolutely sure that there isn't something else going on?

DR. CORBETT: Yes, I would like to answer that.

DR. EAGLSTEIN: I think the question is: if a patient has a headache and you don't see papilledema, what

should be done at that point? Is that the question?

DR. CORBETT: As far as I know there is only one person who really serious believes that there are large numbers of people walking around with pseudotumor that don't have papilledema. Aside from that one report of a number of patients, I am not aware of anybody else who holds the same opinion, and I think that headache is such a ubiguitous symptom and papilledema is such an uncommon finding that the combination of the two, as Dr. Wolfe mentioned, makes it mandatory to be sure that the patient does not have a tumore to begin with. And then if you go ahead and find out whether the patient has pseudotumor. As far as pseudotumor being a neurologic emergency, I would reemphasize that it is not a neurologic emergency. It is emergent to find out whether the person has a tumor. Once that is discovered -- once you're dealing with pseudotumor, you can deal with that in a good, rational, easy pace and it isn't something -- it is not a life nor livelihood threatening condition and it rarely is the cause of permanent visiual deficit. I wrote a paper about a year ago that reported 14 cases of blindness or severe visual loss in a group of 57 patients that were followed through 5 to 41 years. The largest number of those patients were seen prior to the time that there were any forms of treatment available aside from subtemporal compression.

The recognition of the disease occurred at the

time that the patient went blind. Today, patients are being recognized, I see between 10 and 15 new patients a year, which is probably in the neighborhood of two-third to three-quarters of the patients in Iowa that have pseudotumor, and in the last seven years -- six years, we have seen eight people who have required surgical procedures to preserve vision, two of those surgical procedures were done because the patients were doing on dialysis and were expected to have hypotension and we didn't want to put them at further fix for visual loss.

Serious visual loss, when you look prospectively at a group of patients in the modern era with a multiple of drugs available for treatment is unusual.

DR. TABOR: Can I just comment. I think we are talking about semantics to some extent. I don't think anyone would disagree with the statement that papilledema of unknown etiology or undiagnosed cause is a neurologic emergency; so, I think that's really just a semantic difference, but I think to follow up your comments, perhaps Dr. Harper could comment on just how extensive the ophthamologic risk, either undiagnosed or delayed treatment of papilledema related to pseudotumor cerebri is?

DR. HARPER: Well, for undiagnosed or untreated pseudotumor cerebri with papilledema, I refer in large measure to Dr. Corbett's paper that he mentioned. For your incidence,

there was -- 25 percent of the patients had serious visual loss so that untreated papilledema is a serious problem. In this circumstance where we have a presumed cause that can be stopped once the condition is recognized; then, it shouldn't be as serious a problem in the overall view from either the causes stopped and the papilledema goes away at a relatively early stage.

DR. EAGLSTEIN: So, is it fair to say that both Dr. Harper and Dr. Corbett felt the examination of the fundus was indicated after headache occurred rather than before starting Accutane?

DR. HARPER: I would think so.

DR. EAGLSTEIN: And that you would recommend discontinuing the Accutane in a patient with a headache and papilledema, or just a headache?

DR. HARPER: Well, certainly with the headache and the papilledema. With just a headache, without papilledema, I can't really address that. I would think no.

DR. WOLFE: The recommendation was that if the patient gets a headache, they should, on one hand, stop the drug and then go in for medical evaluations. So, we are really talking about the interval between then and whenever they get evaluated. I certainly would think there would be safer to just have them, as recommended, discontinue the drug right away. And if it turns out that there isn't any papilledema