used about an hour ago. Essentially I am going to make independent projections of cystic acne prevalence and incidence based on these data for U.S. males and females 12 to 44 years of age. I think Dr. Stern had a slightly different age group, perhaps 15 to 44; I do not think it is going to make a lot of difference. There may be minor discrepancies between my figures and Dr. Sterns' for what we think are comparable definitions but, remember, for NHANES data every sample person represents 10,000 to 20,000 people in the population, so one misplaced cell could be a difference of 20,000.

(Transparency)

Let me say something about NHANES. It was a national probability survey of the noninstitutionalized coterminous United States population conducted by NCHS from 1971 to 1975, roughly 15 to 20 years ago. Its objectives were an assessment of the health and nutritional status of the United States. It consisted of detailed interviews and laboratory and physical examinations and a whole bunch of health-related items.

I think the sample size is important. It was a sample of approximately 20,000 persons who were examined and approximately half the number -- if you look at people, roughly about 10,000 people 12 to 44 years of age, and in this age group about twice as many females as males.

For those of us who try to make careers out of analyzing and making sense out of NCHS data, it is frustrating, because it has a very complex sampling design. Obviously you cannot take a perfectly random sample by just putting everybody in the United States, 250 million people, their names in a hat and plucking them out and then going all over the place and examining them.

The survey is highly clustered. There were approximately 40 stands where there were examinations made and the stands were carefully chosen by cluster sampling, so when you project up, as with all cluster samples, you get a lot more variability, a lot more variance, and larger standard errors than you would if you had just a simple random sample of the United States. This makes analysis particularly difficult.

(Transparency)

In my presentation, for my estimates, the sources I used were the NCHS published reports, which I think was series 22, No. 232. I just used one item there. I used their own estimate, which Dr. Stern presented. Like Dr. Stern, I used the NCHS public-use tapes to go into the data and reanalyze them in accordance with some definitions give me by the FDA dermatologists and also in trying to reconstruct Dr. Stern's methods.

To project these up to 1990 levels, I used the U.S.

Bureau of the Census estimates for four age-sex groups, males and females, 12 to 17, 18 to 24, 25 to 34, and 35 to 44. Then I used various operational definitions of acne provided by the FDA.

(Transparency)

For each definition of acne I got age- and sex-specific prevalence rates for each of the age-sex groups, then used the population data from the Census to project them up to 1990 levels, and this would give me 1990 estimates of total prevalence. Incidence is equal to prevalence, roughly, divided by average duration of the disease.

What I did is I took the low estimate suggested by Dr. Stern to get one set of incidence rates, and these would be higher and these would be the high. You assumed 8.2 years average duration, which would be the low incidence levels. I will present both numbers.

(Transparency)

The usual methods of getting standard errors from complex survey data are either replication methods or what is called linearization, and there is a set of software provided by a number of groups to get these. These are hard to use and sometimes give you misleading results.

What I did is I took what has been found to be a conservative estimate of the factor by which normal -- or I should say the variances of standard errors that one would

obtain by simple random sampling need to be multiplied to give approximately what would represent the standard error in a cluster survey. This is a conservative estimate.

For most variables this factor is much smaller than 1.414, but I used 1.414 here. From these I obtained 95-percent confidence intervals for the estimates based on the standard errors.

(Transparency)

The items in the examination protocol that I used were the same as Dr. Stern's. There were five major items, one indicating presence of acne vulgaris and whether it was inactive or active. The second was severity: minimal, moderate, severe. The third item was presence or absence of acne cysts and whether they are active or quiescent, then presence or absence of either pit scars or cyst scars. So my analysis, like Dr. Stern's, is based on the five items on the detailed examination form for acne.

(Transparency)

This awful-looking slide gives you some idea of what the numbers look like. I used basically six FDA definitions and three of Dr. Stern's. The first two FDA, I think, are the most important. They are based on any severe active acne vulgaris with active cysts. This would be the most severe definition, the most restrictive. One has to have active cysts and one has to have severe active acne vulgaris

indicated.

This is a prevalence projection for males and females and here are the confidence intervals. To give you some idea of what kind of data we are playing around with, these are the number of cases in parentheses. Multiply them by roughly 20,000 and you come up with these.

The second FDA definition also includes -- to be included in it you have to have active cysts but it will also allow for moderate as well as severe acne vulgaris, so it includes both moderate or severe acne vulgaris, but one has to have active cysts. The raw numbers go up from 10 to 74 for females and from 18 to 83 for males. The less severe you get, the bigger the number is going to be.

I am going to concentrate on these two numbers. Notice the differences in sex ratios. Males to females, for definition one, the most severe is 2.78, almost 3:1 males to females. Then it goes down to less than 1.5:1 when you add the moderates.

I want to talk now about Dr. Stern's definitions. If I have it right, here is his first definition. To get into this, all you have to have is severe active acne vulgaris and one does not need cysts here. As he said very clearly in his presentation, he believed that anyone with severe active acne vulgaris is a candidate for treatment with Accutane, and he included that. That was his most restrictive definition, and

notice a male-to-female ration of 2:1. This is number of cases. They are slightly higher than the FDA one, because the FDA required active cysts.

Let me then talk about Dr. Stern's definition two. In this one he allowed for inclusion of moderate active acne vulgaris if there was evidence of cysting and scarring and he comes up with slightly higher figures and a lower male-female ratio. Notice the confidence intervals are all over the place, no matter which definition you choose.

The one thing that is pretty stable is the male-female sex ratio. As you get from severe to moderate, you go from a higher, generally above two, to a lower definition, and that is important. Statistically, you would expect that the sex ratio would be more stable than the actual estimates, because it is a ratio estimate, where the denominator is negatively correlated with the numerator, and the correlation between numerator and denominator would be high, so the result is that one gets more stable sex ratios than one gets actual numbers.

(Transparency)

These are the same numbers converted to incidence. Here I used the 3.3 average duration. The sex ratios are going to be the same, because all we did was take the prevalences and divide them by the average duration and we come up, for the FDA definition, with 33,000 for females,

91,000 for males, and they get higher as you go to the more moderate definitions.

This is the one which Dr. Stadel focused on. This is assuming a duration of 8.2 years. This would be the incidence and if you look at the FDA incidence, it would be 13,000, with these confidence intervals, and, for males, 36,000. Again, the sex ratio is the same as the prevalences.

For Dr. Stern's more severe definition, I came up with 59,000, roughly, in males, 30,000 in females, and a sex ratio of two. Again, they get bigger and the sex ratio goes down both for the FDA's and Dr. Stern's definitions as one gets more moderate.

Here was the NHANES report definition, which we agreed would not be used because there were some remarkable inconsistencies.

This was the PDS prescriptions. For 1989 there were 56,000 new prescriptions for females, 72,000 for males, a sex ratio of 1.27. I think these are 1990 figures, but I did not make the change in the label. So you have a 1.3 sex ratio for PDS, which corresponds more closely with the less severe definitions of acne as you go down the board.

(Transparency)

Here is a synopsis of the cases. Here it is with 3.3. Here it is with 8.2. This might illustrate more clearly the numbers. Again, let us focus on the sex ratios. With the

severe FDA and the severe Stern you get sex ratios of almost two. With the less severe FDA and the less severe Stern you get sex ratios of about one-and-a-half. The PDS is even smaller than that, a sex ratio of about 1.3, which, again, indicates possibly more of a case mix, tending to be higher in the more moderates.

(Transparency)

An argument one can make is that the prevalence from the NHANES is essentially an estimate of the number of cases, whereas the PDS is what is seen in the physicians' or dermatologists' offices. If, as with many other conditions, females are more likely to seek treatment than males, it could easily account for the lower sex ratio seen in the physicians' offices from the PDS data than what was seen in the actual prevalence rates.

What I did is try to look at the utilization data from NHANES to see if that explains it. If you just take, for example, the severe FDA, where there was a 2.78 male-to-female ratio, the male-to-female ratio for people seeking care would have to be .5 for this to be compatible with the 1.27 that was seen in the PDS data. In other words, one would have to have half as many males as females seeking care for acne of this type in order for the sex ratio of 1.27 to be explained.

What was found in the NHANES data themselves -- again, this is for all skin conditions, not necessarily acne

-- the male-to-female sex ratio is .88, which corresponds more with these more moderate definitions. So the utilization data are more consistent with the more moderate acne definitions, even when taking into account what has been found in the utilization data.

(Transparency)

I did it also from the NHANES data for acne itself -- the other data were for all skin conditions on the dermatological exam. Again, I think it was shown in one of the previous slides (I forget which data source, it could have been the National Ambulatory Medical Care Survey) that most of the prescribing of Accutane was by dermatologists, and this is shown here.

This is from the NHANES data, the percentage of people, males and females, seeking care, those who have acne seeking care from a dermatologist and seeking care from another physician. It is higher for dermatologists than for other physicians. These are based on very small numbers, which is why I showed the other slide first. One can see that the male-to-female ratio of utilization -- there were more males than females seeking care from a dermatologist than is even indicated in the other skin conditions. This right-hand side is based on much scantier data and probably is even more unstable.

I guess my bottom line here is that the estimates of

prevalence from NCHS data are all over the place but the sex ratios appear to be fairly stable and one can make some inferences there. In taking the sex ratios with the utilization, one gets a probable picture, at least from what I can see, that the PDS data might be more reflective of a mix more comparable to the moderate definitions, the FDA two and the Stern definition two.

Thank you.

DR. ANELLO: Dr. Robert O'Neill will now give a further discussion of the incidence and prevalence data and also the PDS data.

PRESENTATION BY ROBERT O'NEILL, PH.D.

DR. O'NEILL: I am going to say in maybe some other ways what Dr. Levy has already said, and then I will try to tie this in with the PDS data.

The motivation for what I am going to talk about has come about as a result of trying to make sense of the similarity or dissimilarity between the estimates coming from the NHANES survey and the estimates coming from the PDS survey in terms of new Accutane users, especially for 1990.

(Transparency)

As you have heard, what we are talking about here in trying to determine the similarities or the differences between these estimates and trying to make sense as to whether the concern that I understand the dermatologists had earlier,

that the estimates for the incidence of severe recalcitrant cystic acne were too low and not what they were seeing, trying to see whether that can be understood in terms of what the NHANES survey is telling us.

The NHANES survey is a very reputable U.S.-based national probability sample and it should be taken seriously in terms of its validity and its ability to be able to make accurate estimates of whatever it is trying to estimate, and I will get into that in a moment.

But as you have heard, what we are talking about here are the definitions of cystic acne can change. The original discussion of the past several meetings was based upon the reported definition in the published report. It is also very sensitive. The incidence of cystic acne is sensitive to the definition, as you have heard, the duration of the disease -- in other words, whether you take the average duration to be eight or 10 or five or four -- the sampling error or the confidence interval of those estimates, and, actually, this was not given in previous NHANES data, but it was today, although in the PDS data the confidence intervals were given to explain the sampling variation.

In fact, it wound up to be much more narrow this time around than they were the last time they reported, because there were some errors in the calculation of that.

Then, finally, the population base. The NHANES

survey is a national probability sample of the noninstitutionalized U.S. population. The PDS estimates are likely not exactly comparable. Why? Because they are coming from a reimbursement plan, coming from third-party reimbursement plans, likely a subset, however representative, but, nonetheless, a subset of the U.S. population.

(Transparency)

To refocus what Dr. Stern was talking about, the published NHANES survey for the prevalence of cystic acne was based upon these three codes. What was in the published survey was the prevalence of cystic acne, the prevalence of acne vulgaris, and the prevalence of acne scars. What you have seen, you only saw this, and this is what you have seen just up until today. That was the estimate that was taken out of the NHANES survey and that is essentially the definition that Dr. David Grame was using.

(Transparency)

To give you some sense of the magnitude of the population (and this is not drawn out to proportion), these are the estimates of the prevalence. This is a graphical display of the prevalence rates for ages 15 to 44 reported from the NHANES survey. This is taken straight out of the published literature.

The important thing to look at here is that the prevalence was 65/1000 population of acne vulgaris in women,

60/1000 were diagnosed -- a summary diagnosis up front -- with acne vulgaris; .6/1000 was the prevalence of cystic acne, which was the definition that we were talking about up until today; and then these are the other codes, which really do not come into play.

I want to point out that the prevalence, the relative prevalence, between males and females is something that is important to understand in the similarities and the differences between the NHANES data and the PDS data, because this is where all the action is. This, here, was where the original estimates were coming from for incidence. You get your incidence estimate by dividing this prevalence rate by the average duration of the disease.

You could see for thi,s what might be considered rare, condition was that it was much more prevalent in females than in males, five to one. But as you dip into the acne vulgaris population, you can see it is almost a one-to-one ratio. In fact, where all the redefinitions have come from is essentially this population right here.

What we are talking about is a restatement and dipping into this population and it is important to recognize that.

(Transparency)

I am not going to spend much time on this, because this is a busy transparency, but it just reflects -- these are

FDA's definitions that we used, and these are Dr. Stern's definitions. It shows that essentially FDA's severe definition only counted an individual if he had active cysts. Dr. Stern also included other individuals who did not have active cysts but had some other conditions. I just point that out to show you some of the similarities and the differences between the definitions.

(Transparency)

This is the FDA definition that we will be focusing on, definition one and definition two, which essentially says that an individual, to be in the most severe category, in essentially the category which is most reflective of what the original intent of severe recalcitrant cystic acne might be, is this particular set of codes that would have had to be in that individual's physical exam.

(Transparency)

From that, these are the incidence rates that were derived from the new definitions. In essence, what we are talking about here is, for definition one (in the blue), this is severe cystic acne. You can see that the incidence rate has jumped somewhat for the females -- now we are talking incidence, not prevalence, it has already been divided by the average duration of the disease, which has been taken to be 8.3 years -- and is 13,000 women in 1990. These are estimates projected by Dr. Levy to the 1990 U.S. population.

Again, looking at the male-female ratio, it is instructive to see that if you compare the relative incidence in the severe category, you are talking about 3:1 in favor of females. If you dip into the more moderate category of cystic acne, you are getting closer to the 1:1 ratio in terms of the incidence of the disease.

This essentially is what you want to buy into. If you buy into the severe definition category, you are talking about a 1990 incidence estimate of somewhere on the order of 13,000 women, plus or minus probably around seven, and I will show you confidence intervals on this in a moment. If you buy into the moderate cystic acne definition, then you are up to another 100,000 women, plus or minus some confidence interval. The combined definition, FDA definition two, adds this plus this and comes up with a definition for severe plus moderate.

That gives you some feel for how the numbers are going to change, depending upon which definition you want to buy into. What I am saying here is this definition, part of this definition, and this definition are dipping back into the original prevalence population that was defined as acne vulgaris.

Again, just to give you some feel for the relative male-to-female ratio, because this helps you interpret who is coming into the PDS survey, because if you look at the PDS survey and try to interpret it in terms of who is coming in,

male- and female-wise, and getting new prescriptions, those male-female ratios are very close to the more moderate cystic acne conditions, consistent with the fact that who is getting treated, as represented by the PDS survey, are some more moderate cases, however you might want to define them.

(Transparency)

This is a graph -- not a very good one -- that Dr. Anderson presented earlier. This is the PDS survey from 1985 to 1986 to 1987, 1988, 1989, and 1990. It is showing the estimates of new Accutane patients from the PDS data base, and it is showing that it is going down for the females and it is going down for the males up to the time of the intervention program, and then, even as a result of the intervention program for the females, it is continuing to go down. That is a significant drop and that is what they have claimed. This is the exact same graph, only it has a line fit through it.

These slopes are significant. This is a different change from here; it shows that subsequent to the intervention program there has been a downward trend in the estimated number of new female Accutane patients. Subsequent to that same point in time there has been not a similar drop in the estimates of the male new Accutane users.

Had this not occurred, we could not have concluded that this downward change was a result of the intervention program. It was a downward trend going on all the time and it

could have been some anomaly just of the sampling procedure that is used in the PDS data base, but the fact that this has leveled off from 1988 to 1990 is important and it suggests that something not due to chance has been responsible for the downward trend in female usage.

(Transparency)

What I am going to show you next are all the sources of data that we are trying to compare and contrast to see whether they hang together and whether they are telling us the same basic message pretty much in terms of is the PDS estimate of 1990 new female users consistent with what the NHANES data would be telling us if we start to choose certain definitions of the incidence of the disease (not the prevalence of the disease)?

(Transparency)

I will walk you through this. These are the 1990 estimates from all the available data sources, with the male-female sex ratios in parentheses. This first estimate right here is the PDS 1990 estimate of new Accutane patients, which is in the ball park of around 55 to 56, with relatively narrow confidence intervals. This is for 1990, with the sex ratio of approximately 1.3.

From the reported NHANES published report, using the original definition -- not the restated definition -- you would come up with an estimate, even with these confidence

intervals, of no higher than approximately 18,000 women per year with cystic acne. I think we all agree that that estimate, as shown by Dr. Stern, is probably not to be relied on because of some inconsistencies in the coding.

So what do we do? We went to a reconfiguration of the definition and FDA came up with a severe cystic acne definition which we feel pretty confident in, and I think the dermatologists can speak to this, certainly, better than I can, but you have two things going on here. You have a measure of the variability of the estimate and you have a measure of whether you want to buy this as the definition or whether you want to buy the next definition, which is FDA's severe plus moderate.

If you go to severe plus moderate, you go up to here, to approximately 110,000. So somewhere between here and here is where you are in the ball park of the 55,000 estimate that the PDS has given you, consistent with the idea that you are pulling in, in the PDS new Accutane users, moderate cystic acne.

If you then buy Dr. Stern's definition, his is in the ball park, too. They are all relatively consistent. His definition raises the point estimate to somewhere around 30,000 per year, with his confidence intervals in the ball park of what the PDS survey is. If you buy his more moderate and severe definition, you are up here.

This is intended to show you that by looking at both these estimates in terms of pulling in more moderate cases and looking at the sex ratios, which are essentially 1.3 -- this one up here is 1.4, here is 1.99, this, here, is 2.78 -- obviously the closer you get to 1.2 or 1.3 you are pulling in more moderate cases, and that is the general feeling that was behind is the drug being overly used in more moderate cases. That is the sense of where these definitions are hanging together.

(Transparency)

I do not want to make a big thing out of this other than to say that if there was not this range of variability and we were trying to make more out of the PDS data base, there are some criticisms of the PDS data base that could be made, saying that, well, the variances are not totally accurate and they assume certain parts of the projections are constant and do not have any sampling error involved in them.

The bottom line to that is that the confidence limits that you are seeing that were reported to us on PDS probably should add another plus or minus -- another 4000 to 5000 should be added to them to compensate for that currently unaccounted-for source of variability. I do not think it is a big-time issue in terms of interpreting what the data are telling us in the previous slide.

Thank you.

DR. ANELLO: You have heard about the NHANES data and the PDS data. I would now like to call on Dr. Richard Platt from the Harvard Community Health Plan to give you an independent assessment of his program on the impact of the pregnancy prevention program.

PRESENTATION BY RICHARD PLATT, M.D.

DR. PLATT: Thank you for allowing me to share some thoughts with you about the way physicians at the Harvard Community Health Plan prescribe isotretinoin.

(Slide)

My colleagues in this endeavor are Dr. Susan Heckbert, who is a physician and epidemiologist, and Dr. Gaudeen Mishali, who is a physician-lawyer, a full-time employee of the Harvard Community Health Plan, whose full-time activities are involved in quality assurance there. My home, actually, is the Harvard Medical School; I do not have a formal affiliation with the Harvard Community Health Plan other than to conduct research involving their use of drugs.

(Slide)

Just a word about the organization. It is a staff model HMO. In the time period that we are covering there were approximately 230,000 members, of whom 81,000 were women who were aged 15 to 44 years. The organization is a good one for doing epidemiologic analyses because it has a fully automated ambulatory medical record. This record includes coded

diagnoses and full-text providers' notes. It also includes laboratory test performance and test results, and also a coded indication of intent to prescribe by the prescriber.

In addition, the organization has an automated pharmacy system. The data I am going to show you, though, come from the prescribers' notes of prescribing.

(Slide)

We identified all the women who were aged 15 to 44 years during the period of interest who had a code for isotretinoin prescribed between March 1, 1987, and February 28, 1990. We reviewed the full-text records of the ambulatory charts to recover the dates on which isotretinoin was prescribed, the prescriber, a history of tubal ligation or hysterectomy, and to determine whether or not pregnancy testing had been performed during the 14 days before the prescription.

(Slide)

There are several caveats I want to review with you. The most important is the data set we are talking about represents about a tenth of a percent of the U.S. population, meaning that the number of prescribers is quite limited. In addition, this HMO has an active quality-assurance program, and it is our expectation that both base-line performance and subsequent changes may be impacted by this fact.

For instance, this HMO had been using a written

consent form for isotretinoin prescribing starting in 1985.

We have limited information on contraceptive practices for these women. Finally, we cannot attribute the changes I am going to review with you to specific interventions, because we have no specific data on information that the prescribers received. Changes which occurred late in this interval could possibly have resulted from early events. And there is the general boilerplate warning about observational data: We cannot prove a cause-and-effect relationship.

(Slide)

Overall, we identified 216 courses that were identified in 207 women. The aggregate prescribing rate was .9/1000 women years. Ninety-nine percent of the courses were initiated by 14 dermatologists, of whom eight did the bulk of the prescribing and prescribed at least 10 courses. Ten of the courses followed a hysterectomy or a tubal ligation, so I will exclude them from most of the rest of my comments. Pregnancy testing was performed overall before 56 percent of courses and 80 percent of the pregnancy tests which were performed were serum HCG tests.

(Slide)

This shows, in blocks of three months, the number of new courses initiated as a function of time. Marked here are the dates of the 1988 advisory committee meeting and the date

that the new patient packaging was implemented. I take Dr. Armstrong's comment seriously about when the right break should be, but by the eyeball test it looks as though there was an immediate response of the prescribers to the information that surrounded the initial advisory committee meeting.

For the rest of this discussion, though, I will break the experience into three time periods: before the first advisory committee meeting; the period between the advisory committee meeting and the time the new packaging was introduced; and the remaining period.

(Slide)

I have aggregated those periods here and show, on the ordinate, the number of courses per month that were initiated. The total height of the bar is all the courses, and shown in a deeper color are the courses that were preceded by pregnancy testing. What I take from this is that the general shape of these changes is approximately like those that have been discussed earlier today.

The proportion of courses preceded by pregnancy testing really did not change very much when looked at in this crude fashion. It is 51 percent during the first time period, 63 percent during the second, and 58 percent during the third. It turns out that change in the overall number of courses and in the percentage for which there was testing is

masked by considerable variation in performance of individual prescribers.

(Slide)

These are data taken from the base-line period, that is, the period before the first FDA advisory committee meeting, and it shows you the prescribing the pretreatment pregnancy testing practices of the eight physicians who prescribed at least 10 courses during the entire three-year period.

They broke into two fairly distinct groups. There were four physicians who tested before at least 40 percent of courses. In the aggregate they tested for 50 of the 70 courses that they prescribed. The other four prescribers tested almost never, two times out of 32 courses initiated. We call these the frequent testers -- and we call these the infrequent testers.

(Slide)

This shows you what happened over time to these two groups. Shown here are the same data I showed you two slides ago, total number of courses per month with the proportion that had pretreatment pregnancy testing, falling some over time, but with no change in the overall proportion tested.

The group who were initially called frequent testers reduced their level of prescribing by over 90 percent. We really cannot talk meaningfully about what happened to their

overall testing performance (they were initially testing at about 70 percent) and, finally, two out of three courses were preceded by testing.

The group which initially tested 6 percent of the time, two out of 32 courses, continued to prescribe at approximately the same rate. During the third period their prescribing, number of courses per month, was slightly higher than the number of courses at the beginning, but it is not a big difference.

However, the proportion of courses preceded by testing increased with each of those time periods, from 6 percent to 30 percent to 56 percent. The fact that there was 50-percent testing during this period was a consequence of the fact that these people did most of the testing.

The fact that approximately 50 percent were tested during this period is a consequence of the fact that these people, who now accounted for essentially all of the prescribing, had increased their prescribing -- not quite to the level that this group had initially, but considerably more than they had originally.

On the other hand, essentially all of the drop in total number of courses came from this group that had severely curtailed their prescribing.

(Slide)

The conclusion, then, is that the number of courses

without pretreatment pregnancy testing fell by 54 percent, from 3.6 to 1.7 courses per month. Overall, prescribing decreased from 1.1 to 0.6 courses per thousand women years, and that is a highly significant difference. Overall, pretreatment pregnancy testing did not change significantly. It changed from 51 percent to 58 percent. But these overall changes mask great inter-physician variation.

(Slide)

There were two distinct patterns of change in physician behavior. Those who initially performed HCG testing frequently reduced their prescribing by more than 90 percent. Those who initially performed HCG testing infrequently did not reduce their prescribing, but increased their testing from 6 to 56 percent.

From the epidemiologist's point of view, I find this an interesting conclusion. It appears that the interventions affected every prescriber for whom we have data. Essentially everyone modified practice. But there are two distinct responses to practice. One was to reduce prescribing. The other was to maintain level prescribing but to increase frequency of testing.

Thank you.

CONCLUDING PRESENTATION BY CHARLES ANELLO, PH.D.

DR. ANELLO: I would like to go back to the six questions I raised at the beginning of this presentation and

try to answer them. Remember, the goal of these questions was to assess the impact of the pregnancy prevention program on use, on pregnancy exposure, and on birth defects.

(Transparency)

The first question is: How many new Accutane prescriptions were issued in 1990 to women 12 to 44 years of age?

(Transparency)

I think we can look at the PDS data as providing an estimate of that number, so we are talking about close to 57,000 women, with small confidence intervals.

(Transparency)

How does the level of prescribing relate to what is expected from the NHANES survey?

(Transparency)

We had Drs. Levy and O'Neill explain to you how the various numbers were derived. We have the 8000, which was twice the number originally explained to be what the incidence rate should be. Then, depending on your decision about which of these various definitions of severe cystic acne to use, you get different numbers. The important thing, though, is that the sex ratio plays a vital role in the ability to interpret the NHANES data versus the PDS data. Keep that in mind.

(Transparency)

What is the evidence of a change in new

prescriptions in Accutane during the period 1988 to 1990?

Although you could look at different evidence, we have the slopes of the regression line for the three years. I think it was pointed out by Dr. O'Neill that that change was, in fact, statistically significant. There was a decline, a little over 4000 per year, given the PDS as the data base to look at.

(Transparency)

Are only women with severe acne being treated?

I rely on two sources of information here. I think that a comparison of the estimates of the incidence of severe acne from NHANES and the Accutane use data from PDS along with information about sex ratios suggests that some women with moderate cystic acne are being treated. Also, from the drug epidemiology study, about 40 percent of the women prescribed Accutane in that study did not have any cysts.

(Transparency)

The next question on the list was: Given the level of prescribing, what is the estimated number of pregnancy exposures each year?

There, Dr. Stadel explained how estimates, given an approximate 57,000 women exposures, not as part of the SEU study. Resulting calculations were somewhere around one in 3000 women per year is being exposed.

(Transparency)

The last question: What is the impact on reported exposures and birth defects?

(Transparency)

This is just a summary of what the firm presented in their package to us. These data are updated a little bit in the presentation earlier this morning (the numbers on exposures were a little larger for the last two values). You can see there has been no apparent change in the number of reported exposures, and we are a little uncertain as to whether or not there has been any change in the number of reported defects.

That concludes the portion of the presentation by the Office of Epidemiology and Biostatistics.

FINAL COMMENTS BY CARL PECK, M.D.

DR. PECK: Given the proximity to lunch time, you will be pleased to learn that I have pocketed my 30-minute version of final comments in favor of a 30-second version.

I have three brief points to make. First of all, I would like to recognize the effort that Dr. Anello and his staff have made to bring to the attention of the committee data from all relevant data sources and to present their interpretation in a balanced fashion.

I would like to reiterate Dr. Lumpkin's sentiments that we are very receptive to the advice of the committee on the questions posed.

We are looking forward to your discussion this afternoon, which will be preceded by the comments that we will receive from a variety of special interest groups, whose comments we also look forward to.

Thank you.

QUESTIONS FROM THE COMMITTEE

DR. DAVIDSON: Given the fact that we have gained some time in the morning's agenda and there may be some advantage in the committee being given the opportunity to ask questions while we are proximate to these two discussions, if there is no objection, I would invite the committee, if they have points of information or other questions of Roche or the FDA, to take advantage of this time to do it.

DR. FLEISS: May I ask for one of the transparencies to be put back up, the one which compares the several estimates of incidence based on the many definitions we have gotten?

(Transparency)

Zero is the lower limit for the confidence interval. That means there is no incidence. There has got to be a better way to construct confidence intervals than one which will give you an impossible value down at the lower end.

DR. LEVY: I am sorry, I did not hear your question.

DR. FLEISS: I am questioning the validity of the method used to construct the confidence interval for a rate

when the lower limit ends up being zero. Or, for all I know, it was originally negative, and you rounded it off to zero. There have got to be better ways to do it. That is my comment.

DR. LEVY: Yes, I agree, there are better ways to do it. It was a huge standard error and I just wanted to indicate a cutoff at zero. It was a rate and a standard error, a rate and another -- actually, a rate --

DR. FLEISS: While we are on that, I can ask you, and perhaps some others, Bob O'Neill pointed out that there are some elements of random variability that have not been incorporated into any of these analyses. On top of that, have any attempts been made to incorporate the imprecision of the mean duration? I mean, 8.3 sounds so precise, but I think we all realize that it is not really 8.3.

DR. STERN: May I speak to that? Since I think both the lower and the upper estimates of the duration of acne came from me, let me tell you their source and, as in my discussions with the FDA, our lack of confidence about them, and I think we all share that.

In my review of the literature I could find only one paper, a British study, that followed people longitudinally with acne, and basically had a one-liner that said of men with moderate and severe acne, as defined in that study, the proportion who were better in so many months was X. Then they

said in women who had these same degrees of acne followed longitudinally the proportion who were better was Y.

I then used life-table techniques to predict for men and women what the average duration of acne is from the study, and I hope the FDA would agree that in presenting those I said these are essentially an envelope of estimates, they are the best that I could find in the literature, they are not necessarily real, and I would like, with permission, to make two additional points.

First of all, this study suggested that duration of acne in men and women is different, and, in fact, I think clinical practice suggests that the duration of severe acne, however you define it, is longer in men than in women. Therefore, in going from prevalence to incidence, one should use the sex-specific duration of acne. I do not know what the actual average durations of acne are. I think the overwhelming opinion among experts would be that it is longer for men than for women. Therefore, you are dividing by a higher number, whatever that is, which would change the incidence sex ratios.

Further, as I tried to make the point in the next-to-last slide, whether you choose this 3.3 or 8.2 number, or some number in-between or outside that interval, is not only on sex, as I have just said, but is also dependent on whether you are looking at severe, as narrowly defined, or severe as

more broadly defined.

As I tried to show in that graph, for example, for that individual, be it male or female, if you are looking at that individual and only counting him for Stern severe, he would only contribute three years of duration out of his 12 years with acne. But if you were counting him in my moderate plus severe, that particular individual would have an average duration of eight years. So which duration number you use has to be both sex-specific and definition-of-severity-specific.

That, I think, adds one further element into looking at the sex ratios more critically. I would also say that I extremely enjoyed Dr. Levy's presentation, because this is the first time I had ever used that data set, and I think he and I were in basically complete agreement, and it gave me great reassurance that although we may differ about which definition to use and some fine points, I think we have strong agreement about what, at least, the prevalences are.

DR. LEVY: Getting back to Dr. Fleiss' point about the confidence intervals for the incidence not taking into account duration, they are prevalence data, so one does not know what the variability in duration is. One can assume a Poisson and get that the duration varies and the mean is equal to the variance, or something like that. One would even get bigger confidence intervals than we see here.

I wanted to make the point that they are big.

DR. FLEISS: They are really even wider, given all the other sources of imprecision that exist.

DR. LEVY: Yes, they are probably wider. That is true of a lot of data.

(Laughter)

DR. SHUPACK: As a practicing dermatologist, there is something in this presentation here that leaves me wanting, in a sense. I appreciate the efforts to quantitate what is quantitatable, but in the final analysis there are many factors which have not been looked at here, including, for one, the emotional impact of the disease, which you really cannot quantify in terms of the number of cysts or the number of pustules or what-have-you, which ends up going into the decision-making process.

I am glad to see duration is finally being paid attention to, but there are aspects to duration which are also quantifiable, and which, again, go into the decision-making progress on a day-to-day basis. For example, how much money has that patient already spent on the treatment of acne during the preceding eight to 10 years, how many drugs has he taken, how many side effects has he already had from the other drugs that he has taken?

So I think that, from a practicing dermatologist's point of view, I appreciate the efforts to quantitate what is quantitatable, but the bottom line is, whatever definition we

pick here, whether it is the narrow definition of severe or the broad definition, it really does not have much of an application to the day-to-day practice of dermatology.

DR. MINUS: Dr. Dai, I would like to ask you a question. On the 91 patients you said became pregnant in 1990, do you have any epidemiology material on those 91 in terms of education -- we are talking about surveys on people who had an average education of 14 years, which is quite a lot -- but I am asking the question from the standpoint of two areas.

Number one, those 91, did they really have the kind of education that would have them understand the complications of the drug?

DR. DAI: Yes, I just pulled the data out. Among those people, I looked at those people who started therapy after January 1, 1990, the most recent cases. I did have the educational level here. Unfortunately, through the spontaneous reporting system, a lot of them we do not know the educational level for. However, among those patients we do know it adds up to about 35 patients and 17 of them had a college education, 16 of them were in high school -- that covers most of them, over 90 percent of the patients. I guess that is what you are asking about.

DR. MINUS: The second question is, out of those 91, the physician who prescribed the medication, do you have the

breakdown on the specialty?

DR. DAI: Yes. Most of them were prescribed by dermatologists. In general, 85 to 90 percent were prescribed by dermatologists.

DR. DAVIDSON: Are there any other questions?

DR. ROY: I would like some clarification. I think I heard from Roche that of the 400 individuals who were identified as being Accutane prescription fillers, that two-thirds of them were in the Slone survey -- or 60 percent of them were in the Slone survey, 40 percent were not. Then Dr. Stadel made estimates that the Slone survey only identified a third of the users. Could we get some clarification, Bruce, on where your numbers came from?

DR. STADEL: My number is based on taking the numerator is the Slone experience of various categories, like new women 12 to 44, and the denominator is PDS beta data for 12 to 44.

Now, what they have done is a different thing. That is based upon all the numbers, there are 50-some-odd thousand prescriptions in the denominator. What they have done is gone to get 400 people and look at the intersect. How many of those 400 people picked up from this source were in theirs?

All I can say is what I did. Sixty percent is not reflected in the national data. It comes out about the order of magnitude that I said. You get different figures depending

on how you define it. It makes some difference, but not as large a one as you might think, to the estimate of pregnancy exposures. I came up with an estimate of 1000 to 3000, a third of the women. If it is half of the women, you get 750 to 2250. On the other hand, my failure rates are probably lower than the real ones from the recent Guttmacher publication.

I kind of feel you can pull this back and forth more or less indefinitely, depending on how much you want to do it. I did the best we could in trying to use a full national set of data. We did not have an opportunity to see these data; they refer to 400 people.

DR. MITCHELL: Bruce is correct that we did not make them available, because they were only recently available to us, the data from the 400 sample. That enrollment rate of 60 percent, in our view, is actually quite compatible with the estimates, if you use the PDS denominator of about 57,000 pregnancies, and if you recognize that about 35,000 women enrolled in the survey in 1990.

What we do not know is what proportion of those women who enrolled in 1990 who had a previous course of Accutane had it within the 12 months preceding, which is a cutoff of the PDS definition. But, roughly, it is a 50 to 60 percent enrollment rate based on the absolute number of enrollees in 1990 against the PDS denominator.

DR. STADEL: I guess if I take my third and your 60 percent and settle at 50, it does not change the dimension -- the order of magnitude for my sort of pregnancy exposure among people not in this programmatic thing is not greatly changed. And other things could fluctuate equally.

DR. MITCHELL: I would disagree with you, and maybe we can talk about that later, in terms of the assumptions about the representativeness, but that is a legitimate area for disagreement.

DR. STADEL: I guess one of the things I tried to emphasize is that I am trying to make an order-of-magnitude estimate for what I think might be occurring in an area that we simply do not know very much about. We know a lot about the women who were enrolled in the Slone survey and, like I said, their contraceptive efficacy rate is impressive.

What we can agree on is there is a large number, a very large number, of women not in the Slone survey, who are not volunteers, where one simply cannot assume that their outcome is going to be the same as the people on the other end. I think, from a national perspective, that it is important to emphasize that.

DR. ROY: But, Bruce, is there any way we can make an estimate of whether those people not in the Slone survey are having an experience so outside what we know as to make an impact? I mean, are we in an area where a lot may be going on

and we just do not have the tools to assess it?

DR. STADEL: To err on the side of caution, I would have to conclude there is a distinct possibility that an important problem could exist that we do not have a hold on. That is, if there were a 1000-to-3000 range of exposed pregnancies and 44 reported, that would be a reporting rate of 400. I do not find that surprising for pregnancy exposure itself.

The big "if" then becomes how many unreported birth defects might be out there, and I guess my answer is that is anybody's guess, as far as I can tell. I do not have any way to estimate it. I could talk on about what underreporting experience has been for other diseases -- that has been done before and it led to more argument than to agreement. So all I will say is, to err on the side of caution, I would have to say there is a good possibility that a meaningful or substantial number of birth defects could be in existence that we do not know about. That is the best I can do. I do not have any other tools.

DR. MCGUIRE: I wanted to ask Dr. Platt if he could identify any features of quality assurance in the Harvard program that contributed to the changes in the prescribing practices and, also, testing practices?

DR. PLATT: Against a background of fairly high current events literacy by the physicians and a program that

had been put in place around 1985, we were unable to identify any specific activities that were implemented during the three years that I am describing.

Since then there has been a very aggressive program to try and deal with failure to do pretreatment pregnancy testing. I think the short answer is I am unaware of specific activities that would have contributed to these changes, activities that were solely self-contained within the organization.

DR. MCGUIRE: I was referring specifically to anything that fell under the rubric of quality assurance.

DR. PLATT: I believe that there was no active quality-assurance topic that had been identified at that time, but I am not absolutely certain of that.

DR. SCHLESSELMAN: Dr. Platt, I have two questions of you, please. The first is, with regard to your analysis of the rates of pregnancy testing and whether urinalysis was restricted to women who were indeed at risk of pregnancy, that is, you excluded women who were sterilized or whose partners were sterilized.

DR. PLATT: We excluded women who, in fact, had had hysterectomy or tubal ligation. What we did not do was exclude women who were using contraception. We thought that we could not define contraception users carefully enough. The answer is, yes, that analysis only dealt with women who were

presumably fertile.

DR. SCHLESSELMAN: The second question has to do with your noting differences in rates of pregnancy testing among the physicians in the HMO. I would like to ask whether you inquired about various strategies. One can administer a pregnancy test. The other way to deal with the possibility of pregnancy prior to taking the drug is simply to insist that the drug be taken after the start of menses. Do you have any way of disentangling whether there might be a strategy used among those who were not actually testing for pregnancy which effectively assures that pregnancy is not in effect at the time the drug is taken?

DR. PLATT: I will be able to give you a patient-by-patient answer later today, if you would like, but the short answer is that it does not appear to have been a common strategy, that is, telling the patient to wait. Among physicians who made some notation in the record about advising the patient of the potential risks, they were generally comments that the patient was aware of the need to avoid pregnancy. I can check during the break on the other.

DR. ROY: I was fascinated that the four dermatologists who comprise the group that did the pregnancy testing near the end of your time period were not even prescribing the product. Now, are they not seeing the patients to whom the product is being prescribed? Is that the

explanation?

DR. PLATT: There has been no change in the overall practice level of any of these eight dermatologists over the period of time. These dermatologists tend to divide their time among several of the practice sites. I think, for our purposes, the level of practice has been constant over this period of time.

One other point, that I did not make in my discussion, is that dividing the group into two can, in some ways, magnify an apparent difference, but if you do this kind of analysis in logistic regression that accounts for each physician separately, you still see the same kind of temporal effect.

DR. DAVIDSON: Could you provide some indication as to the stability of this patient population over this study period?

DR. PLATT: The figures that we used represented the population approximately at the middle of the interval. Over the entire period the population grew by about 20 percent, so it was about 10 to 12 percent lower during the first year, and about 10 to 12 percent higher during the last year. The implication of that would be that -- it would have no implications for proportion with pretreatment pregnancy testing. It would slightly magnify the difference in the number of courses per exposed woman year.

DR. SCHLESSELMAN: The educational effort that you had, was it confined in your area with your physicians to only the Hoffmann-LaRoche effort?

DR. PLATT: I believe that there was no additional activity by the administration of the HMO to educate their physicians, but I am not speaking from great assurance here. My understanding is that there was no particular activity undertaken. All of these physicians, I believe all of them have Harvard Medical School faculty appointments --

DR. STERN: Only a minority of them do.

DR. PLATT: Okay, thanks a lot. I will not finish that sentence, then.

A group of knowledgeable doctors.

(Laughter)

DR. NIEBYL: Back to the four physicians who at first were frequent testers and then decreased their prescribing, could you tell that they were screening the same patient population and checking that certain patients were not good contraceptors and, therefore, prescribing less? What do you think was accounting for the decrease in prescribing?

DR. PLATT: I do not have information back from those physicians on their reasons for reducing prescribing.

DR. NIEBYL: But your basic statement was that the population was not changing a whole lot.

DR. PLATT: That is correct.

DR. NIEBYL: Well, it must be that they were somehow screening out patients because of some factor --

DR. PLATT: That is right. The simplest explanation is that they prescribed less frequently to these women. One of the things that we did not do, for reasons of initially trying to limit the impact on our data request to the Plan, was to look at prescribing to people who are not in this group, to men, to older women -- I do not know if there are many of them who have acne. For a number of reasons, our abilities to do that have improved some, and if that were an important feature, we could look at that.

DR. DAVIDSON: My reason for asking the question about the stability of the group was if the four who reduced their prescribing were in a part of the population that was relatively stable over that period of time, they may have treated the base population around the margins. Not knowing the demography of that, it is difficult to understand, I think, or make some interpretations of it.

DR. ROY: Could I go back to one point, which, given the efforts everyone has made with the NHANES data, I hesitate to bring up, but I wonder to what extent it is perhaps even inappropriate to use that as a source pool of information, because, to use Bruce's analogy, that was at a time when all of these pent-up cases waiting to be treated with this product were in existence. How can we now extrapolate those data to

the current time period? To what extent is that appropriate or inappropriate to do?

DR. STADEL: All I would say is that I thought from a long time ago that a good study of the prevalence, severity, and treatment of acne in the United States at the beginning of this whole issue would have been a great ray of light. We do not have it and we use what we have. This is the only thing we have.

DR. SCHLESSELMAN: This is a response to Subir's question. Actually, wouldn't it be a good situation in which to estimate prevalence, because you do not have the imposition of treatment on the population? So rather than being a bad situation, it would seem at first thought to be a good one, because it gives you, if the survey is properly done, an idea about the number of cases that are arising in the population without any effective treatment under way. Any survey that is done today is going to have an effective treatment, so the prevalence would presumably be somewhat reduced.

DR. DAVIDSON: Are there any other questions from the committee?

DR. TSCHEN: As a practicing dermatologist, I have noted that many patients are now being referred to a school or referral centers for treatment. Do the Roche representatives have any information regarding that practice, or how many patients being treated have had the benefit of two or more

medical opinions?

DR. ARMSTRONG: I would say that we do not have systematic data on that. We have anecdotal reports from physicians who say that they have elected not to prescribe this drug to women and prefer to send their patients to referral centers for evaluation and management.

DR. DAVIDSON: Any other questions?

(No response)

Since the afternoon guests have been given times for their presentations, if there are no further questions from the committee, I think we should adjourn for lunch and reconvene at 1:30.

(Whereupon, at 12:50 p.m., the meeting was recessed, to reconvene at 1:30 p.m., the same day.)

AFTERNOON SESSION

DR. SCHROETER: It is 1:32 and I think we should move ahead on schedule. The next item on our agenda is comments from guest organizations. We have a number of them. Each of the groups has about 15 minutes for their presentation. We have one added group to this list, and that is from the Boston Cooperative Group, from Boston University. The first group is the Health Research Group and I do not have the individual's name representing them but if they would go to the microphone and identify themselves?

(No response)

I presume that they are not present. Maybe they are not in the room yet. Can we then start with the next group and we will call on them later? The next group is the American Academy of Dermatology. Dr. Steve Webster, president of the American Academy of Dermatology?

PRESENTATION BY STEPHEN WEBSTER, M.D.

DR. WEBSTER: Thank you. Mr. Chairman and members of the Advisory Committee, I am Dr. Stephen Webster, a dermatologist with the Gunderson Clinic, in La Crosse, Wisconsin; associate clinical professor of dermatology at the University of Wisconsin and University of Minnesota medical schools.

I appear before you today in my capacity as president of the American Academy of Dermatology. The

American Academy of Dermatology is the largest professional medical society of physicians specializing in diseases of the skin, hair and nails. The Academy is dedicated to advancing the science of dermatologic medicine and surgery to promote the highest possible standards in clinical practice, education and research in dermatology and to enhance patient care.

On behalf of the Academy's more than 8800 members, I want to thank you for the opportunity to meet with you again. I welcome the opportunity to review the Academy's ongoing activity related to the use of isotretinoin or Accutane. Joining me today will be Dr. Peter Pocchi and Dr. Mary Spraker.

It has already been established and presented that Accutane is an extraordinarily effective therapy against severe acne, a condition which we, as dermatologists, were previously unable to successfully treat. Because of time constraints, I will not go into emphasizing this fact as I think it has already been very well made.

The problem, as we all know, is that Accutane is a teratogenic drug and, like a great many other medications, it must not be given during pregnancy. The Academy has consistently stressed this contraindication and danger and we will continue to do so.

Nevertheless, the members of the American Academy of Dermatology, experts who know this disease, its natural

history and the ineffectiveness of alternate therapy for severe acne, believe that the benefits that Accutane offer justify its present and continued use with appropriate warnings and precautions against pregnancy during therapy.

However, because of the potential for serious side effects from Accutane during pregnancy, the Academy has undertaken an unprecedented educational campaign. Since May of 1988, the Academy has sent several "dear colleague" letters regarding Accutane to our entire membership. We have strongly encouraged our members to participate in the Slone Epidemiology Unit study of the female Accutane users.

We also appointed a committee to develop guidelines on the use of Accutane in the treatment of female acne patients of childbearing age. These guidelines were published the in November, 1988 issue of the Journal of the American Academy of Dermatology. Last year we published guidelines on care for acne vulgaris that reiterated the guidelines for prescribing Accutane.

In addition, the Academy has worked with the American College of Obstetrics and Gynecology and has developed a revised patient information brochure regarding birth control which contains information on Accutane.

Within the past year, the Academy produced a video, entitled, "Counseling Dermatologic Patients on the Use of Contraceptives." Copies of this video were included in an

educational package and mailed to all members of the Academy. This mailing was also provided to 108 dermatologic training centers and a letter was sent urging that the video be incorporated in the curriculum of that center.

Last year the Academy sponsored a consensus conference on the classification of acne, and this is of vital importance. The report of the consensus conference on acne classification will be distributed to the Committee and will be further discussed by Dr. Pocchi. This was printed in the March, 1991 issue of the Journal of the American Academy of Dermatology. In an effort to highlight the importance and usefulness of this report as a desk reference for dermatologists, the Academy is sending a special reprint of this report to our entire membership. Again, this will be provided to the Committee and I think it will answer a lot of questions regarding the classification of acne.

I can assure you that we will continue our efforts to properly educate dermatologists regarding the use of Accutane. The Academy remains sensitive to the issues being raised concerning birth defects and to testimony at this and previous hearings. For example, you have previously heard testimony that Accutane is over-prescribed. However, as Dr. Stern pointed out and others in the discussion of the NHANES study, there is some question about these earlier assumptions.

Furthermore, while the Slone study is reassuring,

we are concerned about some of the data. For example, 99 percent of the enrolles were told to avoid pregnancy but only 62 percent reported having had a pregnancy test done prior to the start of treatment. Perhaps the physician did not feel that a pregnancy test was necessary. I know that I, as a physician, may not order a pregnancy test for a patient who is sterile or postmenopausal.

We will report the Slone data to our membership and we will continue to work with the manufacturer and other health professionals to ensure that the use of Accutane is safe and effective. We are convinced that the actions already taken in our continuing medical education program address emphatically the issue of preventing birth defects while still allowing patients with severe cystic acne to have access to this valuable drug.

Thank you for permitting me to speak on behalf of the American Academy of Dermatology and I would like to introduce you to Dr. Peter Pocchi.

PRESENTATION BY PETER POCCHI, M.D.

DR. POCCHI: Thank you very much, Dr. Webster. Mr. Chairman and members of the Advisory Committees, I am Dr. Peter Pocchi and my presentation today deals with the classification of acne, more specifically, a delineation of the criteria that would designate a case of acne as being a severe one.

For the most part, the determination of whether a patient has severe acne or not rests on objective criteria but subjective factors can contribute to such an assessment as well.

At opposite ends of the severity spectrum of acne disease there is rarely dispute as to what constitutes a mild case versus a severe case of acne.

(Slide)

For example, this shows an unequivocal instance of mild inflammatory acne.

(Slide)

Whereas, this second slide demonstrates an obvious example of a severe case of inflammatory acne.

But the central issue to be considered here is that while most cases of acne are less severe than shown in this slide, frequently the acne is still sufficiently severe to warrant the use of systemic modalities that would include oral antibiotics or hormonal therapy for women or Accutane.

(Slide)

Toward an understanding of the difficult issue of categorizing gradations of acne severity, this slide shows, by way of introduction and information for all assembled, a simple classification of the types of acne lesions.

For the sake of this presentation, noninflammatory lesions or comedones, which are blackheads and whiteheads,

can be dispensed with since acne manifested only by comedones cannot really be characterized as severe, moreover, they do not lead to scarring.

Inflammatory lesions, papules and pustules, are smaller than 5 mm. A papule is a pimple and a pustule is a pimple with a little central core of pus. The other type of inflammatory nodule, the third type, is a nodule that is frequently referred to as a cyst. That is somewhat erroneous but I will not go into the reasons for this. The word cystic acne has become so ingrained in the literature that we do retain that term. But a cyst is really a nodule and it is basically a big pimple.

That arbitrarily is defined as an inflammatory lesion that is 5 mm or larger. Therefore, a lesion that is 5 mm is a cyst and a lesion that is 4.5 mm is not.

Immediately, the classification, therefore, of acne is difficult because it is a highly pleomorphic disorder in which the inflammatory lesions vary in size, in density, in severity of the inflammation within them in a given individual and in the same area of involvement of the skin in that individual.

There is also considerable variability in the natural evolution and healing of lesions. Because of the pleomorphic nature of acne, it should be obvious that it is difficult to quantify acne severity by simple enumeration of

lesions.

For this reason, the American Academy of Dermatology sponsored a consensus conference to review the various methods of classifying acne severity. A conclusion reached by a panel of acne experts at the conference was that finite numbers for classifying acne cannot provide an adequate assessment of acne severity. Instead, a pattern diagnosis system of grading acne was proposed.

(Slide)

As this slide shows, the degree of inflammatory acne is designated as mild, moderate or severe based upon a lesion count approximation rather than exact numbering. We will discount mild since that is not a consideration for us. Moderately severe acne would be characterized by the presence of several to many papules and pustules or few to several nodules or cysts. A severe case of acne would have either numerous or extensive papules or pustules or many nodules.

What I think should be appreciated here is that more often than not an individual who has moderate nodular acne will also have substantial numbers of papular and pustular lesions to the extent that the classification for that person would be deemed severe. That is, moderate nodular acne plus moderate papular/pustular acne would equate to severe acne.

(Slide)

Additionally, there are complications or circumstances that may be important in designating a patient as having severe acne. These modifying characteristics or factors are listed on this slide.

It was the opinion of the consensus conference panel on acne classification -- these are divided into objective, subjective and miscellaneous -- that the presence of purulent drainage, serosanguineous discharge, sinus tracks or the presence or active scarring, no matter how mild or moderate the disease, are complications that of themselves would automatically render a case of acne as being severe.

Then there are subjective considerations -- psychological, sociological and occupational. Of special importance among these, as was brought up by Dr. Shupak this morning, is the psychological aspect of this highly visible disorder. Acne, even in its milder forms, can be psychologically devastating and socially stigmatizing.

Finally, there is the lack of therapeutic responsiveness, often taking many months and years to go through a variety of treatments that prove inadequate, and also the difficulty of tolerating acne medications which, strictly speaking, are not factors in the context of a classification system but are, nevertheless, important additional determinants in the decision to employ drugs such as Accutane. Thank you.

PRESENTATION BY MARY SPRAKER, M.D.

DR. SPRAKER: I am Mary Spraker and I speak to you today as a dermatologist and a pediatrician, practicing academic pediatric dermatologist, the immediate past chairman of the American Academy's task force on pediatric dermatology and the current chairman of an AAD ad hoc committee on Accutane. I am also a mother.

The American Academy of Dermatology does not think additional limitations in the distribution or availability of Accutane are reasonable. Clear-cut guidelines for prescribing the drug are listed in the current package insert. Although following the package insert recommendations is voluntary upon the judgment of the prescribing physician, the safe use of the drug for the patient's sake, the desire of every physician to deliver the best care to his patients and the threat of malpractice very strongly encourage the prescribing physician to comply with these guidelines.

If Accutane were not readily available, patients would obtain it elsewhere, from other countries or via a black market, since the drug is so necessary and effective. Restricting the drug to regional centers, as has been proposed by others at past hearings, would result in significant inconvenience for the patient, increased expense and could very well not reduce pregnancy exposures.

A decade ago, when Accutane was in the clinical

trial phase of drug development and so was, by definition, limited to "center use," several pregnancies occurred despite pregnancy prevention counseling.

The mandatory monitoring system now used for the antipsychotic drug Clozapine has led to an extremely expensive annual cost per patient, $7000, due to the distribution system alone plus another $2000 per year for the actual drug. This, in effect, has caused rationing of the drug. Accutane is expensive enough. An average 20-week course of therapy costs approximately $950 for drug alone, plus additional expenses for laboratory tests and office visits.

Another serious drawback to the regional center concept is that the physician, who has best come to know the particular acne patient and has established a good working relationship, would not be able to be involved in the subsequent Accutane therapy. This physician-patient relationship helps the physician evaluate the reliability of the patient and should optimize patient education regarding pregnancy prevention.

Unfortunately, the drug is a teratogen and the age group of patients afflicted with acne is also at highest risk for pregnancy. Therefore, the drug presents interesting and complicated ethical issues which require balancing the needs of the mother and fetus, the prescribing physician and patient.

It is now recommended that the prescribing physician counsel the patient regarding contraception and Roche reimburses the patient for a GYN consultation for such contraceptive information. But is it ethical to insist that every patient take an oral, injectable or implantable contraceptive even if she insists her current contraception is adequate or if she is not sexually active? Occasionally patients develop serious complications from contraceptives. Doesn't the patient have a right to participate in this decision?

Recent FDA approval of an implantable progesterone type contraceptive agent provides us with an additional contraceptive alternative. However, the insertion of an implantable contraceptive would not be acceptable to a large group of Accutane users. A somewhat invasive procedure is required for the placement of the product and the agent itself is fairly expensive.

The patient, once given the alternatives with the prospective pros and cons, has the right to participate in the choice of her contraceptive. We need to recognize that as physicians we can guide our patients but we do not have, and do not want, the power to control them.

Never in the history of drug prescribing has more been done to educate physicians and patients regarding the teratogenicity of a medication. The patient and physician

information methods we have created together are excellent and truly innovative, and will be helpful when other medications with serious side effects are considered in the future. Yet, as we proceed, we need to take great care that the decisions we make regarding Accutane will have important ramifications for many other medications, both old and new. Thank you.

DR. SCHROETER: Thank you. Since we started on time and the Health Research Group was not present, I will ask again if there is somebody from that group who will represent them.

(No response)

If there is not, we will go on to the Teratology Society.

PRESENTATION BY CAROLE A. KIMMEL, Ph.D.

DR. KIMMEL: Good afternoon. I am Carole A. Kimmel, Ph.D., developmental toxicologist in the Office of Research and Development, at the U.S. Environmental Protection Agency. I am speaking to you today in my capacity as president of the Teratology Society.

We appreciate very much the opportunity of addressing this joint meeting of the Dermatologic Drugs and Fertility and Maternal Health Drugs Advisory Committees. We have presented testimony to these Committees on several pervious occasions.

The Teratology Society is a professional organization of basic scientists, pediatricians, obstetricians, toxicologists and other health scientists concerned with the causes, mechanisms, manifestations and prevention of birth defects and other types of developmental abnormalities. Members of the Teratology Society are from academia, government and industry.

As a professional society, we are, and have been, concerned with the developmental defects caused by retinoids. The public affairs committee of our Society earlier wrote a position paper on the use of Vitamin A supplements during pregnancy, and has recently completed a position paper, entitled, "Recommendations for Isotretinoin Use in Women of Childbearing Potential." This paper is scheduled for publication in the July issue of the Society's official journal, Teratology.

My remarks this afternoon will summarize the recommendations in this position paper. The statements made here have been reviewed and approved by the Council of the Teratology Society.

The Teratology Society recognizes that isotretinoin, marketed under the trade name of Accutane, is an effective treatment for severe recalcitrant cystic acne, and has been approved by the FDA only for this condition. Isotretinoin is also a potent human developmental toxicant. Despite pregnancy

category X classification and patient package insert warnings, malformed babies attributable to isotretinoin exposure have been reported every year since 1983.

The Teratology Society contends that it is necessary, therefore, to limit isotretinoin use among fertile women, to those who absolutely require this drug and to those who will reliably use adequate contraception. Thus, the Teratology society recommends that:

Number one, Hoffmann-La Roche should ensure appropriate means to limit distribution of isotretinoin so that women of childbearing potential with an FDA-approved indication are identified and properly educated about the risks of taking isotretinoin before initiating therapy with this agent.

Number two, implantable progesterone-type contraceptive agents should be strongly recommended for female isotretinoin users because these contraceptives reduce the risk of pregnancy up to 10-fold when compared to oral contraceptives. Furthermore, the FDA should hasten the labeling of injectable Depo-Provera for contraceptive use since it can be used for contraceptive purposes over a 5-6-month period, the range of time needed for Accutane therapy, while the implantable products are intended for long-term contraceptive use. In addition, the implantable drug may not be financially affordable for some women.

Number three, the Accutane survey should be continued and rigorously evaluated. If this surveillance cannot determine accurately the rate of exposed pregnancies, the reasons for the exposures and the fate of those pregnancies, then a new monitoring system should be established.

Number four, if implementation of these recommendations cannot ensure the prevention of birth defects, then the manufacturer and the U.S. Food and Drug Administration must consider further restricted availability of isotretinoin.

These recommendations by the Teratology Society are meant to complement and extend the stringent conditions printed in the recently released package insert by the manufacturer.

In summary, to minimize exposure of fertile women to isotretinoin, the Teratology Society recommends that the manufacturer pursue development of a plan to limit distribution of isotretinoin to those patients with an FDA-approved indication.

To further reduce the risk of isotretinoin developmental toxicity, the Teratology Society recommends that female isotretinoin users be strongly urged to utilize implantable or injectable progesterone contraceptive agents. Since the use of the implantable contraceptive is reputed to be costly and is intended for long-term use, the Teratology Society further recommends that the FDA hasten the labeling of the

injectable Depo-Provera for contraceptive use.

Finally, continued postmarketing surveillance to detect inadvertent use is essential to monitor the success of the first two recommendations. The present surveillance system should be continued or replaced by a more rigorous program if necessary.

The Teratology Society recognizes that isotretinoin is a valuable therapeutic agent. However, its inadvertent use during pregnancy is likely to cause serious adverse consequences to the conceptus. The recommendations made by the Teratology Society represent an effort to maintain the availability of isotretinoin for its intended use while reducing or eliminating the possibility of exposure during pregnancy.

The Society would be more than willing to work together with the FDA and these two Advisory Committees to provide expertise on the risks of Accutane exposure during pregnancy. Thank you.

DR. SCHROETER: Thank you. Next, can we have a representative from the American College of Obstetrics and Gynecology?

(No response)

We are all on the Committee.

(Laughter)

Do we have a representative from the American

Academy of Pediatrics?

PRESENTATION BY RICHARD GORMAN, M.D.

DR. GORMAN: Good afternoon. Thank you for the opportunity to address the joint Committees. I have been authorized by the American Academy of Pediatrics to present my views on the current status of isotretinoin to this joint meeting of the Dermatologic Drugs and Fertility and Maternal Health Drugs.

DR. SCHROETER: Could you identify yourself?

DR. GORMAN: My name is Richard Gorman. I am a pediatrician in solo practice in a suburb of Baltimore, and I sit as a member of the American Academy of Pediatrics committee on drugs.

These comments I am about to make have not been reviewed by the executive committee of the American Academy of Pediatrics nor by the committee on drugs. Though my remarks are not to be considered as a position of the Academy, the American Academy of Pediatrics is extremely interested in continuing to monitor the current status of isotretinoin.

In reference to the two questions that are addressed to the Committee today, the American Academy of Pediatrics has reached no consensus opinion. Isotretinoin is effective in the treatment of severe recalcitrant cystic acne. Patients given this agent in doses of 0.5-2.0 mg/kg/day for

15-20 weeks have reduction of sebaceous gland size and activity. A course of treatment usually results in significant clearing of lesions and prolonged remission of physical and emotional scarring of this condition.

However, isotretinoin is a human teratogen. The risk of teratogenesis is of the same order of magnitude as thalidomide, that is, approximately 20-30 percent of exposed pregnancies will be affected. This represents the most serious potential complication.

Moreover, of specific concern to the Academy of Pediatrics, a single report has demonstrated that 50 percent of live born infants, with and without external malformations, born to women who have been taking isotretinoin during pregnancy show subnormal intelligence or other neuropsychological impairments.

The American Academy of Pediatrics, like the joint Committees, awaits the ongoing evolution of data about drug use and the long-term consequences to the pediatric population. Specific concerns that the Academy has, expressed to its membership, include:

The Academy is concerned that specific risk-benefit ratios remain a high profile issue for both the FDA and for Hoffmann-La Roche.

The Academy membership is worried about fetal exposure, as well as decreased birth defects.

A recent review of medical journals indicates that there seem to be expanding unlabeled indications for Accutane in other keratinizing disease states. Fourteen conditions have been reported as being effectively treated by Accutane in medical journals.

The Academy is also concerned that this agent is also used in reproductive females for conditions that do not meet the labeling, that is, both mild acne and acne that is not recalcitrant to previous therapy. Data presented at this meeting leave me not much clearer as to whether or not that is a major problem.

If the Roche pregnancy prevention program is 100 percent effective and the only failure is, in fact, contraception failure, there would still be an ongoing burden to society in the number of patients who are born exposed to this agent.

I think those are all the concerns that have been raised by the membership. I would like to thank the Committee for the opportunity to present today.

DR. SCHROETER: Thank you. Next on our list is the American Academy of Family Physicians. Unfortunately, that representative will not be here. However, a statement to the FDA has been left in our hands and that will be circulated at this time.

We have one more presentation by the Boston

Cooperative Group, Boston University Medical School, by Dr. Jick, associate professor of medicine.

PRESENTATION BY H. JICK, M.D.

(Transparency)

DR. JICK: Thank you very much. As was noted, I am Dr. Jick and I am an associate professor of medicine at Boston University. Our research group has been carrying out a detailed follow-up study of Accutane users for eight years. Having heard about this meeting, I thought it would be worthwhile to present some of the results, particularly as they are relevant to the questions that have been raised at this meeting.

This study has been carried out at the Group Health Cooperative of Puget Sound, which is a health maintenance organization in the Seattle area. It has a membership which averages about 300,000 people per year and there are about 95,000 women members who are age 15-49 years.

Most drugs, including Accutane, are provided at no cost through local pharmacies that are run by this HMO. The pharmacies have been automated since 1976. All prescriptions that are filled out at these pharmacies are recorded on computer and are sent to us, in Boston, for research studies.

The Cooperative also has their own hospitals and patients are regularly hospitalized at their hospitals. All of the hospital discharge diagnoses and relevant details of

these hospitalizations have been automated by computer since 1972.

(Transparency)

So what we essentially have in this population is a list of all drugs that people have gotten since 1976 and a list of all hospitalizations, including deliveries and abortion information.

(Transparency)

We have a population of 300,000 people. All prescriptions have been recorded on computer since 1976 and all hospitalizations also have information automated. We have all that information in Boston.

(Transparency)

We started an Accutane follow-up study virtually the month that Accutane was put on the market and approved in the formulary at Group Health Cooperative. Group Health Cooperative has eight dermatologists and they are the only ones who can prescribe Accutane. From the very start, we identified every Accutane user and followed them up by abstracting the clinical record notes for as long as they were on the drug and for a short period thereafter, all recipients having been notified to us from September, 1982, when the drug came on the market, to June, 1987.

As I said, the clinical records, including laboratory results, were abstracted and sent to us and we coded

them and also put them on computer. In addition, all hospitalizations and recipients of Accutane have been reviewed from the start.

Since 1987, when we stopped this detailed review of the entire clinical record, we have reviewed all of the hospitalizations in "ever" Accutane users from July 1987 through 1990.

(Transparency)

The results of the detailed follow-up study, from 1982-1987, have just recently published in the Archives of Dermatology. If any of you are particularly interested in Accutane, there is the reference.

There were approximately 200 women of childbearing age who received Accutane in that phase of the study. None became pregnant while under medical supervision; 3 women became amenorrheic while on Accutane but subsequent follow up revealed that they were not pregnant.

One woman received Accutane in late 1983/early 1984. She did not return for a visit but she did return in December of 1985 and reported that she had taken 12 Accutane tablets on her own just prior to her visit and that she was, in fact, pregnant. A pregnancy test was positive and she elected to have a therapeutic abortion.

There was one woman during this time who became pregnant after stopping Accutane and she also chose to have a

therapeutic abortion.

(Transparency)

Since July of 1987, as far as we can tell, there have been no pregnancies in current users of Accutane. I should say that the dermatologists at Group Health are highly sophisticated, well trained and extremely concerned and observant dermatologists, and I think they have done everything humanly possible to use this drug properly.

There were 7 pregnancies among 406 females whom we have identified as having used Accutane but these pregnancies occurred after the Accutane was stopped. Of these, 6 of the babies were described as normal and 1 baby had Down's syndrome.

So I thought it would be worthwhile to give you the experience of this very carefully followed cohort of young women at this institution in Seattle. There are over 400 such women and, as far as we can tell, none of them has become pregnant while under the care of a dermatologist. There was 1 woman who self-medicated herself.

Whereas, this is obviously not applicable to the rest of the country, it is a useful experience and I think it does illustrate that under proper conditions it is possible to keep pregnancies down to a minimum.

There is one other comment I would like to make about the experience at Group Health Cooperative that is

relative to the concern about the diagnosis of the severity of the acne. I probably should not say this but my impression is that the treatment at Group Health, which is very careful, is based not so much on any arbitrary category of acne but, rather, on the responsiveness of the patient to other treatments.

We actually did a study a couple of years ago in which we found that over 90 percent of people who were treated for acne had received extensive courses of antibiotics and other drugs which had failed to improve the acne, and only under those circumstances were the patients treated with Accutane. However, we do not have any categorization of the severity of the acne. As I say, primarily the concern seems to be for people who have bad acne that is not controlled by other means.

DR. SCHROETER: Thank you. We are ahead of schedule. I think we will proceed with the Committees discussion. If anyone would like to make comments or to start a dialogue regarding the problems that exist, we can do that. If not, we will move specifically to addressing the two questions and that will focus our discussion.

DR. DAVIDSON: I have one question and one comment about the abnormalities. I just wonder whether or not there has been documented a clear-cut pattern of abnormality that is characteristic of the drug, and have the abnormalities that

have been seen been tested against that characteristic? In most instances, drugs have a characteristic pattern, depending upon the period of gestation at which they are introduced. I just wonder about that.

The companion comment which, in part, raises this question is that, at least as I interpret the data, the occurrence of congenital abnormalities is similar to what the background occurrence is in the general population. I am talking about the ones that are being reported. I am not talking about the incidence in relationship to abortions or other things but what is really being reported here for whatever reasons.

But is there a characteristic pattern and have the abnormalities been graded against that pattern?

DR. SCHROETER: Would someone from Hoffmann-La Roche like to speak to that?

DR. DAI: Yes, there are characteristics associated with Accutane. There are three kinds of abnormalities that are characteristic of Accutane babies. The abnormalities include the CNS system, the cardiovascular system, as well as craniofacial system.

For the craniofacial system the most obvious one is the ear abnormality, which includes the low set ear, the microtia or absolutely no ear, and also stenotic ear canals.

The CNS abnormalities include hydrocephalus and

also other cerebral and cerebellar abnormalities. The cardiovascular abnormalities most commonly seen are those which involve the coronal truncal system, including ventricular septal defect and also other kinds of aortic abnormalities.

Out of some 91 patients that we know of, about 21 patients had all 3 kinds of abnormalities in combination. Most of the others, more than 50-70 percent, had at least 1 ear abnormality.

DR. NIEBYL: Ear abnormalities are rather unique. Anotia, which means no ears, or microtia, which means small ears, are quite unusual in the absence of exposure to various retinoids or Vitamin A derivatives. That is a very unusual, isolated anomaly, whereas, it occurs quite characteristically after exposure to Accutane-type drugs.

DR. DAVIDSON: But my basic question is how many of them fit into that kind of characteristic pattern.

DR. NIEBYL: The data that Dr. Lammer reported when he looked at the prospectively ascertained cases -- it is different if you look at the retrospective ones -- is that about 25 percent of Accutane-exposed pregnancies have these characteristic abnormalities. Then we heard last year at this meeting that another 25 percent have mental retardation even though they appear normal at birth. Do you want to comment on that?

DR. DAI: Yes. That is not true. First of all, of all pregnancies, about 60 or 70 percent have been through a therapeutic abortion. Of those babies who were born, about 25 percent had some kind of congenital malformation. It could be as minor as, say, an inguinal hernia. They are not all characteristic of the Accutane babies.

Now, the low scores that Dr. Lammer presented last year, actually, every single one of them which he classified as having low IQ scores was originally classified as congenitally malformed in my table.

DR. NIEBYL: You included them in the same 25 percent?

DR. DAI: Yes, they are all there.

DR. NIEBYL: But they would not have been included in the ones that were considered characteristic.

DR. DAI: They probably did not have characteristic type of malformations. For example, if a baby has VSD, how do you tell whether it is Accutane or not?

DR. NIEBYL: Right.

DR. DAVIDSON: I think that is problematic. I would like to make an observation, and it has to do with the reporting or the under-reporting of birth defects. Of course, this is anecdotal but, having had a considerable experience in dealing with the professional liability and some related questions in obstetrics, I seriously doubt there

is a significant number of unreported birth defects due to this drug.

DR. NIEBYL: I would agree with that. When a baby is born with significant anomalies and mental retardation, the first thing that everybody asks is whether there was any drug exposure.

DR. SCHROETER: Dr. Stadel, do you want to make a comment?

DR. STADEL: Yes, I would like to. Dr. Franz Rosa, our teratologist is not here. We wrote to the 1600 or so maternal and child health specialists. I thought it is worth reading the pertinent paragraph: Accutane embryopathy involves mainly a triad of brain injury, small external ears and canals and cardioaortic defects. Although brain injury is the most frequent finding -- according to Franz, in 90 percent of known cases -- ear deformities are the most conspicuous observation and can vary from small, low set, posteriorly rotated ears and canals to total absence of ears and canals. Defects of the heart or aortic arch have been found in about half of the cases. It goes on though that, unfortunately, Accutane exposure in pregnancy may be unknown, and so on.

Dr. Rosa has expressed concern to me and I have received this from Dr. Erickson, at CDC, that the obverse question has not been fully answered. That is, if you

evaluate enough babies with birth defects that are not phenotypically clear, how many do you find? Not very much work has been done in that area, to my knowledge. There has been one pilot study done by CDC and that is all I know of.

So I think the up-side is that when you recognize it, it is clear. The down-side is not so clear, that is, as to whether there is any meaningful number of atypical phenotypes. Thank you.

DR. SHUPAK: I would like to ask the representative from the Teratology Society a question. You alluded in your presentation to some data on natural Vitamin A supplementation in pregnant women. Could you share with us some of that report and how this might relate or act as a measure against which we can evaluate Accutane?

DR. KIMMEL: I am not sure I can help you a great deal. In the Vitamin A position paper it was recommended that supplements of no greater than 10,000 IUs be available for women because it was recommended that no greater than that amount of supplementation be used during pregnancy in order to avoid the possibility of malformations in humans from excessive Vitamin A supplementation.

I do not know though that that relates very much to the situation here, except that we know that retinoids in general do tend to be teratogenic when used in unreasonable doses. But I do not have any way of making an equivalent

evaluation between Vitamin A supplementation and isotretinoin.

DR. NIEBYL: There have been a couple of case reports, and that is the extent of the data. The cut-off seems to be about 25,000 IUs, above which you can get embryopathies very similar to Accutane exposure with the typical ear malformations. So it has been recommended not to supplement pregnant women at that level but that is a pretty high level. Nobody needs that for vitamins.

DR. SCHROETER: I have a question regarding the birth defects. Am I clear that in those infants who are born to pregnancy subjected to Accutane and there are no congenital defects, there is mental retardation in a significant number? I thought I remember the people from California saying that it is as high as 50 percent or more.

DR. DAI: You can look at malformation in terms of whether the baby had a CNS malformation, major malformation or any malformation. So what I was talking about was that those people who were classified as having low IQ scores, all of them had some kind of malformation. That is how I classified in my table. But if you ask whether all of them had CNS or not, maybe not every one of them had obvious CNS malformations.

DR. NIEBYL: So a baby could have had an inguinal hernia and later be discovered to have serious mental retardation?

DR. DAI: No, I do not think the person who had inguinal hernia had a low IQ score. Most likely, the baby had some kind of hearing defect.

DR. KIMMEL: There is a publication by Adams and Lammer, who have done the follow-up studies on 5-year olds exposed to Accutane during the first trimester. The figures that I have from that paper are that 52 percent of the 5-year olds that they studied had intellectual deficits and, of those, 37.5 percent had no major malformations, that is, major malformations.

DR. SCHROETER: That was my recollection. Can anyone tell me that there are no problems in differentiating these congenital abnormalities from those of alcohol ingestion? I think there is some overlap in that.

DR. NIEBYL: Oh, yes.

DR. SCHROETER: Has that been excluded from the numbers of infants that have been labeled as Accutane?

DR. DAI: Can you repeat the question?

DR. SCHROETER: Have alcohol birth defects been excluded and can they be readily identified?

DR. DAI: Yes, I think you are correct, alcohol is a very difficult question to ask and you do not know whether the information you gather is reliable or not. The information we have from the spontaneous reporting system is that some of the malformed babies did have alcohol abuse mothers.

DR. SCHROETER: Were those excluded in any way from the numbers you presented to us?

DR. DAI: I think there is a small number of malformations that we know of. But as I said before, alcohol history is very difficult to get reliable information on.

DR. SCHROETER: So what you are telling me is that if the mother has taken alcohol during pregnancy, the birth defects overlap with Accutane and, therefore, are very difficult to differentiate?

DR. DAI: I think that is true.

DR. NIEBYL: Well, some of the central nervous system problems certainly overlap, mental retardation for example. But some of the other characteristics are different. Alcohol syndrome is associated with mid-facial deformities and mid-facial hypoplasia as opposed to the ear malformations which are more typical of Accutane. So there is a little bit of difference but, certainly, when you get a baby with significant central nervous system malformation, it could be either way.

DR. DAI: I would like to clarify one issue. I never excluded anybody with any kind of malformation. The 91 cases of malformations include any kind of malformation for any reason we could think of.

DR. FLEISS: This is association with and not cause by --

DR. SCHROETER: That is right. Any other comments or questions from the two Committees before we delve into the questions specified by the FDA?

DR. KIMMEL: I think it is important to point out that although it is difficult to make these associations sometimes with drug use, in the case of Accutane there were animal data long before the human data. In the primates, in particular, the syndrome of effects that has been characterized in humans is the same. So there is a characteristic pattern of malformations that is associated with Accutane exposure in several different species, including humans.

DR. DAVIDSON: The point that I am interested in, and I think others are, against that background, how many of the malformations being reported fit that characteristic?

DR. NIEBYL: A pretty large number.

DR. DAI: If you are talking about how many of them do have three typical kinds of malformations, including the CNS, ear abnormalities as well as cardiovascular, we know of lower than 30 patients -- I think 21 or 22 patients had a combination of 3 malformations.

DR. FLEISS: May I ask a question? Do the ear defects cause hearing difficulties?

DR. NIEBYL: Yes, they are usually deaf.

DR. FLEISS: Could that affect the diagnosis of mental retardation? A misdiagnosis, in other words?

DR. NIEBYL: It can but it does not necessarily, but they are often associated too in the same infants.

DR. FLEISS: Could that be a problem though when measuring two aspects of the same problems?

DR. MORSETH: My name is Sandy Morseth. I work for the FDA. I do not have any data on it but I think there are cases where mental retardation was first considered and later it was found out that it was a hearing defect or any sensory defect. The first thing that any psychologist is going to do is to look at sensory problems before they diagnose.

DR. SCHROETER: If there are no other comments or specific questions, let's move to the questions proposed to the Committees by the FDA, and I appreciate the FDA simplifying their approach. Oftentimes we get long, drawn out, complicated questions but these are very straightforward and to the point:

Do the Committees believe that further changes should be made in the labeling and/or packaging? We are willing now to entertain any concepts you have in terms of the labeling.

DR. LUMPKIN: I do not mean to presuppose the answer to the second question but one issue, as far as labeling, that has arisen that I would be interested in the Committees' thoughts is when you look at the labeling for Accutane, for example, in the initial contraindications and

warning box, the second sentence reads: There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking Accutane in any amount, even for short periods. Potentially all exposed fetuses can be affected.

As we have gone along and as the labeling of this drug has evolved, we have felt comfortable with the basic truth of that statement. What we are wondering now is, as we have developed more and more data, are we in a position to feel less comfortable about quantifying that statement further, in the sense that a patient and a physician would have more information as to what we mean by "extremely high risk" so that they can make an informed decision of what they want to do? Or, does the Committee feel that by using the broader, "extremely high risk" wording we are doing the best we can at this point in time, as to what the data show, to protect the patient population that is going to be potentially exposed to this drug? I would be interested in your comments on that.

DR. SHUPAK: I think the present warning is adequate and correct and I think any attempts to quantitate it, just based on the last 20 minutes of discussion here, will only lead to false impressions.

DR. FLEISS: I do not recall hearing any data that would make me comfortable with a statement of an actual numeric risk.

DR. SCHLESSELMAN: I would like to ask a question of the dermatologists on the Committee. That is, whether they believe that the drug is presently being used according to the indications and usage?

DR. SCHROETER: That is an excellent question. Is it currently being used as the labeling indicates? Dr. Shupak?

DR. SHUPAK: I would answer yes to that question if we allow that the definition of severity is according to the consensus paper that Dr. Pocchi presented. If one takes into account the broader definitions of severity, the average physician is using it appropriately.

DR. SCHROETER: Maybe we should read the indications and use section. It says: Accutane is indicated for the treatment of severe recalcitrant cystic acne and a single course of therapy has been shown to result in complete ... and so forth.

Recalcitrant, as I interpret it and correct me if I am wrong, means that previous therapies have not been therapeutic. There is indication from the data, if you interpret them liberally, that we have moved away from this in our actual usage to a moderate degree of nodular acne, which may or may not have had previous therapy because we do not have data from the Slone study indicating whether it is "recalcitrant" or not since that was not brought up in those

data.

DR. SHUPAK: I do not think we have moved away from the package insert. I think what we have done is moved away from our definition of severity a little bit because, remember, the wording of the package insert here is based on the initial clinical trials during the drug development phase where truly the most limited -- whatever group you want to refer to, whether it is the Stern group 1 or the FDA group, whatever -- those are the patients who were studied and those are the patients upon whom the approval was given, and those are the patients who are listed in the package insert.

I think that there has been a movement away in clinical practice from that strict group and what we are doing, basically, is revising our definition of severity here and recalcitrance.

DR. MITCHELL: Just a point of clarification, in the Slone survey we do not have information on whether women had failed on the prior therapy but, in fact, 95 percent of the women reported having received prior antibiotic therapy before going on Accutane.

DR. SCHROETER: But none of the details --

DR. MITCHELL: That is right.

DR. MCGUIRE: I think it would not be too difficult to rephrase the indications for isotretinoin that would more accurately reflect standard care in the 1990s. I think that,

as Dr. Shupak said, maybe our definition is changing. But the fact is that we see fewer and fewer of the patients who appear in that obligatory slide that everyone shows with the severe, destructive pustular and cystic acne. There are still some of those patients around but I think that care is now being directed toward people who have either long-term acne or who have scarring acne.

I personally think that those patients deserve this level of care after they have failed other conventional therapy. I think it would not be very difficult to alter this to be more reflective of what is going on and provide both physicians and patients with maybe a higher degree of comfort than this very telegraphic description affords.

DR. LUMPKIN: Just as an answer, I would like to remind the Committees that under the FD&C Act our indications and usage have to be based on data from adequate and well-controlled trials. I think the point that Dr. Shupak is bringing up is that perhaps the interpretation of severe has gone through an evolutionary process. I would submit that if you seriously wanted us to consider changing the wording of the indication in such a manner, it would vary substantially from the data upon which the indication was granted, and that it could be argued that we would need adequate and well-controlled trials, that a different patient population was, indeed, being affected in that manner as opposed to the

anecdotal feelings that people have about what the general use of the drug is.

So there is a bit of a difference in an I&U from adequate and well controlled trials versus its general use in the patient population.

DR. SCHLESSELMAN: Dr. Lumpkin, are you suggesting that a drug which is effective for a severe form of the disease would be less effective for a moderate form of the disease?

DR. LUMPKIN: No, I would not suggest that but I think you have to remember that it is based on two elements, and that is the efficacy and the safety. I think when you are bringing in a risk-benefit ratio, it could be brought up again that you have a different ratio in a more moderately affected patient population, particularly in a drug where safety seems to be the issue and not efficacy. I do not doubt its efficacy but we have to look at both elements of the equation.

DR. CHAMBERS: Wiley Chambers, with the FDA. Just a point of clarification, the actual studies that were done for original approval -- there were several studies done -- and some of them were on severe recalcitrant forms. There were other studies that were done that could be used within labeled indications that supported just use of severe or various forms of cystic acne. So there were several studies

done. They were not all on severe cystic recalcitrant.

DR. SCHROETER: Any other comments? Dr. Tschen?

DR. TSCHEN: I would like to ask how much impact the intervention program had. I would like to know or hear again, once the intervention program is stopped, does the Company anticipate any increased incidence of pregnancy exposure or is there any indication that it will continue to be the same?

DR. ARMSTRONG: I would like to make sure I understand the question. Are you suggesting that we would plan to stop the pregnancy prevention program?

DR. TSCHEN: The three branches of enrollment that you had will continue? Is that correct?

DR. ARMSTRONG: The intention is to continue the pregnancy prevention program. We do not intend to discontinue it.

DR. NIEBYL: I think he was asking whether you were going to do it by phone or by mail since the data seem better by telephone. Wasn't the pregnancy rate lower in the telephone arm?

DR. ARMSTRONG: The numbers were different. I will ask Dr. Mitchell to address that question.

DR. MITCHELL: The survey is intended to continue for as long as the pregnancy prevention program is ongoing. We have observed an absolute difference in the pregnancy

rates among women followed up by telephone versus mail. Those have not even approached statistical significance at this point. What we would plan to do, in concert with our advisory committee with Roche and with FDA, is to consider alternative, perhaps mid-ground interventions if it does turn out that, indeed, the phone arm is entirely more effective than the mail arm. But I think it is premature at this point to make that assumption.

DR. SCHROETER: It might be appropriate at this time to ask the Hoffmann-La Roche group to reiterate the questions that they had for the Committees earlier. You had three questions that you wanted us to address and I think that they have to do with labeling. Therefore, it would be appropriate to address them at this time.

DR. ARMSTRONG: That is correct. The first one is, would use of urine pregnancy tests be acceptable as an alternative to serum pregnancy tests as a baseline procedure, with the understanding that we would expect those urine pregnancy tests to be done by the practitioner in the office as opposed to being given to the patients to be done at home?

The second one is, any recommendations that either of the two Committees might have on how to increase efficacy of the contraceptive program?

The third one is should the labeling be modified to recommend that the prescription be given to the patient only

at the onset of the menstrual cycle?

DR. SCHROETER: Do I hear comments from the Committees regarding these three recommendations?

DR. HANEY: You can give the patient a prescription whenever you want to. She will fill it whenever she chooses. There is not a pharmacist around who is going to ask her when her last period was. So that is crazy. You can give them recommendations. You can have it on your prescription pad. You can do whatever you choose. But she will elect to fill it whenever she wants to and, as you heard, she will take the pill when she chooses to as well. So education is the key. I do not think you can enforce that.

DR. SHUPAK: As far as the urine pregnancy test, I think it is a reasonable alternative to the serum pregnancy test, although I am not sure that the average dermatologist is going to want to start running pregnancy tests in his office because then you have the whole issue of quality control and responsibility for performing a laboratory study, and so on and so forth. But I have no objection to making it either/or.

DR. NIEBYL: The real issue is an issue of sensitivity of the pregnancy test. Why don't you speak to that?

DR. HANEY: Yes, I think you are going to get increasingly urine tests that are going to be sensitive enough to within a week of missed menses to always virtually

be positive. Right now, you have to be a little tricky about the time of day when it was collected. It has to be done by a method that -- you are exactly right -- will not be done in a dermatologist's office writing a prescription once or twice a month. That is crazy. An obstetrician will do that numerous times per day and can afford the effort to do it.

So I would still probably urge some very sensitive and effective test that does not require a practitioner to put in their office a test that, for practical purposes, they cannot run. So right now it does not make a difference whether it is urine or blood but just done in the right place.

DR. NIEBYL: You just have to find out from your hospital what the sensitivity of the pregnancy test is done either way. You can get very sensitive urine pregnancy tests. You can also get very insensitive pregnancy tests that are not positive until a week after the patient misses her period. You need the kind that is positive at the time the patient misses her period or before and there is a whole host of different ones. I do not think it is fair to lump all urine pregnancy tests together in that regard. If you have a very sensitive one, yes, it is as good as serum.

DR. ROY: We could perhaps just recommend that either a sensitive pregnancy test, at the level of less than 50 mmIU/mL, or a quantitative serum pregnancy test should be run and --

DR. NIEBYL: But does it have to be quantitative?

DR. ROY: Yes, maybe semi-quantitative. Most of the serum tests that are semi-quantitative I guess are around 15 mmIU/mL. But either one of those could be done, whichever is available.

DR. SCHROETER: Do the Committees feel that that should be a part of the labeling? The labeling now specifies a serum pregnancy test.

DR. NIEBYL: You would have to look at the data.

DR. MCGUIRE: We are really talking about two things: We are talking about who does it and what we do. Let's deal with the kind of test that is done now. It was my understanding that the thermometer type chromatographic test was very sensitive and was adequate. But that is, unfortunately, something I do not know a whole lot about. So the other half of the Committee has to say if it is sensitive enough. If it is, then I do not think there is a problem.

The other thing that is a little bit confounding is that many of these patients are going to be getting blood tests anyway. So I do not think we should eliminate the serum test because in some cases it is going to be more convenient to bundle in the serum ACG analysis with the cholesterol and triglycerides etc. But if the other half of the Committee says that the urine chromatographic tests that are commercially available are as sensitive as the serum,

then I would propose including that, but not excluding the serum because in some circumstances it may be more convenient to use the serum.

DR. MINUS: I thought we were supposed to be talking about the issue of labeling. It seems to me that we have very sophisticated labeling already and we are still having birth defects. I do not see that increasing the labeling is going to make any difference. We have many patients who cannot even read what is on the label. So changing it is not going to make any difference. I see from the Slone report that the average years of education is 14 years. What about the patients who have 5 years of education who require Accutane? What difference is the labeling going to make to them?

So if we are going to ask ourselves about the labeling changes, I do not feel that labeling is going to make any difference.

DR. LUMPKIN: In answer to that, I would like to say that we ought to remember that the labeling you see here is basically professional labeling. It is not worded or intended to be labeling for the patient, other than the informed consent that is in this particular label. There is labeling, as you are well aware, that is patient-oriented labeling. That is another issue altogether. But just from the FDA's perspective, we have always considered the labeling

that you see for this particular product to be professional labeling and oriented at the practitioner primarily.

DR. BARBO: I would like to raise the issue of giving the patient the prescription only after she has had a normal menstrual period. If you give the patient the prescription and then tell her to take it afterwards, she will fill it and start. When we hear that a number of patients were already pregnant, they may have had a serum test done that is not reported back to them, or they think their period will start. So if you could change that, it would prevent a number of pregnancies I think.

DR. DAVIDSON: I think it is important to education the patient but patients vary on when they get prescriptions filled. You know, depending on the particular set of motivations or convenience, or whatever --

DR. BARBO: Or money.

DR. DAVIDSON: -- or money. I do not think timing the giving of the prescription is going to be the critical issue.

DR. NIEBYL: Because even if you give it after this month, who is to say about next month? You have to make sure that they are effectively using contraception not just this month but for however long the course is going to be.

DR. BARBO: It would be one more finger in the dike, that is all.

DR. NIEBYL: Right. But certainly the screening initially is important too. I think probably for the initial screening a pregnancy test will work. For subsequent therapy you need contraception.

DR. BARBO: But if you give a patient a prescription going out the door and she gets her pregnancy test later, she already has the medication.

DR. NIEBYL: Your point is well taken. In other words, link giving a prescription to the negative pregnancy test. Do not send the test to the lab and write the prescription and then wait for the test to come back in the mail from the lab when she has already had a week of treatment. That could be done. You could make sure that the test is negative before you give the prescription out.

DR. BARBO: And every month she gets her next prescription after you know that she has had a period, not just give her the prescription.

DR. HANEY: Dorothy, a lot of people do not live very approximate to their doctors. They cannot keep coming back to the physician for more prescriptions --

DR. BARBO: He can still call his prescription in.

DR. SCHROETER: In reading the labeling in the black box, it says a negative serum pregnancy test within two weeks prior to beginning therapy. It is also recommended, in parentheses, that pregnancy testing and contraceptive

counseling be repeated on a monthly basis. To encourage compliance with this recommendation, the physician should prescribe no more than one month's supply of the drug.

That is implied in what you are saying but it is not spelled out specifically. Are you asking that this be specifically spelled out?

DR. BARBO: Yes. I do not think some physicians do that.

DR. SCHROETER: How would you recommend changing the wording?

DR. BARBO: That the prescription not be given to the patient until there is a report of a negative pregnancy test or the patient has had a subsequent period.

DR. NIEBYL: In other words, that the monthly renewal of their prescription be dependent on either reporting of normal menses or a negative pregnancy test.

DR. SCHROETER: Then in tandem with that: ... will begin therapy every month only on the second or third day of the next normal menstrual period.

DR. BARBO: That is correct.

DR. SCHROETER: Because if you do not say that, it implies that it is in the initiation of the therapy.

DR. BARBO: I did not mean to exclude that.

DR. SCHROETER: I know you did not but I am bringing attention to it because it is important. Dr. Stern?

DR. STERN: I do not wish to address the issue of how the initial prescription should be given, but with respect to subsequent prescriptions after the initiation of therapy, assuring whether or not menses has occurred or there has been another negative pregnancy test will do nothing to reduce isotretinoin exposure or decision-making with respect to what should be done with those exposures.

I can understand the debate about screening before initiating therapy. But we have seen that even brief exposure, once it has started, can be accompanied by birth defects. The data are very clear on that point. Therefore, having the woman back, ensuring menses and repeat pregnancy tests will not reduce the incidence of isotretinoin exposure, except as it changes women's behavior in terms of going back. If they have been taking it for 28 days and they come back and you get a positive pregnancy test that day and they have been taking it up to that day, they have still been exposed. So only when you are starting therapy should you think about these strategies.

DR. NIEBYL: But they have only been exposed for the two weeks after conception.

DR. STERN: That is correct and there are data that show that that is accompanied by a substantial risk of a birth defect. That is sufficient exposure by our data.

DR. SCHROETER: Only one or two days of therapy,

actually, have been reported as producing --

DR. NIEBYL: Yes, but I would argue that that is not the correct timing. I do not argue that two or three days of therapy is bad but I would argue that it should be at least at the time of organogenesis. Maybe the individual from the Teratology Society can help me, but I would say that you would have to be within the critical period.

DR. ARMSTRONG: In fact, we have data on exposure during the first two weeks following the last missed --

DR. NIEBYL: Oh, following the missed menses, yes.

DR. ARMSTRONG: Well, actually at the time, and the risk is still 25 percent of having significant malformations even if the drug is stopped at the time of the expected next menses.

DR. STERN: Excuse me, you must remember that although the drug is relatively rapidly cleared, if you took it for two weeks from conception to expected next menses and stopped it, if you were so regular that you knew you were a day late, which, of course, is not typical but let's say, more likely, were four days late, and still had one week to clear it, you are now almost a month post-conception.

DR. NIEBYL: I guess the point is that it is still better to have taken it for five days than for five weeks. But maybe it is just as bad to take it for five days.

DR. SCHROETER: Dr. Barbo, does that change your

position on this?

DR. BARBO: No, I am trying to prevent the woman from getting it at all if she could be pregnant. That does not change it at all. I am trying to stop that very thing from happening.

DR. NIEBYL: No, but we are talking about the monthly pregnancy test business.

DR. BARBO: Well, if she does not have a period, you have at least caught it. True, you will not catch all of them but you have a better chance of her not getting pregnant in the next cycle. But it is not going to stop all of them. The first one is the most important.

DR. SCHROETER: Yes, we agree on that. But in subsequent menses if you do have a pregnancy test and it is positive, in 25 percent of the cases you have already caused birth defects.

DR. BARBO: I did not ask for a pregnancy test every month. I recognize some of that.

DR. NIEBYL: But the labeling does.

DR. SCHROETER: The labeling does and that is what I called your attention to.

DR. BARBO: I do not think it is happening though.

DR. NIEBYL: The argument then is that the pregnancy test should be done a week after conception. It should be done three weeks after the last period because at that point

if you stopped it, it would clear -- I mean, if you are going to do it once a month at all, you should do it earlier is what you are saying, at a time when you can really use an extremely sensitive test and perhaps avoid exposure in a critical period.

DR. ARMSTRONG: Our concern in asking about pregnancy testing is under a scenario in which that would increase the number of patients who were treated before starting therapy. If doctors could do a test in the office that would test a higher percentage of patients, we might identify some patients who are pregnant before they start their medication.

DR. NIEBYL: In other words, the patient who would refuse to get a blood test but would get a urine test?

DR. ARMSTRONG: Yes, you could ask a patient to provide a urine sample, measure that, get an answer immediately and make a decision. Also the cost of a urine pregnancy test is substantially lower where that is a concern. In fact, there is a letter to the editor in a recent issue of Clinical Chemistry, by Dr. Immanuel Emancipator, I think, from NIH, suggesting that the current labeling for Accutane, specifically citing Accutane, was, in his opinion, not logical because urine pregnancy tests are much cheaper, much more easily obtained and might provide as much information.

He cites an earlier study that he had done where a

large number, nearly 1000, simultaneous urine and serum specimens were obtained. The urine specimens were tested by junior high school students in a university lab, with supervision but done by junior high school students, nonetheless, and there was concordance in all but 4 instances. In the 4 instances, it turned out that in 3 cases the urine pregnancy test was accurate and the serum pregnancy test was incorrect, therefore, recommending that urine pregnancy tests would be a reasonable alternative assuming you are using monoclonal antibodies, an ELISA and a sensitive assay, and so on.

That was really the basis for our question. If that is a reasonable presumption, having that as an alternative where this type of office urine pregnancy test might be done.

DR. HANEY: But the real question is not that. The real question is how many dermatologists will have urine tests in their office?

DR. ARMSTRONG: I think that is a realistic question. But if there is the option for some, whether it is one percent or ten percent --

DR. HANEY: No argument, but just say sensitive test. That is all you have to say. The doctor can choose if he wants to collect a urine sample in the office or get blood in the office and send it to a lab that will do it. I am