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P R O C E E D I N G S

DR. HULKA: We are ready to start the June 2 meeting, the second day of our meeting of the Fertility and Maternal Health Drugs Advisory Committee to the FDA. I would like to start by recognizing two of our members for whom this is the last meeting. They have been wonderful people for us to work with in their professional competency, their advice and their hard work on this Committee; also their excellent "colleagueship". I want to mention them to you, Dr. Paul McDonough and Dr. Paul Manganiello. If you would like to say a few words, we would appreciate it.

DR. MCDONOUGH: All I can say is that being on this Committee has been an exercise in humility considering all the complex issues that we have had to deal with and, of course, the opportunity to interact with some very wonderful people. Thank you.

DR. MANGANIELLO: I would like to second that, especially the interaction between the Committee members and the information that was disseminated by the FDA with the various presentations over the last couple of years. I think I can honestly say that I am going to be leaving this Committee receiving much more than I really contributed. I would like to thank the FDA, Dr. Corfman and all the staff who have made my four years here really enjoyable. Thank you very much.

DR. HULKA : We thank you and we will miss you both. The next thing is a matter of announcement. I think we have our dates straight now for the next three meetings. So take these down. It is still October 26 and 27 of 1989. That is the next meeting. Then it is February 22 and 23 of 1990 and June 24 and 15 of 1990. If there are any problems, be sure and let Dr. Corfman know because we will be trying to stay with those dates.

We will now start the open public hearing. We have a representative from the Public Citizen.

PRESENTATION BY DOUGLAS L. TEICH

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

I would once again like to thank the FDA for an opportunity to state our views on this important issues. This morning I will continue where I left off yesterday and outline our views on the use of bromocriptine (Parlodel) for the suppression of lactation.

Yesterday we heard presentations seriously questioning the need for pharmacologic suppression of lactation. Bear in mind that in 1980, when the FDA approved bromocriptine for this indication, the Agency assumed that this use was justified and, therefore, its analysis aimed to demonstrate that the drug was superior to the other agents, for example

PACE and Deladumone, being used for this purpose at the time.

It is in this context that I address first the lack of efficacy of bromocriptine and, second, its disturbing safety profile in view of the indication for a benign and self-limited condition and, third, the regulatory history of the drug.

Efficacy -- bromocriptine has only limited efficacy when compared to placebo. As FDA's Dr. Vanaja Ragavan pointed out last year in her review of the original NDA submission for this drug, 24 individual studies were submitted, with 19-30 patients per study and, therefore, only 7-15 patients per study arm. Lack of uniformity of protocol was apparent. There was tremendous variation in the rating criteria for engorgement and lactation and variation, as well, by the person doing the rating and in the use of ancillary measures such as breast binders.

There were only six placebo-controlled studies in the original submission, of which two were double-blind. Most of the studies were highly flawed by a failure to follow patients for a full month postpartum so as to evaluate rebound symptoms .

In the study number 48, for example, patients were followed for only 14 days. At day 7, 62 percent of the treated patients were free of secretion and congestion, which rose to 69 percent by day 14. Thus, 31 percent of treated

patients were still symptomatic after the recommended 2-week course of therapy, no better than the results of placebo studies demonstrating that some of 8-33 percent of women have severe or prolonged discomfort. Furthermore, this study did not even attempt to address rebound phenomena.

In the placebo control arm of Dr. Niebyl's study of TACE, fewer than 10 percent of women required an analgesic, and significant symptoms had resolved in 90 percent by day 8. Of course, these women do not develop rebound lactation. All studies that followed bromocriptine-treated women past the end of the 2 weeks of recommended treatment revealed significant rates of rebound, as high as 71 percent in one study.

Dr. Ragavan concluded last year that because of rebound, bromocriptine merely delays lactation to the third week in many cases. Her concerns echoed those of the original medical officer who criticized the submission for "the paucity of true placebo patients . . . the propriety of the investigators comparing estrogens given for 7 days with Parlodel given for 14 days, the incomplete information on rebound in some studies".

Unfortunately, the solution to this problem in 1980 was to approve a 14-day course, without adequate assessment of the frequency of rebound lactation thereafter. That is how we have ended up with a 14-day treatment for a condition which normally resolves in 90 percent of women by the end of

the first week.

In light of this lack of data supporting efficacy, I wish to make several criticisms very briefly of Dr. Walstatter's presentation yesterday. First, despite what he said in his comment that the drug should never be used routinely, and despite the Committee's recommendation a year ago that the drug should not be used routinely for lactation suppression, it clearly is used routinely as there are many hospitals where there are pre-written, xeroxed scripts where the patient's name merely has to be filled out, and there are also routine orders that have to be just ticked off to give the patient routine bromocriptine.

As the Committee realized yesterday, the statements on hospital availability of the drug are ridiculous, given that the drug is available for several other well-known indications .

Finally, the study that Dr. Walstatter presented yesterday was very flawed in at least six respects. First, invitation of patients by letter, which clearly can select a population; second, lack of random assignment to the two groups; third, there was no placebo control; fourth, the question of a blinded telephone interview -- I think he sort of said up here, at the microphone, that the interview was blinded but I was not sure; and the final comment is the question of length of therapy. It was not clear to me whether

the patients were treated for 14 days or 21 days, which is certainly in the labeling and is certainly done. If the patients were treated for 14 days, then an interview 19-20 days out may be too early to pick up rebound. If it is a 21-day course, it is certainly too early to measure rebound. Finally, it was not clear whether or not questions were even asked to assess the extent of rebound.

Safety -- last year this Committee heard a vigorous debate on the safety of bromocriptine for lactation suppression. I fear that we are all a year older but not any wiser when it comes to this issue. The eagerly-awaited answers from the ERI study may be undermined by the flaws in that study and the Committee will be left, as it was in the case of the estrogens, with a judgment call.

In the summary basis of approval for this drug, the frequency of so-called minor side effects was outlined. These included, of 271 women across the trials, 77 (28 percent) with blood pressure drops of greater than 20 mmHg, with 14/ 77 (5 percent of the total) experiencing a drop greater than 40 mmHg. This well-described phenomenon may have improved somewhat with the labeling change that the drug should be given no sooner than 4 hours after delivery, although this has not been well documented. In addition, 62 women (22 percent) reported one or more other side effects, such as headache in 8.5 percent; nausea in 8 percent;

dizziness in 7 percent; vomiting and rash.

We must ask once again, given the benign, self-limited condition for which this drug is prescribed, whether we can justify causing patients these other forms of discomfort. In fact, the number of women with significant side effects from the drug, not including those having rebound lactation after the treatment is stopped, is equal to or greater than the number who would have had marked discomfort from untreated lactation which, as we heard yesterday, can be managed conservatively.

I will not dwell on the suggestion of serious life-threatening adverse reactions associated with bromocriptine which have arisen during the postmarketing surveillance of the drug, I am certain that we will be hearing more about such events as seizures, strokes, myocardial infarctions and acute psychotic reactions, later today.

I only wish to update the number of reports of these rare and serious events. By our count, there are now eight cases of myocardial infarction in the setting of postpartum lactation suppression with bromocriptine. We have been notified of 4 additional cases since the June, 1988 update and we have asked that these be reported to the FDA. As of November of 1988, there have been 10 reports of stroke, of which at least 2 were fatal; 29 reports of seizures, some followed by permanent necrologic impairment; and 15 cases of

acute psychosis, all in association with this drug.

According to the FDA's Epidemiology Branch, since the June, 1988 meeting of this Committee, there have been 35 ADRs for bromocriptine, including 10-15 of serious consequence. I believe Wendy Nelson will update you on this later on.

It is clear that, fortunately, these remain very rare events. It is just as clear that it requires an extremely large epidemiologic study to test the statistical significance of their association with bromocriptine and even permit causal inference. Studies like the ERI study, with only enough statistical power to detect a 5-fold increase in the risk of stroke, would probably be insensitive to small increases of risk of myocardial infarction or of acute psychosis. As we know, the ERI group did not search their data base for adverse outcomes other than seizure or stroke.

The point is that this Committee will not solve its regulatory quandary through an epidemiologic study because this is not fundamentally an epidemiologic question. Even if a large study defined the attributable risk of stroke, heart attack, or psychotic reaction as less than 1/10,000, we are left with the same question: Is any incidence of such serious side effects acceptable when the condition for which the drug is prescribed is brief and self-limited and the drug itself is of such unproven efficacy?

Finally, a brief regulatory history -- I am sure that Dr. Corfman, of the FDA, will review this subject thoroughly. I only wish to mention some highlights. As we know, bromocriptine was approved for the suppression of Lactation in 1980. By February of 1983, the FDA had become aware of a number of serious side effects and, in August of that year, asked Sandoz, the sole manufacturer, to change the Labeling in accordance with regulations to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. This change was not made until December, 1984, 22 months after the FDA first voiced its concern.

In February, 1987, after a review of the ADRs, the FDA once again requested Sandoz to make a label change, listing uncontrolled hypertension as a contraindication to the use of the drug. In addition, the Company was also asked to include the increasing number of reports of hypertensive crises, strokes and myocardial infarctions, which had occurred since the last label change, in 1984, and to send a "dear doctor" letter alerting all obstetrician and family practitioners to the health risks accompanying the postpartum use of the drug. In April, 1987, Sandoz agreed.

However, an informal survey of ACOG members attending a meeting, in November of 1987, revealed that only 1/10 committee members asked recalled having received a "dear

doctor" letter. In January, 1988, it was not clear who had received this later, some 8 months after the Company vowed to send it. The FDA once again asked Sandoz whether physicians, other than ACOG fellows, had been notified of the health risks of this drug.

At last year's meeting of this Committee, Dr. Corfman commented that on April 1, 1988, Sandoz had sent a copy of their warning letter to everyone on a mailing list provided by ACOG. Thus, a full year had elapsed during which thousands of physicians and patients were unaware of serious risks associated with bromocriptine.

I believe that this history reminds us that only rigorous regulation of pharmaceutical manufacturers, rather than voluntary compliance schemes, is necessary to protect the public's health. Remember that according to the National Drug and Therapeutic Index, some 53 percent of all prescriptions written for bromocriptine in the U.S. were for suppression of lactation. According to the analysis by Wendy Nelson, between 480,000-940,000 women are receiving this drug each year, at a cost of more than $30 per 2-week course, generating revenues of 12-14 million dollars annually. These economic realities alone make it highly unlikely that Sandoz will volunteer to remove this indication from the bromocriptine approval.

In summary, you have heard the evidence on the

question of need for the pharmacologic suppression of lactation. I believe you will learn more about bromocriptine's lack of efficacy. The high incidence of less severe side effects, in the face of the drug's marginal efficacy, was itself sufficient cause to promptly withdraw this indication from the NDA approval for the drug. The growing awareness of life-threatening ADRs, such as strokes and MIs, makes immediate withdrawal of this indication imperative. Thank you.

DR. HULKA: Thank you. Does anyone else from the floor want to make a comment or does anyone have a question? We have no other formalrequeststo speak at this time.

(No response)

We will now close the open public hearing part of the meeting. We will go on to Dr. Phil Corfman, of the FDA, who will present on Committee recommendations and FDA actions concerning the use of bromocriptine for the prevention of postpartum breast engorgement.

PRESENTATION BY PHILIP A. CORFMAN

(Slide)

DR. CORFMAN: I have two slides and I will simply talk through the slides. In April of 1977, this Committee was asked to review the use of bromocriptine for this indication, as well as other indications. At that time, the Committee did approve bromocriptine for other indications but

they said, quote, "it does not feel that there is as yet sufficient evidence to support the use of bromocriptine for the suppression of postpartum lactation".

By February of 1980, the sponsor had provided enough evidence to convince the FDA staff that approval was warranted. My view is that times have changed and that we have a different perspective now on the use of this drug and also the impact or importance or value of the efficacy data that was provided at that time.

By 1982, the record shows that the medical officer who was responsible for this drug for this indication recommended that the label include warnings of possible adverse reactions. That was an internal recommendation.

By the next year, May of 1983, the Agency met with the sponsor and asked that the label include these warnings that have already been referred to. The sponsor was not exactly forthcoming. So the FDA took upon its own initiative to issue in the Drug Bulletin, which goes to practicing physicians, an article on possible adverse reactions.

(Slide)

In 1987, three years later, the Agency sent a letter to the sponsor asking that the label be changed to reflect these adverse reactions, possible adverse reactions, and that a letter be sent to all physicians who may prescribe this drug.

Again the sponsor was not particularly forthcoming. So in April of 1987, this Committee had a meeting scheduled to discuss this issue. After the meeting was scheduled, the sponsor met with the Agency and agreed to change the label and to send the letter. So the meeting was cancelled.

Then by July of 1987, the Agency accepted the text of the letter and the label change and reminded the sponsor that the letter should be sent to all members of the American College of Obstetricians and Gynecologists. The spokesperson for the Public Citizen has referred to that.

So because of the continued reports of adverse reactions, and because of a concern within our group about the use of this drug, we brought the issue back to the Committee last year, in June of 1988. We addressed very briefly what we had spent a lot of time on yesterday, that is, the need for such a drug which, I must say, is a rather unique issue to ask a Committee to discuss. From my perspective, usually you do not question whether a drug is needed for cancer, heart disease or infection. There it is used perhaps for a quality of life indication. The Committee was asked to address that issue yesterday and answer the questions.

But there was a study that was reported in progress last year, the ERI study, and the Committee elected to defer the discussion of the use of this drug for this indication

until today, when it has a chance to consider the ERI study.

That, very quickly, is a review of what has happened and that is all I have to say.

DR. HULKA: Questions? Jim?

DR. SCHLESSELMAN: Dr. Corfman, couldyouexplain why the FDA felt the matter of indication for use of bromocriptine was sufficiently important to bring to the Advisory Committee in 1977, but apparently did not bring this issue before the Committee to advise on whether the indication should be approved with regard to the 1980 approval? I infer from your presentation that that was a staff decision, made without the advice of the Committee. I am just curious why something like that happened.

DR. CORFMAN: Well, your function, as you know, is to advise us on questions that we elect to bring to your attention, unless you call us and say you want to discuss something. But you are advisory to the Agency and I can simply answer that, Jim, by saying that it was not felt sufficiently suitable for Committee discussion during that time.

It was brought to the Committee in 1977 because we have a policy of asking Committee advice on new drugs for a new use. It is almost a mandatory requirement. For instance, at the last meeting you discussed Norplant partly for that reason.

I would just answer your question by saying that we did not feel that warranted Committee discussion until last year.

DR. HULKA: Thank you. Dr. Rarick, from the FDA, will speak on efficacy of bromocriptine for the prevention of postpartum breast engorgement.

PRESENTATION BY LISA RARICK

(Slide)

DR. RARICK: We will begin our review of efficacy with the mechanism of action of bromocriptine for anybody who is unaware of the drug. It is a dopaminergic inhibitor of prolactin secretion. As we know, prolactin increases during pregnancy. The levels are given here. In late pregnancy there is a very high level. The reason women do not start lactating before delivery is that during pregnancy they have high levels of estrogen and progesterone and at the time of delivery, since the estrogen and progesterone levels decrease, their inhibitory effect on the breast is withdrawn and women can lactate. After delivery, if there is no stimulation, levels usually decrease back to normal by the seventh day.

(Slide)

Original approval, as you saw, was in the 1979-1980 range. The original approval for the supplemental application for this indication included 24 studies in 748 patients. As you can see, that is approximately 20-30

?atients per study. There were 12 U.S. and 12 foreign studies .

The sponsor claimed 8 double-blind U.S. studies to ɔe considered their 2 studies upon which their claim of :fficacy was based.

(Slide)

I am going to review these 8 studies briefly. The :irst 4 studies were actually dose-range studies; they were ıot comparison studies. There were 119 patients in these ;tudies, divided into various dosage groups. Since we are .ooking at the 5 mg per day group, we will look at that group ıere. In the 119 patients, of those in the 5 mg a day group, .hey had 70 percent effectiveness in preventing congestion .nd secretion but, again, no comparison group. They say that :ngorgement was rare and they have no rebound information.

(Slide)

The fifth study is a comparison study. It is .ouble-blinded placebo versus Parlodel, with 15 patients in ach arm, for 14-day therapy of 5 mg a day. As we can see, here are a few problems with this study. The placebo had 7 ropouts due to failure treatment, leaving 8 patients in that roup. The Parlodel group had 2 dropouts due to headache, ɔlurred vision and dizziness, leaving 13 patients in that ırm.

In the remaining placebo patients there was 30

percent engorgement. In the remaining Parlodel patients there was 8 percent engorgement. Congestion and secretion in the placebo patients was rated to be slight, and in the Parolodel patients it was rated to be absent to slight.

There were 4 side effects in the Parlodel group, including 3 patients with decrease of systolic blood pressure greater than 40 mmHg. Here we have no rebound information available.

(Slide)

The last 3 studies were comparison studies again but not versus placebo, instead, versus ethinyl estradiol. They were double-blind. Parlodel was given for 14 days; ethinyl estradiol for 7 days and placebo for the last 7 days.

They claimed overall similar efficacy between the 2 groups . In the Parlodel group, for example, they stated engorgement at 10 percent; congestion and secretion, absent or slight. They do report 24 percent of side effects in their 41 patients on Parlodel, including dizziness, nausea, vomiting and headache.

Of these 3 studies, 2 of them did have rebound data available in 30 of the patients, showing 70-87 percent rebound of secretion after 14 days of therapy.

(Slide)

In the overall review of the supplemental application of the total 24 studies, the FDA mentioned 3 things:

rhey felt that 14-day treatment of 5-7.5 mg per day was considered effective. In those studies where data were available, rebound was found to be between 47-87 percent of subjects for all the 24 studies. Their third note was regarding the side effects. They report 112 symptoms in 62 of the 271 U.S. patients.

In the 5 mg per day group, there were 124 U.S. ?atients, 25 percent of whom reported at least 1 side effect, with the major players here being dizziness, headache and nausea and vomiting.

They do make special mention of the hypotension, which is 22 percent of the U.S. subjects in the 5 mg per day group.

(Slide)

They do include a table of hypotension. It is a .ittle bit busy. This is-actually the number of patients in each category, with the dose on the left. As you can see, when they discuss hypotension, they mean anything greater than a 20 mmHg drop in systolic blood pressure, and it can range up to 59 mmHg.

(Slide)

To look at efficacy from the literature, as we did yesterday on our other drugs, we will review. 8 articles. Most of these are double-blinded studies from the 1970s.

(Slide)

This shows that they are double-blinded. The first three are versus other drugs; the fourth is a placebo comparison.

Varga's study had 20 subjects in the Parlodel arm, showing engorgement in the Parlodel group of 5 percent and rebound of 20 percent in the Parlodel group. This was a 9-day therapy with Parlodel. With DES they had 40 percent rebound in this study. So they did feel that they had efficacy compared to DES.

Brun, in 1973, had only 9 patients in their Parlodel arm. It was not blinded. It was 15-day therapy with no post-treatment follow up.

Utian was a study versus TACE with 16 patients in their Parlodel arm. There were 80 percent of those patients without any symptoms and rebound of 6 percent.

Walker is a placebo study, in 1975, with 32 patients in each arm. They could show significantly better scores on lactation, engorgement, pain and tenderness, but only on days 4 and 7 of their 14-day study. Rebound was 10 percent in the Parlodel group.

(Slide)

Dewhurst, in 1977, again is a placebo study, which is double-blinded. I am counting here the number of subjects who finished the study in the Parlodel group of 17. They started out with 26. It was a 4-week study, all by question-

naire. They gave 18 days of therapy. As you can tell from 26 to 17, there were many dropouts. They did feel that there was a significantly better result with Parlodel during their first week but after the first week there was no difference between the Parlodel and placebo groups.

Steemstrup, in 1977, had 20 patients. At day 7 they evaluated patients and again at day 14. At day 7, they found 80 percent effectiveness in their Parlodel group but they do note 40 percent rebound.

Yuen, in 1977 again, was a global assessment by the nurse who gave "more effective than TACE". They did notice significantly decreased blood pressure on day 2.

Shapiro was a binder study versus placebo study so it was not blinded, in 1984. They had 25 patients and had the results that bromocriptine was more effective in their first week but the binder being more effective on the third week of their 3-week study. There was rebound of 24 percent in the Parlodel group, with 32 percent side effects in the Parlodel arm.

(Slide)

Yesterday you mentioned can Parlodel be used for symptoms? There are various scant data in the literature that address this issue. I will just touch on that briefly. None of them were double-blinded or placebo-controlled. It is difficult to answer this question, depending on how you

Look at the need issue, whether a patient was given Parlodel for symptoms or given nothing.

But in the literature we do have this 1977 study of 36 women with engorgement. They were treated with 1 dose of 2.5 mg of bromocriptine. Of course, these were also women that were not going to continue lactating. Of these, 28 patients said they had relief with 2 dose and 6 patients had another dose with relief and 2 patients continued to be engorged after the first day. It is difficult to know what that really tells us.

(Slide)

Brun, in their study also included 5 subjects who were already lactating. Again, these were subjects who were Lactating and decided not to breastfeed on day 6-19 post-?artum. They were given bromocriptine and all stopped Lactating. One wonders if they had any controls if they would have stopped lactating as quickly. It is hard to say.

(Slide)

There are 2 more articles that refer to the use of bromocriptine after lactation was begun. There were 10 ?atients in the Walker study with discomfort on day 3. They treated them with 5.0 mg per day and had symptoms diminish rapidly. Again, that is hard to interpret.

Varga, in 1972, just quotes that in several patients -- no number given -- bromocriptine was found to be

effective not only when administered immediately postpartum but also when lactation was established.

(Slide)

The Committee members have the current label now before them. In terms of looking at the current labeling in case you do decide to change the labeling in some respects, I just wanted the audience also to know what is currently in the label.

There is an indications and usage section in the physician label that mentions prevention of physiologic lactation. In the physician label there are warnings, including symptomatic hypertension, stroke, seizures, severe headaches, visual disturbances, acute MIs and hypotension.

(Slide)

The physician label goes on with a section called precautions . Under physiologic lactation, it includes hypotension, hypertension, headache and CNS toxicity.

(Slide)

And in the information to the patient section, although this is not a patient information pamphlet, it includes under adverse reactions, physiologic lactation side effects, hypotension and the serious reactions as already mentioned. Then there is a dosage and administration section.

In conclusion, we reviewed many studies from the

original approval and from the literature. Bromocriptine, depending on how you interpret the results, and by various different interpreters' analyses, I am sure it can be felt to be possibly effective, both theoretically and by the different interpretations of these studies.

In light of our current questions of need and possible safety concerns, we again ask the Committee for recommendations in use of this product.

Thank you. Any questions?

DR. HULKA: Questions from the Committee? Questions from the floor?

(No response)

It seems a bit early to break since we just started. We do have the ERI study, Epidemiological Resources, Inc. study, on which we heard just a few preliminary words a year ago. We have now received the full report of this study and if the presenter is ready at this time, Dr. Rothman, to present the study, we would be ready to hear it.

PRESENTATION BY DONNA FUNCH

DR. FUNCH: I am Donna Funch. I worked with Dr. Rothman on the study. I am going to start by giving you a brief history of the study and I will describe the study design. Dr. Rothman will present the study findings.

(Transparency)

This is going to reiterate a little bit what you

have already heard. In 1980 bromocriptine was approved for use in the United States as a lactation preventor. In 1984, the Food and Drug Administration Drug Bulletin announced that the labeling of bromocriptine was being revised to reflect reports of postpartum hypertension, stroke and seizures associated with the use of bromocriptine.

At that time, the announcement was based on 17 case reports. There have been fewer than 100 adverse reaction reports for these 3 outcomes since 1980. These reports are difficult to interpret since bromocriptine has been used by millions of women in the United States since its introduction.

For this reason, ERI was asked by Sandoz, in 1986, to conduct an epidemiologic study to examine the relation between bromocriptine and these possible adverse outcomes. The protocol for this study was submitted to Dr. Sobel and Faiche (phonetic), at the FDA, and after minor modifications, was judged to be acceptable.

Hypotension was excluded from study since its less severe nature and was inconsistently documented in the medical records. The other outcomes, puerperal strokes and seizures are relatively rare events, with the risk of stroke estimated between 0.25/10,000 births and 0.4/10,000, and the risk of seizure estimated at 1.9/10,000 births.

Since hundreds of thousands of pregnancies would have to be examined to identify a reasonable number of cases

for study, we determined that the only feasible design was a case control study based on hospital records. Even using this approach, relatively few strokes were expected.

In planning the study, the issue of study size was discussed between Sandoz and the FDA. In a letter to Dr. Westlin, at Sandoz, dated July 29, 1986, Dr. Sobel addressed the issue of study size and wrote as follows: In reference to the proposed study to determine whether an increased risk of stroke and seizure exists for patients taking bromocriptine for postpartum lactation suppression, we believe that a study that is capable of detecting a relative risk of 2 would be the most acceptable to us. however, we recognize that a study that can determine tne existence of this level of risk would be impractical because of the very large population base of deliveries that would be required. We, therefore, will accept a study that will provide power to detect at least a relative risk of 5.

Using the guidelines suggested by Dr. Sobel, and assuming a ratio of 8 controls for each case, it was calculated that a study with 40 cases of seizure would yield a power of 98 percent to yield a relative risk of 5. A study of 10 cases of stroke would yield a power of 68 percent.

It was agreed by Sandoz, ERI and the FDA that a study should be directed primarily at evaluating the risk of seizures and that whatever stroke cases could be detected

within the population would also be studied.

The study proposal anticipated identifying about 40 cases of seizure and 10 cases of stroke. In fact, as you will see in one of the later tables, we ended up with 43 cases of seizure and 10 cases of stroke.

(Transparency)

This figure outlines study procedure. We have 3 data sources. Medimetrik is a private organization that maintains computerized data on a number of hospitals across the country. Maine Health Information Center is a non-profit health data consortium that collects data from hospitals in Maine. Saskatchewan Health collects hospitalization data on all residents of Saskatchewan.

Cases in the study were between the ages of 15-44 and experienced a seizure or stroke during the hospitalization for delivery or within 30 days from the date of delivery. Controls were matched to cases on age, hospital of delivery and month and year of delivery.

(Transparency)

Table I summarizes information on the data sources, including the number of ICD-9 codes we had available for case identification. The births occurred between 1981 and 1986. Our matching target as a maximum of 8 controls per case. You can see the total number of cases and controls for each data source in the bottom portion of the table. We had a total of

228,779 births from 58 hospitals. From that, we were able to identify 43 cases of seizure with 319 matched controls, and 10 cases of stroke with 77 matched controls.

(Transparency)

This figure outlines data collection procedures. The first step involved record review of all potential cases. These were women with ICD-9 codes suggesting both delivery and a stroke or seizure.

These records were reviewed and if the event was judged to be postpartum, the record was abstracted. If the neurologic event occurred during a readmission, the abstracter abstracted data from both the readmission and the delivery Hospitalization.

These data were evaluated by Dr. wolf, the neurologist. He had no information at the time he made his evaluation as to whether or not the case had used bromocriptine. Once the cases were determined, we identified controls for those cases and their data were also abstracted.

(Transparency)

You can see the types of data that we collected in this figure. I just want to comment that when at all possible, we xeroxed all information in the medical records relevant to medication administration. We also xeroxed all information relating to the necrologic event for the cases. Overall, we were able to obtain at least some xeroxed

nformation for 95 percent of the study subjects.

(Transparency)

Table IV -- 1 might note that the table numbers go y the same numbers that are in the final report, for those f you who have a copy -- just reviews the time of events in 'elation to delivery by data source. Most of the events did ccur within 48 hours of delivery. The data sources did vary omewhat by their ability to identify cases through readmis-ion. Maine Health Information Center and Saskatchewan Health ould identify readmission and Medimetrik could not.

Dr. Rothman will now present the study findings.

PRESENTATION BY KENNETH J. ROTHMAN

(Transparency)

DR. ROTHMAN: You have the report. The report gives the results of very many analyses that we did but not all of them. We conducted quite a few analyses during last summer and we presented the most important ones in the report. Even so, there are too many results to present now. Since you have the report, I am just going to summarize some of the highlights.

First I am going to talk about the seizure findings. Since we do not have very much to say about stroke, I will just present the small amount about the strike findings at the end.

This table, Table V from the report, gives the

crude data for seizure findings, bromocriptine and seizure. This is a 2 X 2 table. It is a very simple display of the data but it turns out to be quite an apt summary of the findings for the relation of bromocriptine and seizure.

As you can see, we had 43 cases of postpartum seizure and 4 of these cases had received bromocriptine. We had 319 matched controls and 37 of them had received bromocriptine. If we calculate the relative risk estimate, which can be calculated from this 2 X 2 table by taking 4 times 282 and dividing that by the product of 37 by 39, we get an estimate of the relative risk here of 0.78. The relative risk would be 1 if there is no effect. The fact that it is 0.78 indicates that the bromocriptine users, the women who had received bromocriptine, are estimated to be at 22 percent lower risk of seizure than the women who did not get bromocriptine.

That is only an estimate and it has a certain amount of statistical instability associated with it. You can get an idea of that from the confidence interval. We present a 90 percent confidence interval which is, for me, quite consistent. I always present 90 percent confidence intervals . As you can see, it goes from 0.29 to 1.87. So this gives you an idea of the range that we have for the possible values for the relative risk that these data are consistent with.

This is just a crude summary. We did many other analyses looking at confounding factors and subgroups. I am going to present some of those. But in the end, we think that this is quite a fair summary of our overall findings for bromocriptine and seizure.

One important analysis to conduct in a study where there is individual matching of controls is an analysis that epidemiologists often refer to as a matched analysis. It is an analysis that takes into account the matching procedure and corrects for biases that may be introduced by the fact that the controls are selected with regard to certain factors that could be related to the exposure.

We corrected the matched analysis. The results of that are in the report. The relative risk estimate that we got from the matched analysis was similar to this. It was 0.68 and it was close enough to thins that we inferred from that that it would not be important for us to keep the matched sets intact through the rest of the analysis. This is a fairly standard approach in epidemiologic analyses. It was not terribly surprising since it happens quite often. But it enabled us to conduct stratified analyses that are a lot simpler to present. So that makes my job a little easier today.

(Transparency)

This is another 2 X 2 table, again, a crude summary

of the data. But in this table the exposure definition has been changed slightly. Exposure is now restricted to a slightly narrower time window. The time window is the interval of time that extends no more than 7 days before the event of seizure in this slide that the case experienced. So if the seizure occurred on day 15, for example, unless there was some indication that there was continuing exposure at least out through day 8, we would count the individual as not exposed, unless there was exposure in that 7-day window.

We calculated exposure for the control subjects according to the time window that would have applied to the case that the control was matched to because we did not have an event that occurred for the control.

Changing the exposure definition in this way eliminated 1 exposed case. We have now 3/43. It eliminated corresponding proportion of exposed controls. The relative risk estimate remained 0.78. So narrowing the time window did not seem to make a difference in the effect estimate.

(Transparency)

This is one example of some of the analyses that we conducted to control for confounding factors. One of the confounding factors we were interested in controlling was Hypertension. This is a slide that indicates control of diastolic hypertension.

The method that that we are using to control here

.s the method of stratification. We divided data into :ategories of the potential confounding factor. We calculate :he odds ratio within the categories and if it is appropriate, :hat is, if it does not vary excessively, we can combine :hese estimates over the strata into a summary estimate.

That is what we have done in this slide. The iumbers within strata are somewhat sparse but the summary :stimate is not really any less stable statistically than :rude data because it does represent the information sum- iarized over the three strata.

Several subjects (14) had to be put into a category)f uncertain because we did not have information on diastolic)lood pressure. We did have information on the others. We livided them into the 2 categories you see, according to the Definition on the slide, and the summary estimate was a :elative risk of 0.75, very close to the finding that we had vithout controlling for confounding by diastolic hypertension, vhich indicates that this was not a confounding factor in our inalysis.

(Transparency)

Another factor that we were interested in as a)otential confounding factor was seizure history. In this analysis we defined a history of seizures as either a mention in the medical record of a seizure history or an indication that the woman was taking anticonvulsants. So either of

these was taken as an indication of seizure history.

We still had quite a number of subjects for whom we did not have definite information one way or the other about seizure history. We had to class these individuals into a third category that we labeled "uncertain".

I would like to point out in this slide that if you look at those subjects who did have information about seizure history, if you look first at the cases, you see that among 29 cases that had information about seizure history, 27/29 had a positive history of seizures -- 27/29, a very high proportion of these seizure cases for whom we had information, did have a history of seizures.

Among the controls the distribution is also very striking, but in the opposite direction. Only 4/146, for whom there was information one way or the other about seizure history, had a history of seizures.

I suspect that among the uncertain subjects, if we really knew the seizure history distributions, it would also be quite different for the cases and the controls.

One thing that this tells us is that seizure history is an overwhelmingly strong risk factor for the presence of postpartum seizure. But that fact alone does not mean that it would be a confounding factor in an analysis. It means that it would be something important to look at. But when we stratify by seizure history, as best we can in this slide,

and then summarize the findings over these strata, the relative risk estimate is still 0.78, the same as the crude finding. So for this analysis, it did not seem that seizure history was a confounding factor. Attempting to control for it did not seem to make any difference.

(Transparency)

We looked at the presence of preeclampsia as a potential confounding factor. It was not. The summary relative risk was 0.78. We were also interested in whether or not women who had signs of preeclampsia would somehow be a susceptible subgroup to some hypothetical effect of bromocriptine or seizures. So we were interested in the relative risk estimate in the stratum labeled "preeclampsia" but, as you can see, the relative risk estimate from that stratum was, in fact, O. So there did not seem to be an especially susceptible subgroup.

(Transparency)

In this table we conducted a similar analysis, looking at the effect of type of anesthetic. We divided the anesthesias received during delivery into three categories, none, general and other. Again we found that there was no confounding, or no substantial confounding by type of anesthetic . There was a special interest in this case in women who had received a general anesthetic to see if this was an especially susceptible subgroup but, again, this was a

stratum that had a relative risk estimate of 0.

I should emphasize that these stratum-specific relative risk estimates are based on relatively few subjects. So they have a substantial amount of statistical instability. But the best estimate that we can make, for example, for general anesthesia in this analysis is that there does not seem to be any special effect of bromocriptine in that subgroup.

Those will suffice, I think, for the analyses demonstrating our control of confounding variables. We also conducted analyses, and I will show you one as an example in a few minutes, where we used multivariate modeling to control simultaneously for several confounding factors. The results of those analyses were very, very similar to the results of these stratified analyses and I prefer to present the stratified data since you can actually see the frequencies.

In the next couple of analyses I am going to present findings that are restricted to certain types of the cases, subsets of the cases, that represent seizures that might be considered a subgroup of all the seizures that we identified.

(Transparency)

In this example we singled out seizures that were generalized seizures, thinking that this would be a subgroup of more severe seizure cases and, therefore, might be worthy

of special interest. Actually, 31/43 seizure cases experienced generalized seizures. For this subgroup the relative risk estimate was also around 0.8. So it did not seem that there was a specially different phenomenon occurring in this subgroup.

(Transparency)

This table examines the subgroup of cases, 11, that we defined as late-occurring seizures. In this analysis it was defined as cases that occurred more than 72 hours after delivery. We pursued this topic, in part, because Bruce Stadel, of the FDA, called us and told us that this ought to be a group to be examined; it was of special interest. I think it was because of an appearance that stemmed from some of the adverse reports that the FDA had received.

Among these 11 cases, we do have some small numbers here but the risk estimate was 2.86. This was the first relative risk estimate you have seen in my presentation that shows an effect greater than 1, the first positive effect as opposed to a negative effect that we found.

(Transparency)

That, in itself, was interesting. But this crude estimate, it turns out, was confounded by seizure history. When we attempt to control seizure history for this subgroup of cases -- and this gets a little bit dicey since the numbers do get quite small within this stratum, but since we

know that seizure history is an overwhelmingly strong risk factor, it is essential in any analysis to make sure that it is under control. In this case it did look as if there were some confounding by seizure history because when we attempted to control for it, the effect estimate is small. It is still above 1.0; it is 1.6 but it is considerably different from 2.86.

In any case, we were still interested in this particular subgroup because of the positive finding. I should say that we explored different definitions of late-occurring cases . We also divided late occurring from early occurring at 48 hours. We repeated these analyses and we got the same result. We also used 96 hours and we got the same result. We took 72 after looking at the distribution of time and we thought that that was a reasonable cutting point to separate out a group that looked like early cases from late cases. But the actual division did not seem to matter very much, that is, where the boundary was drawn.

We were interested in this finding since it was the only positive effect that we had found up to this point and we wanted to explore it a little. We did explore it in one particular way. We noticed that there were 3/11 cases of late-occurring seizures that had been exposed to bromocriptine. We found in one of our analyses that the apparent effect -- I should emphasize that in epidemiologic terms that

this would be considered a very modest effect, with a relative risk of 1.6. That is not to make a statement about the public health implications of that finding, but in terms of the strength of association, ordinarily epidemiologists would describe this as a weak association. This association seems to be concentrated within an unusual subgroup of subjects, the subgroup of subjects who had received ergonovine after delivery.

(Transparency)

If we stratify by ergonovine, and now we are stretching the data I think to the limits since we have a fair number of small frequencies in this display, but we see that the relative risk estimate among the stratum where women received ergonovine postpartum is 49, whereas, in the other stratum is was 0.88. So the effect among late-occurring cases does seem to be concentrated in this subgroup that received ergonovine, although that is not a statement that I can make as a definitive one because the numbers are small and there is a fair amount of statistical uncertainty with this finding.

On the other hand, the discrepancy between these two effect estimates in these two strata is remarkable and that is why I am remarking upon it.

(Transparency)

This is the only table I am showing you that is not

in the report. Although we did mention this particular finding, I did not put the table in the report. But it is just to show you the same table as you saw on a preceding slide but now for the early-occurring cases.

There are two reasons to look at this. One reason is that if you look at the summary estimate, summarizing the bromocriptine effect as estimated among these early-occurring cases across these 2 strata, you see that the relative risk estimate here is 0.24, strongly negative. It would correspond in the other direction to a relative risk of about 4. What this shows is that if you take a small subgroup of cases and you find a positive relation, where the totality of cases overall have a modest negative association, then for the remaining subjects there would be an even stronger negative association and that is what we find here.

I think more important though in this slide is the information about the relation between bromocriptine and seizures among those who received ergonovine and experience early-occurring seizures.

I think it would have added to some biological plausibility to find that the apparent interaction that we saw for late-occurring cases also existed for early-occurring cases . I think this would have sparked much more interest on my part in pursuing a biological explanation for this finding. But , indeed, we do not see the same pattern. We

see a relative risk estimate of 0 here. Although quite unstable, I admit that, it, nevertheless, does not seem to point in that same direction and this detracts somewhat from the biological explanation.

There are other reasons to be unsatisfied with a biological explanation for the apparent interaction that I showed you. The main one is resting on pharmacodynamics. It seems that ergonovine will be cleared from the body in a natter of hours. Of the 2 cases of seizure that have exposure to ergonovine and to bromocriptine and later experienced a seizure, 1 of these seizures occurred 5 days after the ergonovine and the other occurred more than 20 days after the ergonovine was administered. So in terms of current knowledge, we would have a lot of difficulty explaining that biologically. So it may well be just a peculiarity of the data that does not have a biological explanation but it was certainly interesting enough to report.

(Transparency)

This analysis was an attempt to focus on what we thought might be a low risk subgroup of cases. We excluded those seizure cases that had experienced a seizure late in the prepartum period or that that had preeclampsia. The remaining cases (28) might be considered a low risk subgroup.

The reason to focus on a low risk subgroup is that very often when there is an effect hidden in a body of data,

the effect can be magnified by focusing on people who have a low baseline risk because, since we are measuring the relative increase in risk here, if the baseline risk is low, then the relative increase might be large if there is a certain added risk from the drug, for example. So I think it is a fairly standard approach to take a look at low risk subgroups to see if there is an effect that happens to be strong in that group.

Of course, this assumes that there would not be any interaction. So this is not the only kind of analysis one would do. But when we did this, we found that in this low risk subgroup the effect estimate was not any larger than in the crude. In fact, it was slightly smaller.

(Transparency)

This is the one example I am going to show you of the multivariate analyses that we did. This was a logistic analysis. There are two types that one uses in case-control studies, conditional, which keeps the matched sets intact in the analysis, and ordinarily it would be appropriate for matched data, except that we had already demonstrated that it was not necessary to keep the sets intact. We did conditional logistic analyses and got results very close to these results from the unconditional model which ignores the matching.

In this model we have an effect estimate for bromocriptine which is 0.68, close to what you have seen for

1 ıe crude data. We also put in a separate term indicating
2 :posure to TACE or Deladumone. We had some exposures to
3 ıese agents as well in our study, although not as many as to
4 'omocriptine. The effect estimate for TACE or Deladumone
5 ıs considerably lower than that for bromocriptine.
6 I think the interesting part of this multivariate
7 ›del are the findings for seizure history. We did this
8 ıalysis to look at the components of seizure history. I
9 .id there were two components to seizure history in our
10 .rly analyses, mention in the medical record and use of
11 .ticonvulsants . We wanted to see how those two components
12 'edicted risk. We were partially interested in that and
13 .rtially interested in controlling them separately.
14 We found that positive seizure history had a
15 ılative risk estimate from this multivariate model, which is
16 ry strong, 183. That is statistically very "unstable but
17 so quite high. Current anticonvulsant use had a relative
18 sk estimate that was also quite high, 9, although nowhere
19 ar as strong as the estimate for seizure history.
20 At first that surprised us but we had a chance to
21 .ink about it and we appreciated the fact that anticon-
22 lsants are, in general, to prevent seizures and that is
23 'obably responsible for the difference between the effect
24 timates for anticonvulsants and seizure history with no
25 ıntion of anticonvulsant use.

(Transparency)

The last slide that I will present is a slide showing you the stroke data. This is a 2 X 2 table summarizing the stroke findings. We had 10 stroke cases and 1 of these cases received bromocriptine. We had 77 matched controls; 1 control was exposed to bromocriptine. The relative risk estimate here is high, 8.4, because the relative risk is estimated by taking 1 times 76 and dividing that by 1 times 9.

We do not think this table is very informative and I would like to tell you why. Despite the large effect estimate, you can see right away that the effect estimate is very unstable. That is part of the reason but that is not the entire reason.

This was actually a disappointing finding for us. From the great imprecision in this table, one might infer that we really did not have a lot of information on stroke, although last year I was somewhat non-committal about it. I said that we do not know exactly what we would learn but it was worth looking at it. We were disappointed here. The disappointment stems from an anomaly in these data that contributes to the great imprecision of this estimate. The anomaly is that the proportion of controls that had taken bromocriptine in this 2 X 2 table is exceptionally low, 1/77.

Our seizure study, which had a much larger control

series, the proportion of controls who received bromocriptine was about 12 percent. From data that the FDA has presented from general hospital populations, 12 percent looks like a number that is quite typical. In fact, all of the information that we have leads us to believe that 12 percent is about what one should expect.

Had we gotten 12 percent in the control series in this 2 X 2 table, we would have had an effect estimate near 1 and it would also have been somewhat more stable than this estimate. But we do not feel it proper, naturally, to discard our control series just because we do not like the results but we are a little bit concerned that it does not fit in with what we would expect based upon other data.

We thought about this and we tried to explain it. We thought it may be, because these controls were matched to this particular series of cases of stroke, that there were characteristics of these stroke cases that led to a small proportion of exposed controls. We examined all of the characteristics of these cases that might have been related to exposure to see if that could account for it. But nothing that we examined could account for it.

So in the end, we did not really have a good explanation for why we got this anomalous result for this control series. It may not even be completely just to call it anomalous. This is the result that we got. But it does

ot square with our other findings.

If we think about the meaning of the data, now that e look at what we actually got, I do want to point out that f we make the usual statistical assumptions that would be pplied to a 2 X 2 table, if we apply the usual statistical model, which is the hypergeometric model, and we consider the margins of the 2 X 2 table to be constant, to be fixed, and hat the only thing that might vary is the body of the table, hen we realize that for the number of exposed cases in this able there are only 3 outcomes that we could have gotten tatistically. We could have gotten 0, we could have gotten or we could have gotten 2, if we take 2 as the fixed number n the total in the bottom row.

So with only 3 outcomes, getting 1 exposed case is he intermediate outcome. If it had been 0, the relative isk estimate would have been 0. This was by far the most ikely outcome, given these margins for this 2 X 2 table. If t had been 2, the relative risk estimate would have been nfinity, an extreme association in a positive direction as pposed to an extreme association in a negative direction. 'he only intermediate outcome was the one that we actually bserved, which, under the null hypothesis, had more than 20 ercent probability.

So in the end, we just thought that there was not uch that we could learn about strokes from these data and we

were disappointed in that. We thought that if there were a serious interest in learning about the relation between bromocriptine and strokes, it would require an epidemiologic study that was targeted on strokes, rather than targeted on seizures.

That is all I am going to present. I would be happy to answer questions.

DR. HULKA: Questions? Yes, Paul?

DR. MANGANIELLO: I have two questions about the way you controlled for the cases and the controls. Why did pick 95 mmHg diastolic and 160 mmHg systolic rather than, for instance, taking a conservative approach by saying 90 mmHg diastolic and 140 mmHg systolic?

DR. ROTHMAN: That question has actually come up several times. I am glad you asked it. We had a very simple rule for choosing 95 mmHg diastolic and 160 mmHg systolic. We had assembled an outside advisory committee to advise us on how to conduct the study. We asked them for the analysis of hypertension -- what would you recommend to us as the cut-off values? That is what they told us. So that is what we pursued.

The reason that they gave us those values is because these are the cut-off values that had been used in large epidemiologic studies, such as Farmingham's.

DR. NIEBYL: In other words, your advisers were

nternal medicine people, not obstetrical people? Because 40/90 are the usual obstetrical numbers that we use in postpartum patients.

DR. ROTHMAN: I believe that we also reanalyzed the ata using different numbers and it did not change the esults. But we reported those values for the reasons I gave ou .

DR. MANGANIELLO: In your final report, on page 24, ou say that we do not know how long patients took bromo- riptine but the usual course is for 2 weeks, which would ave ended bromocriptine exposure 8 days before a seizure. hen in some of the tables, such as Table IV, in the 3 data ases that you use, the only data base that had seizure cases eyond 22 days was the Saskatchewan value. If you assume hat patients take bromocriptine for 14 days, then everybody ould fall into the range of exposure.

DR. ROTHMAN: I am not exactly sure of your question.

DR. MANGANIELLO: On Table VII all the patients all within the guidelines of 21 days.

DR. ROTHMAN: Remember, on Table IV, not all of hose cases are exposed cases. This is just the timing of he events since delivery. Only some of these people ever eceived bromocriptine. Does that help you?

DR. MANGANIELLO: Could you just explain Table VII

a little better?

DR. ROTHMAN: I will try. If you look at Table V first, Table V gives you exposure any time following delivery and before the seizure for the cases. For the controls, any time following delivery and before the time of the seizure for the matched case. So this is the maximum amount of exposure that we could measure under any reasonable set of assumptions, 4 cases and 37 controls.

In Table VII we have eliminated some of the people who were counted as exposed in Table V because the exposure did not come within the 7-day period before the seizure. There was only 1 case where that occurred.

DR. MANGANIELLO: There are 3 cases and 28 controls who were taking bromocriptine. If you have assumed that 14 days is the usual course of therapy and you are taking 7 days for Table VII of drug ingestion, then everybody would fall within -- I do not see how you got from Table V to Table VII.

DR. ROTHMAN: The people in Table IV represent all the cases, many of whom never received bromocriptine at any time, 90 percent of whom never received bromocriptine.

DR. NIEBYL: Those are cases, not controls.

DR. ROTHMAN: There are no controls on Table IV. You have to remember that 90 percent of people on Table IV never received bromocriptine at any time.

DR. NIEBYL: They had seizures but did not have

bromocriptine.

DR. MANGANIELLO: I see. I am sorry, okay.

DR. ROTHMAN: I am sorry that was not clear --

DR. MANGANIELLO: That is all right.

DR. ROTHMAN: Is there another question?

DR. SCHLESSELMAN: Dr. Rothman, would you please comment on Table XXVIII?

DR. ROTHMAN: Is there any particular aspect that you want me to comment on?

DR. SCHLESSELMAN: You were remarking about the relationship between bromocriptine and ergonovine and its apparent association with late-occurring seizures, no evidence of their joint association with early-occurring seizures in your presentation of the stratified analyses. You did not comment on, say, Table XXVIII, which relates to all seizures, regardless of whether they were early or late occurring --

DR. ROTHMAN: Right.

DR. SCHLESSELMAN: -- in relation to the joint occurrence of these two exposures.

DR. ROTHMAN: This is a summary of the findings for all seizure cases. If you compare Table XXVIII with Table XXIX, you will see that the relative risk estimate for those who had joint exposure to bromocriptine and ergonovine, for the late-occurring seizure cases (Table XXIX) was very strong. It was about 20. But in the totality of the cases,

it is about 4.5.

My interpretation of that is that the interaction effect is concentrated in those late-occurring cases. As you saw from the stratified data that I presented before, among the early-occurring cases there does not appear to be any such interaction. That is my interpretation of the comparison of those two models.

DR. HULKA: I would like to ask you a question going back to page 12. This has to do with how subjects got into the study or who did not get into the study. Maybe you could repeat a little bit of this. I notice there was nothing in a visual display or table showing what we might call losses before the study starts. It is not immediately obvious how this could affect you results but it is always a potential for bias. So I am wondering what you did to evaluate, not only just the numbers of hospitals in each of these systems that did not cooperate and get into the data that you analyzed, but how that might have related to total numbers of deliveries, and numbers of deliveries in those hospitals that did not participate. Certainly, one can envision that some hospitals might have a greater propensity to this routine use of bromocriptine than other hospitals.

DR. ROTHMAN: That is certainly true. There was a very large winnowing process in the selection of subjects that actually got into the study, as there needs to be, among

the universe of all possible deliveries that we might have access to. I think we were first constricted by those data sources that were cooperative and would be able to provide Information to us. We eliminated hospitals that were not using bromocriptine at all because they were not going to contribute to our study. We also eliminated, as you probably read in the discussion, a promising data source that just was not going to provide enough cases to make it worth the administrative costs of getting that data source to cooperate with us. We had to train people at each site in order to abstract the records, and so forth.

So t here was that part of the process to get the set of cooperating hospitals. In Maine there were many small hospitals that we just did not include because it was too much effort to go to them and it was unlikely, we felt, that we could get a substantial number of individually matched controls from those hospitals. So there were many pragmatic issues in the selection process.

The concern epidemiologically would be if there would be a bias introduced by any of that selection and we did not see how that selection would alter the effect estimates that we were getting. Obviously, the process is related to the prevalence of Parlodel use. But that, in itself, as you know, would not present any problems of bias.

The next phase that might be of concern to you, I

think, would be, first of all, the identification of cases and, second of all, the identification of matched controls. In the identification of cases, our biggest problem was how to find them and, in particular, how to find all of them since some of the events that we were looking for might occur after patients were discharged.

That is why you may have noticed that in our report there was a fair amount of discussion about readmissions. In one of our data sources, in Medimetrik, we could not link readmission to the original hospitalization. For that data source we were only able to ascertain what we have described as early-occurring cases.

The Saskatchewan data source provided us direct information on readmission through record linkage. In Maine we were indirectly able to identify readmission through another source. We could scan the data in Maine and by matching demographic information we could find readmission.

So we think that we did miss some of the events that occurred in the hospitalized population through readmissions. That, in itself, again is not a concern as far as bias goes, as far as we can tell. But it is a concern possibly as far as the size of the study goes in that, otherwise if we had been able to find more of these cases, we my have been able to have a few more subjects that we could have analyzed. We could not think of a way in which the

readmission problem would have biased our study findings seriously.

The problem of identifying controls was essentially the same in this study as in any other study of individual matching. We set a target which was very high in the study, eight controls per case. The reason is because cases were limited and we wanted to get as much information from that limited case series as we could. So we wanted a large control series. We found that we could identify within our matching criteria eight controls for each case for most of the cases. But there were a few that occurred in relatively small hospitals in which there were not enough deliveries to find eight controls. We relaxed the matching criteria in a couple of cases and in some cases we just had to settle for fewer than eight.

I think that part of the process, the identification of the controls, is the part that potentially could have introduced a bias if Parlodel use were strikingly related to hospital size, for example, and we could only get eight controls, our target number, in big hospitals. That might have been a problem. But it should not have been a problem in matched analyses. It would only have been a problem in crude analyses. Since we got similar results in those analyses, we did not think there was any serious bias introduced by that either.

So obviously there was a lot of winnowing down in this study, as in any study, and it ought to be a subject of concern. But we could not theorize any important source of bias that would have done the thing that would have been of most concern, which is to eradicate a strong association between bromocriptine and seizures. Sorry to be so long-winded.

DR. HULKA: Other questions? Comments? It is now 10:45 and maybe we could take a 15-minute break --

DR. ROTHMAN: Excuse me, may I make one final comment --

DR. HULKA: Sure.

DR. ROTHMAN: -- just in relation to the remarks that Dr. Teich made this morning? I just wanted to say that since he put it on the record that it seemed as if ERI was somehow negligent in not searching its data base for other outcomes -- that is what he said -- well, that is just a simple piece of misinformation. These are not ERI's data bases, in the first place. ERI conducted a case-control study, which means that we first identified people who had selected outcomes. These outcomes were dictated to us; we did not choose them.

But to do the kind of study that Dr. Teich was describing, one would have had to do a completely different kind of study. One would have first had to identify a very

large series of women taking bromocriptine and then look at the outcomes. That was not the research design that we conducted, nor could one have conducted that within one order of magnitude" of the cost that this research was conducted at.

DR. HULKA: We will reconvene then at 11:00.

(Brief recess)

DR. HULKA: We will continue this morning's session with presentations. Dr. Tom Gross, of the FDA, will present a critique of the ERI study.

PRESENTATION BY THOMAS P. GROSS

(Slide)

DR. GROSS: Good morning. My comments regarding the ERI study will be limited to the following areas: quality of study design; quality of data sources; relative risk of early versus late onset of disease; and assessment of risk.

(Slide)

In terms of quality of study design, ERI appropriately chose case-control methodology for use in conducting these studies considering the rarity of seizures and strokes in the postpartum period. Their choice of data sources was appropriately considered but may have fallen short in an important aspect of case ascertainment. More will be said about this later.

Verification of cases and ascertainment of controls is appropriate. The potential confounding factcrs identified

For study inclusion seemed appropriate, as did the time windows for bromocriptine exposure.

Finally, the investigators' data collection procedures, training and quality control checks, presented in detail in their report, seem sufficient.

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The issue of the quality of data sources is really one of adequacy of case ascertainment. Data that address this issue were gleaned from the ERI report and are presented by source in several variables, namely, the proportion of hospitals recruited; the proportion of cases that were readmissions; the proportion of postpartum seizure and stroke cases that were late onset; and point estimates of relative risk for postpartum seizures. Due to small numbers of cases, data relevant to postpartum stroke are presented but the focus of discussion will be on seizures.

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Of the 3 data sources, only Saskatchewan Health had all potential study hospitals recruited. We do not know how hospitals not included in the study from the other two data bases may have differed from those included in terms of potential case and control characteristics.

As was noted by ERI, only Saskatchewan Health used unique and consistent patient identifiers that allowed for seemingly complete case ascertainment, including, and

importantly so, readmissions. No readmission could be identified through Medimetrik and, likely, only a portion through MHIC since, in this data base, readmission to a hospital different from the hospital of delivery had to be identified using matching demographic variables, a less precise method than using unique identifiers.

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Thus, 75 percent of all identified cases from Saskatchewan Health were readmission, compared to 35 percent for MHIC and O percent for Medimetrik. Unfortunately, the ability to identify readmission by postpartum seizure or stroke diagnosis or time of onset of illness, that is, early versus late, was not possible given the data that is presented in the report.

An argument was presented by ERI that the proportion of cases that were readmission for Saskatchewan Health was artifactually high since only 2 diagnostic codes, compared to several for the other data sources, were available for case identification. Thus, some events might not get coded during the delivery hospitalization but may on readmission.

However, considering the seriousness of postpartum seizure and stroke, it seems more likely that these events occurring during the delivery hospitalization would get recorded as one of the two diagnostic codes available. If so, then the proportion of cases that were readmission would

not be artifactually high.

Since it is probable that readmission cases are more likely to be late onset, one might expect that the proportion of cases that are late onset by data source varies in a fashion similar to readmission proportions.

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And they do, from 55 percent in Saskatchewan Health for the proportion of seizures that are late onset to 11 percent in Medimetrik. The number of stroke cases are too small to detect notable trends.

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If one proceeds to examine the relative risk point estimates by data source for seizures overall, one again notices a similar pattern to that proportion of cases that were readmission for late onset. This variability in relative risk est-imates may be partially explained by noting that the estimate for Saskatchewan Health data (2.86) corresponds closely to the relative risk estimate for late onset cases, as it should since the majority of its cases are late onset. The analogy is similar for Medimetrik and MHIC data.

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In summary, the variability in relative risk estimates parallels the variability in the proportion of seizure cases that were late onset and the proportion of

ases that were readmissions. Thus, the ability to identify hese late onset cases through readmissions is critical to he relevant risk estimate. The trend in these estimates hen suggests that case under-ascertainment in terms of the potential to identify readmission and, therefore, late onset ases may be related to bromocriptine use. If so, this would ias relative risk estimates to unity for no risk.

In considering this possibility, it is understood hat the readmission data in the report are not available by iagnosis or by time to onset, data which would shed light on he validity of the argument.

Given the apparent difference in the quality of ata sources in terms of recruitment of hospitals and ability o identify readmissions, it may be prudent to place greater eight on relative risk estimates from Saskatchewan Health han the other data sources. For this reason, any pooled elative risk point estimate, as that of 0.78 for overall eizure risk, may not best represent risk since it obscures hese differences.

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As the report notes, any attempt to interpret ausally the positive association for late onset seizures, hat is, a relative risk point estimate of 2.86, should ddress the negative association among the remaining early nset cases, that is, a relative point risk estimate of 0.25.

The report claims that "a reduction in seizure risk is consistent with reports of anti-seizure activity for bromocriptine in various species, including humans". However, this does not explain the increased risk noted for late onset seizures. As an explanation for this, the report notes that concomitant ergonovine exposure greatly increased risk for late onset seizure "whereas either exposure alone in the absence of the other did not appear to elevate risk for seizure at all".

However, as also noted in the report, the rapid clearance of ergonovine, with clinical effects lasting only up to 3 hours, is difficult to reconcile with seizure onset 5 and 25 days after receiving ergonovine in the 2 known exposed cases. Any attempt to explain such effects "reach beyond what is currently known about the biologic effects of ergonovine".

We considered other possibilities, mainly selection bias and delayed onset of seizures, in attempts to explain the apparent negative association in early onset cases. Although selection bias, without going into detail, did not appear to explain the negative association, delay in seizure onset introduced by bromocriptine might. Thus, if bromocriptine had such an effect, one would detect relatively more late onset and relatively less early onset seizures than expected if there were no such effect.

pertinent to this discussion is the question as to whether the early and late onset seizure cases differ qualitatively. The report notes that 10/11 late onset seizure cases were non-eclamptic, compared to 22/32 early onset cases. It could be argued that if the late onset seizure cases are, indeed, caused by bromocriptine, then one might expect them to differ in certain aspects from the non-eclamptic early onset seizure cases. This could be true despite the lack of association between bromocriptine and non-eclamptic seizures in general, as noted in the report.

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As predicted in the previous Advisory Committee hearing, the greatest limitation to these studies was the small number of cases identified. The rarity of the outcome and the infrequency of exposure made interpretation of the results more difficult. However, the findings relative" to seizure risk were somewhat informative, whereas the findings relative to stroke risk were predictably less so.

With regard to the latter, with only l/10 stroke cases and 1/77 stroke controls exposed to bromocriptine, the relative risk point estimate was unstable at 8.4, with a 90 percent exact confidence interval of 0.4-1.62.

As was true for the authors of the report, a reasonable explanation for the marked disparity in exposure prevalence to bromocriptine among controls in the two studies

cannot be offered. Suffice it to say, a larger study is needed to sufficiently answer the issue of the risk of postpartum stroke following exposure to bromocriptine.

It has been shown that the crude data for late onset seizures are most consistent, with an almost 3-fold increase in risk, with a range of possible effects based on 90 percent confidence intervals from a 21 percent reduction in risk to an almost 9-fold increase. Adjusting for seizure history results in a relative risk estimate still most consistent with an increase in risk of 61 percent.

In an attempt to interpret these data, it has been shown that the relative risk estimates for crude overall seizure risk vary by data source and that the variation may be linked to the ability to completely ascertain readmission cases. The best estimate may reside in that data source with full recruitment of its hospitals and seemingly complete case ascertainment.

Of equal concern that an explanation for the apparent negative association of early onset seizures with bromocriptine is the consideration of delayed seizure onset induced by bromocriptine. The corollary to this issue, that of a positive association noted in late onset seizures, was attributed in the report to ergonovine exposure in 2 of the only 4 seizure cases who used bromocriptine. Although this explanation stands on firm ground statistically, its biologic

pPlausibility remains to be shown.

In summary, the data are too sparse to assess the ffect of bromocriptine exposure on postpartum stroke but uggest an increased risk for late onset postpartum seizure ollowing bromocriptine use for lactation prevention. This uggested risk might be weighed against potential benefits. hank you.

DR. HULKA: Questions?

DR. MANGANIELLO: Can I ask a question of Dr. Rothman?

DR. HULKA: Maybe we will have questions here first nd then we can have a discussion.

DR. MANGANIELLO: Okay. Basically, it is about the uestion that you raised earlier about readmission to ospitals and the question that you are raising here also. I guess I am not certain why a different data base was not btained, such as looking at a particular outcome with eizures. There are individuals who have looked at outcomes y trying to look at, let's say, a health maintenance rganization or a third party carrier, like Blue Cross and Blue Shield. Dr. Jack Linberg has done that with prosta- ectomies . Can Dr. Rothman indicate if there was a problem in rying to generate data for this particular topic, utilizing data base which would kind of cross over different hospi- als?

DR. ROTHMAN : The answer is that we approached every data base that we knew about that might have information that we could use. There were certain requirements that had to be employed for us to be able to use it. The diagnoses had to be computerized. We had to be able to have access to the medical records and the data base had to be big enough to be worthwhile training abstracters to go in there.

For example, one of the data bases that we did approach was an HMO but we calculated that the number of deliveries in that data base were such that we would only have two or three cases from that entire source and it was not worthwhile.

So we studied all those data bases that could provide us with any reasonable amount of information. There was none that we omitted that could have added to our resources for this study. If we had heard of any others, we would have certainly used them.

DR. HULKA: Are there other questions of Dr. Gross?

DR. SCHLESSELMAN: Dr. Gross, with regard to your point about the apparently better case ascertainment in Saskatchewan, would you please comment about this in light of the reported rates of seizure by summary of data sources? If one looks in Table I of the ERI report, the seizure rate per 10,000 is reported to be 1.4 in Saskatchewan, as opposed to 1.8 at MHIC and 2.5 in Medimetrik. Of course, there might be

environmental or other factors in the population that account for some variability in the rates but the seizure rate, in fact, is lowest in Saskatchewan, where you are arguing that the case ascertainment is, in fact, the best.

DR. GROSS: I do not think those are mutually exclusive considerations. You can still have low seizure rates with good case ascertainment. We did look at those rates. They do not differ statistically significantly at the 0.05 level. So although they appear to be different, statistically they are not. But just because you have a low background rate, it does not necessarily mean that you cannot have good case ascertainment. It certainly makes it more difficult but I do not think it necessarily excludes the possibility.

If you look at the three data sources, Medimetrik did not identify any readmissions. I think that is a real problem in terms of coming up with a pooled estimate for the relative risk -- including a data source where you do not have any information essentially on readmission and, therefore, very little information on late onset disease, since it is most likely that readmission are linked to late onset disease -- I think that is the point I really wanted to stress . The best estimate may actually lie somewhere between MHIC and Saskatchewan Health. Assuming that we may be missing some early onset cases in Saskatchewan Health, which

would tend to lower the risk in that data base, and it is likely we are missing some late onset cases in MHIC, which would tend to increase that risk, so the overall true risk may fall somewhere in between those two data sources.

DR. SCHLESSELMAN: Could you please repeat for me the rationale which was raised for focusing on late onset cases, that raised this issue initially?

DR. GROSS: I cannot really expound on that fully. I was not around at the time. If there is somebody else that can?

DR. NIEBYL: I think it is a good question from the obstetrical point of view because patients who have seizures related to the pregnancy, such as eclamptic seizures, usually seize within the first 24-48 hours. So that would be a group that you could attribute to other causes. So looking at late seizures might be more likely to be associated with other factors.

DR. GROSS: You will also hear Wendy Nelson this afternoon concerning our spontaneous reports of seizures and strokes, as well as some other adverse events. If I am correct, the preponderance of the seizure reports, if not all of them, are late onset cases, that is, greater than 72 hours .

DR. NIEBYL: That is because that would be unusual. If a patient seizes within the first 24 hours postpartum,

especially if she is hypertensive and had preeclampsia, there are other explanations for that. Whereas, in a late onset seizure you would question whether there might be some other things going on.

DR. HULKA: Further questions? Yes?

DR. GRAHAM: David Graham, from FDA. Just to give you sort of an added perspective on what Dr. Gross was just saying, I am a neurologist by training, and with the late onset seizures, with most of the patients out of the hospital, you would probably expect 100 percent of those patients to be readmitted to hospital, or a very high proportion, especially if the woman had no prior history of seizures, the rule of thumb would probably be to admit that patient to hospital. So if you have evidence that you are not ascertaining those cases through a readmission mechanism, then you really cannot say anything about it. You are missing a whole universe. I think that is the point that Dr. Gross is trying to make. It ties in with the clinical mode of presentation of the disease as well.

DR. RAGAVAN: I just want to make one comment. In my review of the NDA folder, there is one question that has come up and maybe we can lay it to rest. That is, something called late onset eclampsia, which has been reported and has never been very well studied. It has been mentioned in the NDA folder many times. Dr. Niebyl, maybe you could clarify

for us what this is and whether it is associated with pregnancy so that we can lay that question to rest.

DR. NIEBYL: We do not know. But the vast majority of seizures attributable to preeclampsia occur within the first 24-48 hours. If a patient seizes a week or 2 weeks after delivery -- 1 mean some people could label that late onset eclampsia but I think most of the cases justify a thorough necrologic evaluation for something else being the explanation. I do not know exactly the answer to your question. Some people use late onset eclampsia to mean later than 24 hours. But still it is usually within 72 hours. So when you talk about 3 weeks postpartum you are talking about something that is very unlikely to be related to preeclampsia.

DR. HULKA: Other questions or comments for Dr. Gross? Is there any discussion of the study generally? Dr. Rothman?

DR. ROTHMAN: I would just like to make a couple of comments. First of all, I want to make sure there is no misunderstanding about one aspect of our study. It takes a long time to do an epidemiologic study. When this study was planned there was no interest that anyone ever voiced to us about late onset cases. The focus after the fact on late onset cases, after all the data were collected and as the analysis was already under way, was something we were having to accede to.

But to criticize a study design because the study design could not capture all the late onset cases, I think is a little bit unfair to us since this was something that had never been discussed by anybody when the study was planned. If we had planned it with this in mind, we certainly would have planned it somewhat differently or at least we would have considered that in the planning stage. So I want to make sure that it is understood that this was an issue that came up after the data were collected and not when the study was being planned.

The other thing I would like to say is that I am a little disappointed in the critique because I think that every one of the issues that was raised is discussed in our report. We put a lot of work into that and we tried to give you a balanced interpretation of the findings. Unfortunately, I think Dr. Gross just selected comments out of our report and gave it a different inflection. It sounds a little different coming from him than it would, I think, coming from me and I am a little disappointed in that because these are issues that we have discussed and considered.

I am a little wary of the concept that seems to have been presented that you can pick out a single finding or a subgroup finding and start to emphasize it and disregard everything else. I think you have to look at the whole picture and give a balanced interpretation to that. That part

of the critique was disappointing to me. That is all I have to say.

DR. HULKA: Well, those of us involved in epidemiologic research are certainly commend your report and study for the obvious work and care that has gone on to create this .

If we could go on to our first presentation scheduled for the afternoon, I believe Wendy Nelson, of the FDA, is in the audience and is ready to present her report on update on reports of adverse reaction to bromocriptine.

PRESENTATION BY WENDY NELSON

(Slide)

MS. NELSON: The purpose of my presentations to summarize the adverse drug experiences associated with Parlodel that are in the FDA spontaneous reporting system. I am going to summarize the adverse event reports received by FDA in 1988, and also provide an overall summary of the events reported over the past ten years, since Parlodel was first approved for prevention of physiological lactation.

Before I do this, I would like to take a few moments simply to describe the FDA spontaneous reporting system for those of you who may not be familiar with it and review briefly some of the limitations of spontaneous reporting.

The spontaneous reporting system, as the Committee

probably already knows, is a computerized data base that contains reports of suspected adverse drug reactions that are submitted by health professionals, pharmaceutical manufacturers and individual consumers. When a report is received by FDA, it is reviewed by a member of our Office, the Office of Epidemiology. The adverse events are coded according to a medical thesaurus and the report is entered into a computer where it can then be readily accessed.

This slide just lists some of the general limitations of spontaneous reporting, which are important to bear in mind as we look at the spontaneous reports. First, the information is often incomplete and we may lack adequate information to fully assess the relationship between the drug exposure and the event.

Second, suspected adverse reactions are underreported and although we do not know what proportion of adverse events are actually being reported, recent FDA-sponsored studies in a couple of states to study adverse drug reaction reporting suggest that only 1-5 percent of suspected events are actually reported to us.

Third, reporting may be biased by such factors as recent publicity about a drug, either in an article in a medical journal or in a newspaper.

Fourth, because we do not know what proportion of events are being reported, we cannot determine the rate of

event occurrence in the population using the drug. Therefore, we cannot estimate what proportion of women taking Parlodel are actually experiencing these events.

Finally, and most importantly, one cannot necessarily infer causality from an adverse drug reaction report. In evaluating the relationship between any exposure and event, one must always be alert to the possibility of confounding and that is the existence of some third factor that may be related to both drug exposure and the outcome. Common confounders may include the patient's underlying illness or concomitant medications.

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With these caveats in mind, we will turn to the reports themselves. What I did, I searched the spontaneous reporting system for all domestic adverse event reports in which Parlodel was given to prevent physiologic lactation. I reviewed only those events that had a serious outcome. By FDA definition, that is that the patient required inpatient hospitalization or died as a result of the event.

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This slide summarizes all of the serious events associated with Parlodel therapy for the prevention of physiologic lactation that are in the FDA spontaneous reporting system through 1988. I would like to point out here that year is the year the report was received by FDA and

entered into the system, not necessarily the year the event occurred. Sometimes the event onset and when the report is actually received by us can differ by a few years,

In the first column, 1979-87, the data are summarized for these first 9 years and these are the data that I presented to the Committee a year ago. The second column are the data just for 1988. I assume these are new data for the Committee. In the third column I simply totalled them all. In parentheses I have indicated the number of deaths. So for cerebrovascular accident there were a total of 18 reports and 6/18 died as a result of the event.

As you can see, necrologic and cardiovascular events predominate. In 1988, the only other events of note are 3 reports of postpartum psychosis. Then at the bottom I have listed 1 report of syncope, although when I spoke to the pharmacist who reported the event, he said they felt that this was a hysterical reaction. The only reason I included it here is because the young woman was hospitalized overnight for observation. But was felt to be hysterical.

So in summary, over the past 10 years, on the bottom line of the slide you see that there were a total of 85 serious reports of events that were attributed to Parlodel and there were a total of 10 deaths. So 10/85 died.

For the remainder of my presentation I am going to focus on the first 5 events, seizures, cerebrovascular

events, hypertension, myocardial infarction and sudden death.

(Slide)

Looking now at seizures, in 1988 there were 7 reports of seizures in women 18-36 years old. I have included in this group a woman who was thought to have developed seizures secondary to cortical vein thrombosis.

Three of the women were white; one woman was black; one was Hispanic and race was not specified for one. The seizures occurred between the fourth and eighth postpartum day and for all but one patient they were accompanied by severe headache. Six of the seven patients had taken Parlodel for three to eight days preceding the event and duration of Parlodel use was unknown for one woman. Six of the seven women were not preeclamptic by history. One woman reportedly developed edema during the latter part of her pregnancy but had an uneventful C. section and was discharged at 72 hours. This woman developed seizures on postpartum day six.

Information on underlying illness was available for five of the seven women. These five women were reportedly healthy and had no underlying medical conditions. Five of the seven women had received at least one other medication postpartum. Two women received Percocet; two received a nonsteroidal anti-inflammatory drug for pain; one woman received Sudafed. Five of the women recovered. Unfortunately, long-term outcome was unknown for two patients.

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This slide shows the distribution of seizures by days postpartum. On the X axis I have days postpartum, day 0 meaning day of delivery. On the Y axis I have number of cases. The 25 green boxes represent cases reported between 1979-1987. These were presented to you last year. The 7 orange boxes represent cases reported to us in 1988.

As you can see, cases occurred between 3-17 postpartum day, with a clustering between the 5-10 days postpartum. I have not shown on this slide 4 cases that were reported before 1988 whose dates of onset we could not be certain of. It has merely been reported that the event occurred in association with Parlodel but the date of the event was not specified.

Again, I should point out here that the reason we do not have cases before day 3 may reflect the fact that if cases are expected to occur during this time period, they might not be reported. Whereas, cases occurring after 3-4 days might be viewed as an unusual event and, therefore, be reported to us. So I think we have to bear this in mind.

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Turning now to cerebrovascular events, this slide lists the 10 cerebrovascular events that were reported in 1988 and their outcomes. I would like to acknowledge the assistance of Dr. Graham, in our Office, who is a neurologist

and who did review these with me.

I have listed the events as they were reported by the physician. We have sagittal sinus thrombosis, hemorrhagic stroke, stroke not otherwise specified, venus sinus thrombosis, cortical vein thrombosis and this is the woman who was included in the seizure group previously, subarachnoid hemorrhage, intracerebral hemorrhage and one report of transient ischemic attack. That is why I called it a cerebrovascular event. Three of the patients died and two survived but are severely disabled now. The two cases with an asterisk are literature reports from 1984 that were entered into our system this past year.

(Slide)

This graph shows the distribution of the cerebrovascular events by days postpartum. Again the X axis is ?ostpartum days; the Y axis is the number of cases. The green boxes represent cases reported between 1980-1987 and the orange boxes were reported in 1988.

If we were to include the young woman who had seizures and cortical vein thrombosis, she had her event on day 5. So there would be an additional orange box on day 5.

With the exception of the case that occurred at day), and as I recall, this woman had her event and died within 15 hours of delivery, the events occurred between 4-26 days ?ostpartum.

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The 9 patients who had cerebrovascular events in 1988 ranged from 22-38 years old; 4 patients were white, 4 were black and race was not specified for 1 patient.

Information on duration of Parlodel use was known for all but 1 of the patients. And 8 patients had taken Parlodel for 3-13 days prior to their event and all events occurred while the patient was receiving the drug.

Information on concomitant medication was known for 7/9 women; 5 women were not taking any other medications, other than Parlodel; 1 patient received acetaminophen and there was 1 patient with a history of hypertension who was taking Aldomet; 7/9 women did not have a history of pre-eclampsia. The 1 woman who had a transient ischemic attack was described as having mild toxemia by her physician on the basis of moderately elevated blood pressure and trace proteinuria. Also in this group there was 1 woman who had a 5-year history of hypertension. And 8/9 women had no significant underlying illnesses . The 1 woman who did have a 5-year history of hypertension also had sickle cell trait.

I would also like to point out that for the 1988 cases I was able to actually contact the majority of the reporting physicians who verified the information, as well as being able to give me more complete follow-up information. So history of preeclampsia and that kind of thing was

validated.

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In 1988 there were 3 reports of new onset hypertension in women ages 25-35 that occurred 2-10 days postpartum. None of the women had been preeclamptic. Hypertension was accompanied by severe headache for 2/3 patients. ?atient number 1 was a 25-year old black female who had no ıistory of hypertension and whose highest blood pressure recorded during pregnancy was 120/76. She presented to the emergency room on the 6th postpartum day with a blood pressure of 200/110. Parlodel was discontinued. She was treated with beta blockers and her blood pressure returned to baseline ir. 24 hours. Concomitant medications included only Darvocet and ibuprofen.

Patient 2 was a 26-year old while female who also ıad no history of hypertension and who received Parlodel for 3 days and on the 8th day she presented to the ER with a blood pressure of 200/120. She was hospitalized and treated with Nipride and recovered. The only other medication she was taking was Tylenol.

The third patient was a 35-year old woman whose baseline blood pressure was in the 120/60-80 range. After 2 days of Parlodel, here blood pressure was 140/100. She was also receiving a variety of other analgesics, Demerol, codeine, Tylenol, as well as antibiotics. Parlodel was

discontinued and her blood pressure returned to baseline within 2 days. She was not treated with any other antihypertensives.

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The remaining 2 events are 1 report of myocardial infarction and 1 report of sudden death. I will describe these very briefly. The first patient was a 22-year old black female who had an uneventful pregnancy and delivery. She began taking Parlodel on postpartum day 2. On postpartum day 10 she presented to the emergency room with severe chest pain and a blood pressure of 180/120. Cardiac catheterization revealed moderate stenosis of the left anterior descending artery, with no other evidence of atherosclerotic heart disease. The patient survived with necrologic deficits secondary to anoxia that she suffered during her cardiac arrest.

The second patient was a 25-year old white female whose only underlying medical disorder was obesity. The patient was described as having mild preeclampsia on the basis of moderately elevated blood pressure, moderate edema and trace proteinuria. She had an uncomplicated cesarean section and was discharged home on postpartum day 3. The physician stated that the patient had probably received Parlodel for 4 days postpartum with no other concomitant medications. On postpartum day 5, the patient reportedly

awoke from a nap, collapsed and died. On autopsy, she was found to have, and I quote, vascular changes consistent with sepsis, although no organism was ever identified. There were no signs of stroke or pulmonary emboli on autopsy.

So in summary, I have presented to you the serious adverse drug experience for Parlodel since it was first approved for prevention of physiological lactation. My conclusion this year is much the same as my conclusion last year. That is, there is no single instance where we can be certain that Parlodel was responsible for the event. However, when the individual necrologic and cardiovascular events are viewed in the aggregate, they suggest that Parlodel may pose a risk that we feel warrants further consideration by the Committee. Thank you.

DR. HULKA: Questions? Comments?

DR. ROY: Was the myocardial infarction patient a " smoker?

MS. NELSON: Yes, she was.

DR. BARBO: Do you have any information that more of these fall out in the over 30 age group or over 35 age group who had cardiovascular events or is it a spread?

MS. NELSON: It appears to be spread out. The one MI was a 22-year old woman. Which of the events do you mean?

DR. BARBO: Any of the cardiovascular events. I am just wondering if there is any family history or do you not

have that information for these patients?

MS. NELSON: When I spoke to the physicians I asked if they knew of any family history or the patient's own history and, for the most part, it was all negative.

DR. RAGAVAN: In my review, although I do not remember the exact details, but as I recall, most of the patients were in their early 20s. Very few of them were older patients, which goes along with the use of Parlodel and lactation in the younger patients.

DR. TEICH: Dr. Douglas Teich, from Health Research Group. I have three comments. The first is that I think it is worth noting that if you look at the number of reports, for example, with cerebrovascular events, the number reported this year is equal the number reported for the previous 8-year interval. If you look at seizures, it is roughly 25 percent of the total that was reported last year, which suggests at least that the labeling may have been effecting in alerting physicians to the possible association and points out again why the labeling and the letter to physicians is so important in at least trying to make the spontaneous reports somewhat resemble what is going on out there.

Along similar lines, the second point is that there is tremendous under-reporting of these events, as evidenced, for example, by a couple of cases of myocardial infarction in association with bromocriptine that we have learned about in

the last year. When I pursued these cases, which we hear about through attorneys, for example, we find out that the original describing physician has never reported them to the FDA . It is sort of the first time that it has been suggested or thought of, which gives at least some anecdotal impact to what you have described.

Finally, often in the approval of these drugs or later on, the FDA has increasingly looked at foreign adverse drug reactions. We know that this drug is used overseas. I was wondering whether or not you have any data bearing on foreign adverse drug reactions.

MS. NELSON: We do get foreign reports into the spontaneous reporting system. In 1988, I believe there were only one or two foreign reports but I did not feel 1 could include them because generally we do not like to group foreign and domestic together because foreign use may differ in some way from the way Parlodel is used here. So we did not really think it was fair to combine them. But there were only a couple.

MS. FLORY: I am Margaret Flory, from Sandoz. I just want to comment on the number of adverse reactions which were reported to the FDA during 1988. Let me also mention things that make reports happen, such as "dear doctor" letters, which were sent out in 1988.

I believe that at the meeting last year of this

group there was some comment that the FDA did not have their hands on some of the information that Sandoz had. So after that time, some information was resubmitted to the FDA. So that is why so many of them are dated '88. In some of the reports a physician would say, 1 got your letter and that reminds me of a case that I had a year and a half ago. Thank you .

DR. WENTZ: You said resubmitted. Are you suggesting that these cases were previously reported and there is implication?

MS. FLORY: I am, indeed, saying that they were submitted earlier. I do not know whether they are double-reported in the FDA system. We were unable last year to discuss them.

MS. NELSON: We are very careful and I check by state of reporter, age, date of onset, date of delivery, and [am virtually 100 percent certain that these are not at all duplicated.

MS . FLORY : And I am not suggesting that there is any duplication.

DR. HULKA: I would just reinforce your point that when any sort of event occurs, such as our meeting last year and the discussion of Parlodel, this is the sort of thing that gets known around that does then stimulate reporting. That is a well-known phenomenon that potentially biases

reporting.

DR. WOLF: I am Phil Wolf. I am from Boston University and I worked in the ERI study. I just wonder if Wendy could tell us how many cases or postpartum seizures and strokes occurred in the U.S. last year so as to put this into perspective, or in 1980 or in 1978.

MS. NELSON: You mean how many women between 15-44?

DR. WOLF: Had stroke, yes, or a postpartum seizure.

MS. NELSON: I do not know that information offhand. The only information I have, and I do not think it is really applicable, is what was presented at last year's meeting in trying to derive rates of postpartum CVA and rates of eclampsia. I do not know if anyone from my office has any insight into that. I do not have that information offhand.

DR. HULKA: Our plan had been to have presentations this morning until one o'clock and then break for lunch. I do not know what the Committee's thinking is or how Sandoz feels. I believe Dr. Winter is the coordinating person for the Sandoz presentations that were scheduled for later today. What is your feeling about having a little bit now?

DR. WINTER: Quite frankly, I prefer that we keep our presentation intact and, therefore, rather than starting and breaking, if possible, this would be an ideal time to have a general break.

DR. HULKA: All right. Could you plan then to have

your group here promptly at one o'clock? We will be here promptly at one o'clock. Thank you.

(Whereupon, at 12:00 noon, the Committee adjourned for lunch, to reconvene at 1:05 p.m.)

AFTERNOON SESSION

DR. CORFMAN: We are going to Start now, please. I have to deal with an issue the Chairman does not want to confront, and that is that Jennifer cannot make the February meeting on 22 and 23. So we would like to propose that it be February 8 and 9.

(General discussion about dates)

DR. CORFMAN: We will have to leave it the way it is then for 22 and 23.

DR. HULKA: Dr. David Winter, of Sandoz, will start the presentation.

PRESENTATION BY DAVID WINTER

{Transparency)

DR. WINTER: Thank you, Dr. Hulks and members of the Committee, for the opportunity to speak with you today. must say that we left here last night with a genuine sense 'f concern and, quite frankly, surprise at the haste with hich the Committee sought to dispose of the issues presented o it as they concerned bromocriptine, even before we had the pportunity to make our presentation.

We are especially surprised by the Committee's onclusion yesterday that not only should pharmacologic gents not be used routinely for the prevention of postpartum actation, with which I wholeheartedly agree, but also that here are apparently no circumstances which would ever

justify their use prophylactically.

This is not the impression we were left with following last year's Committee meeting and it is not a position to which we can subscribe. last year the Committee indicated that drugs should not be used routinely in the prophylaxis of postpartum breast engorgement. Its major concern was education of patients and physicians so that informed choice could be made. We know of nothing that has occurred during the part year to have changed that position. No new safety issues have arisen during that time.

We believe that there are women who either cannot or choose not to breastfeed for any number of reasons, and who have benefited from some form of symptomatic treatment, pharmacologic or otherwise. The choice of therapy must be left to an informed decision made jointly by the patient and the physician and Sandoz intends to present to you today concrete proposals to heighten awareness of both physicians and patients to all available options. Parlodel is only one among several alternatives that should be explored once a patient has made the decision not to breastfeed.

It must be kept in mind, however, that Parlodel is hardly a new or unfamiliar therapeutic alternative. It has already been shown by all applicable statutory standards to be safe and effective for the indication of prevention of postpartum lactation. Since its introduction nine years ago

for this indication, it has been used successfully by more than four million women. Many physicians believe that it has value when used under appropriate circumstances. Indeed, we could have filled this room many times over with such physicians and I find it hard to believe that they are all guilty of mismanaging their patients because the treatment option they and their patients selected does not conform to this Committee's own treatment preferences, however sound.

Quite frankly, as a physician, I understand that you have strong personal views on the best way to care for patients in the postpartum period and I respect your opinions and would not presume to alter them today. Sandoz asks only that you allow other physicians and their patients the same freedom to choose a course of patient care by not recommending the removal of a demonstrably safe and effective, albeit pharmacologic, alternative for this indication.

Today we intend to revisit some of the issues explored with you last year at this time. You have already heard the results of the epidemiologic study we commissioned to address the issue of certain adverse reactions occurring in bromocriptine-treated patients.

I plan to start this portion of our presentation with a brief review of the efficacy data from the Parlodel NDA and the world literature. I will also address the issue of rebound which I know is of concern to some Committee

members. Next, to correct some misstatements made during the open public session of this morning, I have asked John Lambert, the Sandoz head of statistics and biomedical operations, to set the record straight.

In response to concerns expressed by other members of the Committee last year about the pharmacology of bromocriptine, we have asked Dr. Edward Flueckiger to briefly review this pharmacology. Dr. Flueckiger is uniquely qualified to do this since he was the prime pharmacologist responsible for the development of this compound.

Dr. Philip Wolf will then review the necrologic complications that have been reported in patients during the postpartum period. Dr. Wolf, as you heard this morning, was the blinded evaluator in the ERI study that you heard about.

Then Dr. Charles Hennekens will give you an overview of the clinical and epidemiologic data obtained to date. Then I will return with some concluding remarks and present some action steps that Sandoz is prepared to take to help resolve any concerns that still may remain in the minds of the Committee members or FDA representatives regarding the use of bromocriptine for the prevention of postpartum lactation.

(Transparency)

I would like to start now with a review of selected parts of the data from the NDA. I recognize that you have

heard some of this, this morning. I will only point out that we also have reviewed it. We are quite familiar with that data and we have selected portions of it that we would like to present. We think they are the critical portions and, in some ways, perhaps the conclusions, particularly in regard to rebound, may differ significantly from that which has already been presented.

As an aside, I might point out that when a large number of studies are submitted in any dossier, it is often easy to pick out one or two that perhaps would serve one point of view better than another. In that regard, as was done this morning, perhaps we are equally guilty but, nonetheless, we have picked those studies which we consider critical studies for the NDA.

Just to review briefly with you, first of all, I will discuss very quickly" four U.S. double-blind, randomized trials. I think one has to draw distinctions between the double-blind, randomized, parallel group studies and other types of reports which are in the literature.

As you can see, the format was rather similar. The first study is placebo-controlled; 5 mg daily of Parlodel versus placebo; a 14-day study period and, in fact, there were follow-up evaluations at day 21 and 28.

The 3 studies which were lumped together, under number 2, did meet the statistical criteria for pooling, and

they involved an active control. You can see that there. In this case, the active control was used at 1 mg a day for 3 days, the next 4 days at 0.1 and then onto a placebo period. The follow-up evaluations in the first group were at 1 week and 2 weeks, namely, 21 and 28 days later. For the active control, the l-week and 2-week follow-up evaluations were at days 14 and 21.

(Transparency)

One point that evoked some confusion, and one that I think we must look at very carefully, is the issue of endpoints . I will discuss this a bit later, when we describe rebound. I think one must understand what endpoints were used to properly evaluate a study. In this case, as you notice, on mammary secretion we used very severe endpoints. Under "slight" for secretion, you notice, that hand breast pumps were applied. If any secretion came from that, it was called "slight". I think most of you would agree that this is a very, very severe endpoint and most people would not use it in a study today. In fact, I think it followed up on our early studies on lactorrhea that we ended up using a very severe endpoint. "Moderate" and "severe", one can see are quite clear there.

For mammary congestion, which was a second end point, one sees again the criteria and how we did it on a 4-point scale. For acute mammary engorgement, this was either

a "yes" or a "no", So those data have to be handled slightly differently.

(Transparency)

If we look now at study 48, and we will have additional comments to make about study 48 a bit later, one can see here the percent or patients exhibiting suppression, in black for placebo and in red for bromocriptine. One can see that on average it is roughly between 35-45 percent on Parlodel and a large number on placebo.

(Transparency)

If we go to the next endpoint, we can see here, in looking at congestion, a marked spread between these curves. Almost all these points in the early part of the curve are statistically significant. One cannot say so for the latter parts of the curve since, in these studies, as you have heard, there was such a high number of dropouts in the placebo group for lack of effect that there were too few to do the adequate statistical calculations. That number was down to 3 by the time we got out there, which I find an interesting comment in and of itself.

(Transparency)

Finally, if we look at engorgement, one can see again the difference between the two groups, the bromocriptine group being in red and the placebo group again being in black.

(Transparency)

If we go on now and take a look at the active control trials, we see a rather interesting situation here, that certainly during the first 6 days, if not 7, of therapy both groups showed an equal response. It was at the time, and perhaps there was a little breakthrough at day 7, that the patients in the EE group went on placebo and again one sees a marked separation of these curves.

(Transparency)

This holds up when we look at congestion too. We find again both compounds showing essentially equal efficacy.

(Transparency)

And then a separation of the curves. Then finally in engorgement one sees the identical point. As I will discuss later on, we were able to look at rebound in these patients. I am not sure where the statements came from that rebound was not considered. I will show you those data in a little bit.

(Transparency)

If we can go on now to some of the European studies, here we have to look at these a bit differently. As you might expect, they were done differently. The treatment duration in most of these studies was 7 days. We have picked here 4 placebo-controlled, randomized trials.

As one sees, there is a number of doses that were

used. We felt the only ones that were appropriate to consider here were those that used 5 or 6 mg daily because that corresponds more closely to the dose used in the U.S. trials . In fact, the comparisons against placebo were done with these doses. One can see on the bottom the multiple stars which do represent points of significant difference.

(Transparency)

If I show you graphically how this appears, you can see in this pool of the studies of the 4 placebo-controlled trials, that again bromocriptine therapy is in red and the placebo is in black. You can see again the marked differences which were statistically different.

(Transparency)

This slide shows congestion. One sees again the same situation.

(Transparency)

I would now like to discuss rebound. Before I do, I will return again to this slide, stressing the rating scales, because in this schematic what we have done is combine "absence" and "slight" in mammary secretion and we have basically called it absent. We feel that in practice today and, in fact, if we started these studies today, rather than in 1972-73 when they sere started, slightly different endpoints would be used. We feel that common sense will allow us to combine us "absent" and "slight", given that the

use of hand pumps is rarely used in clinical trials today.

(Transparency)

If I can then show you a summary slide looking at that group versus active control, 3 studies combined, which is appropriate, it looks across 3 parameters: secretion, congestion and engorgement at week 1 and week 2. CB is an old designation for bromocriptine. It shows that at week 1 there was 10 percent of patients with rebound either exceeding "absent" or "slight", whereas, in the estradiol group there was 21 percent exhibiting "moderate" and 3 percent "severe" rebound.

Interestingly enough, at week 2 there were some patients on bromocriptine who did exhibit rebound at week 2. There were a few of them there.

If we look at congestion, we see again very little rebound in that measure at week 1 and certainly nothing after week 2. In engorgement we see again 2 percent; in 1 case 8 percent and in the other slight rebound, both at week 1 and week 2.

I think an interesting point here is that comparing the 2 treatments, when we notice the efficacy parameters the 2 seem to have rather equal efficacy during the time they were both used but, clearly, there appears at least in the secretion endpoint, and perhaps in engorgement, a difference in rebound.

(Transparency)

Finally, I would like to review some studies from the literature. We went through the literature and found 10 studies which seemed to lend themselves to analysis for our purposes, the purposes being that the drug was used in approximately the same way that bromocriptine is used in the U.S. We did not consider studies that treated patients for 21 or 28 days since that is clearly not part of our labeling in the United States.

We found 10 such studies. I have a slide which gives the exact citations of them. In these studies, and there are 5 on this slide, one sees the total N in the second column on the left and the number of subjects on bromocriptine. The next column to the right, of course, is the comparison group. Then come the efficacy parameters seen. But, most importantly, in the final column is the percentage of rebound seen in these studies.

I think a word of caution is definitely needed here. It is quite honestly impossible to directly compare these studies. Different endpoints were used. We know that. Different approaches were taken and in many cases the concept of rebound was but barely alluded to, noted without any detailed explanation on how that assessment was made. So I offer this only as statements from the literature and one has to weigh the validity of these statements. I will say no

more about it than that.

I think what is interesting to note is the wide range of rebound cited in these studies. Again, it gives you the comparisons there, ranging, if I read that correctly, from 2 percent as a low in one group up to 48 percent in another study.

What is of interest to me is the very large study in which 370 patients were examined. Again, allowing for the softness of these data, nonetheless, they come Up with a value of 7 percent.

(Transparency)

This slide shows 5 additional studies. These studies range from rather small to modest in size. Again the comparison groups are with various types of comparisons. Again the rebound is in the far right column. One ranges Erom 4.5 in one study up to 40 percent in another. There is a wide range of rebound, as cited in these studies.

(Transparency)

On the final slide I have taken the liberty, as I think most people would doing this, to just combine the lumbers. One can argue the appropriateness of this but, nonetheless, out of some 600-some odd patients, it looks like the incidence of rebound across these studies was 12.3 percent, which is somewhat similar to the incidence we got in a prospective, randomized control trial. Finally, there was

a rather large review article, in 1985, with between 10-20 percent of women.

So I am using three different data sources. We can certainly criticize any single one of them. But that is what is in the literature. That is what other authors have said, regardless of how they did it. This seems to be somewhat of a convergence, roughly between 10-20 percent of rebound. I think that this is a rather interesting point in and of itself.

At this time I would like to introduce Dr. John Lambert, who does have a few comments to make regarding some statements made in the public session this morning. Excuse me, perhaps you would like some questions right now. I am a little ahead of myself.

DR. HULKA: Any questions on the efficacy issues?

DR. NIEBYL: It seemed to me that in some of the slides the treatment period is 14 days and that the evaluation time was at day 14. Was I misreading that?

DR. WINTER: At day 21 and day 28, except for the EE group and that was 14 and 21 because, remember, they were on placebo for that 1 weeks.

DR. NIEBYL: Right. But none of the studies of Parlodel looked at rebound before day 21?

DR. WINTER: No.No, it was l-week and 2-week time points .

DR. NIEBYL: After the drug was stopped?

DR. WINTER: Exactly.

DR. SCHLESSELMAN: Dr. Winter, the studies then were not double-blind if the treatment regimens and the follow up differed for the control group versus the treatment group? Am I correct in that?

DR. WINTER: Those patients were carried through -- no, they were double-blind. Admittedly, they had different treatments but every effort was made to keep them blinded. They went on placebo for that other week in order to keep up the blinding portion. So they were kept on, to the best of my memory, on this as close as one could to keeping it a true double-blind trial, yes.

DR. NIEBYL: You said that rebound was rarely troublesome, or at least it said that in the summary article that you quoted. Were there any data to show that the amount of leakage or engorgement with rebound was any different from what you would get in the initial period in the placebo-treated patients?

DR. WINTER: I really cannot comment on the other person's article. As you well know from reading the literature, it is so difficult to relate one study to another. I think we used an extraordinarily -- in fact, too much so -- conservative endpoints. I really believe we did. I just cannot see people going through what we did to really try and

find out if there is truly any secretion or not. But we did it that way and we must live with those data.

DR. HULKA: I wanted to ask you, maybe something similar to Jim Schlesselman's, specifically about one of your early slides when you were pointing out two American studies, one with a placebo and I believe that there were 15 women in your treatment arm and another 15 women in the placebo arm. I wondered about a couple of things. Specifically, of that study, which I gather you think is one of the better studies, if that was double-blind; if the placebo had the looks of Parlodel and if the subjects and the physicians and other who worked with the patients were blind to what the patients were getting.

DR. WINTER: Yes, all efforts were made to keep this a true double-blind study. In the case of Parlodel, it is relatively simple. With some of our injectable and other types of compounds it is very difficult sometimes to keep a true double blind. But in this case we manufactured our own placebo tablets which look in color, in shape and in size exactly like the Parlodel.

It is true that in any double-blind trial one has potential problems. If one drug has more side effects than another and the clinicians are particularly astute, there are ways that perhaps they can get some inkling. But barring this, every effort is made to keep a trial truly double-

blind.

DR. HULKA: And in that trial you indicated that quite a number of the 15 placebo women dropped out of the trial. Do you have the information on the actual number that dropped out? On what days they dropped out and the reasons for the dropout?

DR. WINTER: Yes. The reason was straightforward, it was lack of efficacy.

DR. HULKA: Meaning?

DR. WINTER: The drug did not work and they wanted something that would and they dropped out of the trial. I have a backup slide which gives day by day how many patients were in that trial. Yes, we have all that information.

DR. HULKA: And did you collect data on their subjective reaction to comfort and discomfort?

DR. WINTER: We collected the information which we have put in our case report form design before the trial started. So we asked the questions, and there are certain questions that are asked, we collect that information but we do not go much beyond what has been said in that because it potentially offers a way of breaking blinds if you start going into extra information.

DR. HULKA: Well, I meant uniformly of all women in the study as the days went by, on a regular, uniform basis. Did you get information on their perception of pain?

DR. WINTER: Certain questions are asked but the study, quite honestly, was not designed to get at that level of subjective information.

DR. HULKA: I see.

DR. WINTER: Unfortunately, we do not have that.

DR. HULKA: Thank you.

DR. WENTZ: I missed the number of times or how exactly the hand pump was used to measure secretion. How often was this used?

(Transparency)

DR. WINTER: It was applied and the pumping was done two times in succession in order to try and evaluate at that point in the day when the evaluations were done for all subjects.

DR. WENTZ: It was done daily?

DR. WINTER: Yes.

DR. WENTZ: Do you have any randomized, double-blind, placebo-controlled study in which a hand pump was not used?

DR. WINTER: The American studies were done with a hand pump. To the best of my knowledge, the European studies were not. That would constitute the second set of slides. Perhaps someone from Sandoz can correct me if I have mis-spoken on this. Is that correct, Dick?

DR. ELTON: No, they were not.

DR. WINTER: A hand pump was not used in European studies. So the second group of 4 placebo-controlled trials that I showed and identified as European studies were done without a hand pump.

DR. MANGANIELLO: You mentioned to Dr. Hulka that the individuals who dropped out they wanted an alternate form of treatment for breast engorgement. I think you have to make an assumption that if you delivery, most likely you will lactate to a certain degree and you will have some breast engorgement and you will have some leakage of milk, and the methods that you are supposed to be comparing Parlodel to would be, say, traditional methods, such as breast support and analgesics or just breast support by itself. What alternate methods were these people offered?

I think what Dr. Wentz was alluding to is that if you are going to be using a breast pump to measure the amount of leakage, you are, in fact, stimulating or prolonging the symptoms that the patient is trying to get rid of. So what alternate methods were these people offered and were these people all counseled as far as using some kind of breast support and other ways of trying to alleviate the symptoms, rather than just saying goodbye?

DR. WINTER: I will answer the second part and I will try and get some help from my colleagues. The way most studies are conducted is that at a fixed point in time, if a

patient wishes to withdraw from that trial, in spite of additional counseling and every effort being made to keep the patient in the trial, it is the patient's right to withdraw. rhey withdraw at that point in time. As far as the study is concerned, it is over; it is declared a failure. What they subsequently to onto is really of no concern to the study. So we do not have that information.

In terms of support during the trial, I will have to ask Dr. Elton's help on that. Were there any special aids given to one or both groups during that trial?

DR. ELTON: No, there were not. They were enrolled in the trial prior to delivery; made their selection at that point. Following delivery, they either went into the program or did not. If they went into the program, they were randomized to either arm.

DR. WINTER: And both received the same, which is probably nothing, in terms of additional support, as you are suggesting. So the two groups were the same, as best as we could keep them, although I do admit we were in a bit of a Catch-22 with this intensity of trying to elicit secretion. But, anyway, the groups were handled the same and did not have any additional support.

DR. CORFMAN: Perhaps I misunderstood one of the earlier graphics, Dave, but I thought you showed more congestion in the Parlodel group and less in the placebo-

controlled group. They were not the same before treatment or the same after treatment. I wonder if you could explain that.

DR. WINTER: Do you mean the numbers?

DR. CORFMAN: No. For congestion I would expect that they would be the same before treatment and after several weeks.

(Transparency)

You have another one like that but that is what I am thinking of.

DR. WINTER: That is congestion.

DR. CORFMAN: Wouldn't you expect them to start out somewhat the same and end up somewhat the same?

DR. RARICK: I have a question on that. Did you also combine your rating scales for these?

DR. WINTER: No.

DR. RARICK: Just for rebound?

DR. WINTER: Just for rebound.

DR. RARICK: That would be one interesting point. I know my numbers were 40-88 percent rebound from these same studies that he discussed, most likely because we did not combine 0 and 1 because for the rest of the study for congestion, secretion and engorgement we did not combine 0 and 1 as being absent.

DR. WINTER: Yes. We really felt that for rebound

purposes it was justified, given the severity of that.

DR. RARICK: Well, if that is true, then they should be put together for all of them. For this trial the placebo rating for congestion and secretion was slight.

DR. WINTER: It would make the efficacy look even better.

DR. RARICK: I doubt it.

DR. WINTER: It would.

DR. RARICK: Anyway, if you are wondering why our numbers are different, we did just evaluate the same studies, I did the same 4 this morning and I gave you rebound data of 40-87 percent in these studies. Most likely, I assume, our reading is different because he puts together his rating of O and 1. He does not put it together for his whole study but just for the rebound data. As you go back to his rating scale, O is “absent” and 1 is “slight”. He uses those numbers for congestion, secretion and engorgement during the study but now in rebound he is combining those 2 groups.

DR. WINTER: We can show you a slide. We have it done both ways and, quite honestly, during this part of the study they are very similar.

DR. CORFMAN: Would you address my question? Why aren’t they the same at the end of 13 days?

DR. NIEBYL: It seems to me that one of the problems of using a hand pump as an endpoint is that if you

give the hand pump to somebody on Parlodel, you are not going to get very much reaction. But if you give a hand pump to somebody who is on a placebo, that is going to stimulate lactation even further. So it is going to make your placebo group look a lot worse, I would think.

I would think the proper way to do it would be to give both groups ice packs and breast support because the placebo group there might be a lot lower if they were not using a hand pump.

DR. CORFMAN: Is the answer to my question then that they were using hand pumps?

DR. NIEBYL: They were all using hand pumps.

DR. WINTER: Yes.

DR. NIEBYL: And a hand pump is the worst thing to do to somebody who is trying to not lactate.

DR. WINTER: Well, we certainly would not design the study this way today. There is no question about that.

DR. NIEBYL: That may explain some of the differences and why we say we do not get as much trouble in the placebo group when we give everybody breast support and ice packs because I do not think anybody would say that in someone in whom you are trying to inhibit lactation you should pump them every 12 hours to see if they are lactating or not.

DR. ELTON: I think I should clarify that the hand

pump was only used if there was not overt secretion in any of the patients. So it was not a routine thing but, rather, if they were attempting to find out whether there was any secretion at all in those patients who, for all intents and purposes, appeared not to be secreting.

DR. CORFMAN: But why is there that continued 40 percent difference?

DR. ELTON: I think probably the reason is because of the numbers of patients. As you go out further, you get a few outliers and it becomes a little bit more fictitious at that point.

DR. WINTER: In the placebo group but not in the Parlodel group.

DR. ELTON: Yes. In the placebo group you end up with those few patients which can give you quite a marked change in percentage.

DR. WENTZ: Now I am totally confused. You told me that each patient in the placebo and in the Parlodel-treated group used the hand pump once a day at a designated time. On that rating thing the pump had to be used twice and then you rated it as the first category down, I think it was category "slight" or maybe it had a number attached to it, if it had as much as two drops. You just said that they did not do it at all unless they had overt secretion.

DR. WINTER: No, there was no need to. No, if

there was significant secretion or marked to severe secretion, obviously there was no need to use the pump. The pump was used if they did not see anything to check whether it was absent or slight.

DR. WENTZ: I do have a question for Jennifer since I am not an obstetrician, in your experience over several institutions in different parts of the country, how long does it take a postpartum patient who is not stimulating her breasts to achieve lack of secretion?

DR. NIEBYL: Just several days, a few days.

DR. WENTZ: So what you have done is a beautiful study showing that with the hand pump you can prolong it at a 40 percent difference out to -- I think it was 14 days, wasn't it? Thanks.

DR. ROY: Could I get some clarification? Did I recollect what you said correctly, that in the placebo failures who went on to some other form of therapy, because that was not in the protocol, you have no information on those individuals?

DR. WINTER: Once they leave the study, ordinarily anything you collect is really considered anecdotal. The study is over at the termination of the paper --

DR. ROY: I suppose you could consider it that way but if you chose to include whatever was done and subject that to analysis, then that would at least be some in for-

nation.

DR. WINTER: Absolutely.

DR. ROY: Do we have any information about whether those patients were then treated with Parlodel and whether they responded or not?

DR. WINTER: We just do not have that information. We did not build it into the study. You are talking about a two-phase study, which can clearly be done.

DR. NIEBYL: Are they dropped from the numbers then up to day 14? If they dropped out of the study on day 4, they were not included later?

DR. WINTER: That is why the line is very flat and that is why you cannot do much statistically when you are down to two or three patients. So it falls apart at that end.

DR. NIEBYL: I guess what Subir is asking is if a patient is not treated prophylactically and if she gets engorged, we heard about a small number of patients yesterday and the question was really do you have any more data about whether the drug works therapeutically, as well as prophylactically.

DR. WINTER: Not prospective data. We have the same anecdotal data.

DR. NIEBYL: Uncontrolled, yes. Okay.

DR. WINTER: John Lambert will now make some

comments.

PRESENTATION BY JOHN LAMBERT

DR. LAMBERT : Thank you, Dave, and thanks to the Committee for letting me make some brief remarks. I am John Lambert, director of biomedical operations for the Sandoz Research Institute.

In response to the Public Citizen Health Research Group statement, which was circulated today, I would like to take a few minutes to provide some perspectives in the interest of fair balance. The statement also included some reference to comments from Dr. Ragavan's review last year. One of the statements was that only 2/6 placebo-controlled studies in the NDA were double blind. The fact is that all 6 were double blind and, in fact, 17/24 studies in the NDA were double blind.

Study 48 demonstrated a very significant advantage for Parlodel over placebo. In answer to one of Dr. Hulks's questions about dropouts, a little more specific information is that 12/15 placebo-treated patients discontinued on or before day 7. Several of those were at day 3 or day 4; 7 of these were for treatment failure; 5 were for the reason of being unable to follow up.

By contrast, no Parlodel-treated patients discontinued due to treatment failure. Two did discontinue due to side effects.

Fairness and scientific method dictate the appropriateness of mentioning concurrently timed placebo data, which was not done in the Public Citizen Health Research Group statement. NDA data show for this study that in terms of secretion, for example, at day 7 Parlodel had 9/14 (64 percent) of patients symptom free, and by that we are being consistent with the NDA definition of symptom free. The placebo group had 1/9 or 11 percent. At day 14 Parlodel had 9/13 symptom free for secretion (69 percent), as opposed to placebo, 1/3 or 33 percent.

For congestion, at day 7 the figures were 8/14 symptom free for Parlodel (57 percent); 1/9 (11 percent) on placebo. At day 14 for congestion, 9/13 were symptom free on Parlodel (69 percent); 33 percent (1/3) on placebo.

In spite of relatively small sample sizes, many significant differences, consistently favoring Parlodel over placebo, were noted. This occurred at almost every study day from 3-7, with 2-sided levels of significance between 0.001 and 0.05. The drug was very effective at early stages, for example, with 100 percent success in preventing engorgement at days 3 and 4 in spite of 71 percent and 64 percent success in that regard for placebo on those respective days. All differences at all time points for all efficacy variables in this study favored Parlodel over placebo.

Dr. Hulks raised another question that was connected

with whether or not all patients enrolled were followed up in some global way. The answer to that question is yes and in terms of global evaluation to cover all patients enrolled, and on the 5-point scale, where 1 represents very good and 5 represents very poor, the average response for Parlodel on that scale in terms of this global was 1.8; the average response for placebo patients on this scale was 3.4. That was statistically significant with a 2-sided p value of less than 0.01.

In particular, in terms of the extreme points on that scale, Parlodel had 7/15 patients globally rated very good; placebo had 1/15. In terms of the other extreme, the very poor, Parlodel had 1/15 patients and placebo had 5/15 patients.

This and other studies cannot fairly be faulted for failure to follow up patients for one month postpartum for rebound. In fact, many were followed for up to 2 weeks post-study if they were eligible for inclusion in analysis of rebound.

The designs were medically and scientifically acceptable to the sponsor and the Agency. Too few placebo patients remained at study end for fair comparisons on rebound relative to placebo.

It should also be noted that although 31 percent of Parlodel-treated patients did exhibit some secretion or

congestion at day 14, all of this was slight, in fact, 4/13 at that point. This was so determined according to a rating scale so severe in its definition of "slight" that a reasonable case has been made for combining the categories "slight" with the category "none", as Dr. Winter has discussed.

I should mention an additional point. I think it is still appropriate during the study days to reflect efficacy in terms of any symptoms or no symptoms and then to proceed with the analysis that was presented on rebound because at the end of the study the same modification of the definition was used as in the follow up for rebound.

Narrative statements drawing broad conclusions based on very selective and not well-defined sampling from large volumes of material are prone to great potential for bias . For example, direct comparisons between specific treatment groups, isolated from different studies, as implied in the Public Citizen Health Research Group statement, is not appropriate. In particular, it is inappropriate to directly compare Parlodel end of study results from study 48 to those of placebo-treated patients in other placebo-controlled studies using different doses of Parlodel and shorter time frames.

Rebound was, as I pointed out, in fact, addressed by this and other studies. Study 48 results, for example, appeared in the corresponding study reports submitted to the

NDA . All patients eligible, and I will quote some figures from the original definition, if you will, all patients eligible, that is, truly symptom free at day 14, which would be day 7 on ethinyl estradiol, were, indeed, followed for up to 2 weeks if they remained eligible for rebound post-study.

Those figures indicated that at week 1 post-treatment 2/9 (22 percent) of Parlodel-treated patients exhibited rebound. The figures were 22 percent for congestion and O percent for engorgement. At the second post-treatment week follow up, the percentages for rebound in all cases were). As Dr. Winter has shown, these results are conservative in light of a more realistic definition of rebound.

Regarding estrogen versus Parlodel comparisons, the fact is that Parlodel 14-day treatment results were never compared to estrogen 7-day results. All comparisons were based on equal exposure time.

Further, when estrogen treatment was eliminated during the study, significant worsening of symptomatology occurred for patients in that group. This did not occur for patients in the Parlodel group. Thank you.

DR. HULKA: Questions?

DR. MANGANIELLO: Dr. Lambert, I could not quite get the figures when you were stating a dropout rate for the placebo group. Could you go over the actual numbers again? You were saying that on day 3 so many individuals dropped

out . Out of what?

DR. LAMBERT: Yes, I indicated that of the 15 placebo-treated patients, 12 had discontinued on or before day 7; 7 of these were for treatment failure; 5 were for the reason "unable to follow up". We do have a slide where we could show that in further detail. I believe that there was sort of an even distribution. Most of them happened on day 3, day 4 and day 7.

DR. MANGANIELLO: So I guess it is conceivable that the 5 people who did not have a reason may not have had any complaints.

DR. LAMBERT: That is conceivable. They left the study.

DR. MANGANIELLO: Okay.

DR. LAMBERT: We were unable to follow them.

DR. MANGANIELLO: So you only had 7 individuals who left the study because of the fact that they had residual symptoms.

DR. WENTZ: I do not know to whom to address this question so it might have to go to someone else. Did you measure prolactin levels before and after the use of the hand pump in placebo-treated patients?

DR. LAMBERT: No.

DR. ELTON: Could I just make a point of clarification? I think in 1972, when these studies were started,

there was not really a reliable radioimmunoassay for prolactin anyway. So it was really a difficult issue to address at that point in time. Nowadays it would be very easy but not at that time.

DR. RARICK: Dr. Hulks, I have just a few clarifications. His first comment that they do have double-blind studies, out of the 24, 17 are double blind, that is true. They are not all placebo and, in fact, the majority are not placebo double-blinded; there are various other therapies.

I would disagree that you treated your estrogen group with 14 days of estrogen --

DR. LAMBERT: I did not say that.

DR. RARICK: You did.

DR. LAMBERT: The estrogen was only 7 days. What I said was that comparisons between Parlodel, based on 14-day treatment, were not made with estrogen 7-day treatment. If we made a comparison between Parlodel and estrogen, it was at 7 days versus 7 days.

DR. RARICK: I see, okay. My other comment would be when you discuss who is eligible for rebound data, your eligibility required that they have no symptoms at 14 days?

DR. LAMBERT: In the analysis of rebound that was presented by Dr. Winter the eligibility was determined by the patient at the end of study, which for Parlodel would represent 14 days and for ethinyl estradiol would represent 7

days, if they had none or slight according to that severe definition. Then that same criterion was used in any further follow up.

DR. RARICK: And as you remember, they had 70 percent no symptom patients at 14 days. That only leaves 30 percent of the patients for rebound follow up, which leaves 4 patients in that study for follow up.

DR. MANGANIELLO: How many placebo, no drug, studies have been done? That is, not a comparison to an active drug but just plain placebo?

DR. RARICK: In their NDA or in general?

DR. MANGANIELLO: In general.

DR. RARICK: I can recall from the top of my head five placebo controls, two from the NDA and three from the literature. They may have other numbers.

DR. LAMBERT: Not with me right here. .

DR. ROY: Lisa, I think I misunderstood something you said. You said that if at the end of their Parlodel treatment 70 percent --

DR. RARICK: He quoted 70 percent had no symptoms.

DR. ROY: So they would be the ones who would be eligible --

DR. LAMBERT: That is correct.

DR. RARICK: I am sorry, that is correct.

DR. WINTER: Just to answer the question on how many

placebo control trials, I showed data from 1 U.S. placebo-controlled, double-blind, randomized, parallel group. We also presented data from 4 European trials of similar design but of a different duration of therapy. But there were these 5 in the submission.

DR. HULKA: Thank you. I wonder if we could go on with the next presenter?

DR. WINTER: The next speaker is Dr. Flueckiger.

PRESENTATION BY E. FLUECKIGER

(Slide)

DR. FLUECKIGER: Ladies and gentlemen, I shall first acquaint you with the basic profile of actions of bromocriptine and I shall then deal with the cardiovascular actions of bromocriptine, especially the question of hypertensive versus hypotensive actions. I shall finally show you two slides on the action of bromocriptine in two experimental models of epileptic seizures.

In this first slide I just want to show you that bromocriptine, the active principal of Parlodel, is a 2-bromo-derivative of a natural ergot alkaloid, alpha-ergocryptine.

(Slide)

Alpha-ergocryptine is a member of a big family of ergot compounds which all have in common the tetracyclic structure, which is depicted here, the tetracyclic structure,

n-6-methyl ergolene moiety. The different groups of ergot alkaloids differ by the various substituents to this moiety,

(Slide)

The interesting thing bout this ergolene moiety is that three neurotransmitters, namely, noradrenaline, dopamine and serotonin, can be viewed as partial structures of the ergolene moiety. In this slide, on the left side, noradrenaline is on the ergolene moiety; then comes dopamine and, finally, serotonin.

So from this point of view, it is not astonishing that the ergolene moiety has affinity to receptors of these three types of neurotransmitters.

(Slide)

You see the most simple of these compounds, 6-methyl-9-ergolene moiety is an alpha stimulant on the uterus. It is a serotonin receptor blocking agent and it is a prolactin secretion inhibitor, which means a dopamine receptor agonist. This is all included in this simple molecule.

Now, the difference between all the available ergot compounds is the way they are substituted around this nucleus. This will alter the relative activities of the individual actions which I have pointed out here.

(Slide)

Thus, bromocriptine is a 2-bromo derivative of a

'compound which a highly uterotonic compound and is a vasoconstricter compound. By adding the bromo in position 2, both these agonist actions are reduced and 2-bromo-alpha-ergocryptine becomes an alpha-blocking agent, for instance, and a serotonin antagonist.

What I show on this slide is, in fact, that very small changes on the substituents, on the additions, to this nucleus will make, in the case of prolactin secretion inhibition, a major effect on the quantitative aspects.

On the right-hand side of the molecule you see changes in the structure which may even lower the prolactin secretion to a fifth of the intact molecule. So it is not only the ergolene moiety, but the whole surrounding which will decide on the actual profile of action of any ergot compound.

(Slide)

Thus, I should like to show you that the methysergide is especially prominent as a serotonin receptor blocking agent, with a figure of 1000. On the other hand, bromocriptine is very inactive as a 5HT receptor blocking agent. It has quite an appreciable alpha-blocking activity and its most important actions are as inhibition of fertility in rats, which means prolactin secretion inhibition, and in a model for Parkinson's in which bromocriptine will induce contralateral turning. That is on the second to the last

line. These two actions, inhibition of fertility in the rat and inducing of these contralateral turns in the rat, are two effects of dopamine receptor stimulation.

(Slide)

Now, here I just want to show you prolactin secretion inhibition from a publication from Yale University, a very early study in this direction. You see that bromocriptine dose dependently reduces prolactin release from the pituitary into culture. That is a curve inscribed with tartaric acid as a solvent for bromocriptine. Then you see that addition of dopamine antagonists, like d-butaclomol, will shift the dose-response curve of bromocriptine to higher doses of concentrations, meaning that there is a dose-dependent antagonism to the effect of bromocriptine. With these three curves bromocriptine is clearly defined as a dopamine agonist.

(Slide)

Now, dopamine receptors do not only occur in the brain or in the pituitary. Dopamine receptors occur in very many parts of the periphery. In today's discussion, I should like to point out the dopamine receptor populations on arterial smooth muscles, especially in regions like the mesenteric and splenic area, where dopamine receptor stimulation leads to relaxation of the muscles, which means a reduction of resistance to blood flow.

Another very important point is that dopamine receptors are found on the nervous structures. Here we have two sets. In the sympathetic neurons there are neurons which are sensitive to dopamine and which control the transmission through this ganglionic node. The second is that sympathetic neurons on their nerve endings have dopamine receptors which are inhibitory to the release of the physiological transmission of noradrenaline. So if you stimulate the end of a sympathetic neuron by bromocriptine or a dopamine-acting drug, the release of noradrenaline will be reduced. This has consequences in the cardiovascular aspects.

(Slide)

In this experiment a pithed cat had stimulation of the sympathetic accelerans nerve to the heart. This stimulation had a certain intensity. You see here that bromocriptine dose-dependently inhibits this sympathetic effect, the accelerans nerve effect in the heart. That is the curve indicated as O.

In this case, injection of the dopamine antagonist haloperidol will shift the dose-response curve of bromocriptine to higher doses, which means that the effect of bromocriptine is inhibited by a dopamine receptor blocking agent, showing again that this effect was a dopamine-like action.

(Slide)

In this experiment is shown materially that noradrenaline from cat heart, when stimulated, is released and that the release of noradrenaline is reduced in the case where bromocriptine (black columns) is being infused or injected into this heart preparation.

So bromocriptine will reduce the effect of the accelerans nerve from the heart, will reduce heart beat frequency because it reduces the release of the neurotransmitter from the sympathetic neuron.

(Slide)

So in the pithed rat, which is stimulated electrically to have a normal heart frequency and a normal blood pressure, bromocriptine reduces the blood pressure induced by this sympathetic stimulation. At higher doses (the triangles) in the same preparation bromocriptine will inhibit the effect of an injected dose of phenylephrine, which is an alpha-receptor stimulant. So it shows that at higher concentrations bromocriptine will also show in the rat some alpha receptor blocking activity, as initially indicated.

(Slide)

Now I should like to turn to models of hypertension, experimental models of hypertension in laboratory animals. I speak about three different models which are widely used in pharmacological laboratories. There are many publications concerning such effects as I am talking about. All authors

agree that bromocriptine lowers blood pressure in hypertensive models. The mechanism of action by which this will occur are differently interpreted by different authors.

In this first slide, I have a paper from Beecham Laboratories in which bromocriptine is found to lower blood pressure in the spontaneously hypertensive rat through its alpha-blocking action. It will block noradrenaline or adrenaline released from the renal medulla. It will block the alpha-stimulant action and, therefore, convert adrenaline into a beta stimulant, which leads to vasodilatation. That is the interpretation of those experiments.

(Slide)

In another case, the question whether the adrenal medulla is involved in these hypertensive actions is negated. It is postulated that dopaminergic effects in the central nervous system or in the periphery are involved.

(Slide)

In this study, the authors come to the conclusion, by using different types of dopamine receptor blocking agents, that the effect of bromocriptine to lower blood pressure in the spontaneously hypertensive rat is due to a central mode of action on the dopaminergic system.

So everybody agrees that blood pressure goes down. There are different interpretations why it goes down.

(Slide)

We now come to a different model, namely, the DOCA salt hypertensive model. DOCA stands for desoxycorticosterone acetate, which is an adrenal corticoid which, with a major action, retains sodium chloride within the body or reduces the loss of sodium chloride from the body. In addition, these animals are given sodium chloride solution to drink so they will rather quickly show a volume expansion hypertension which is not only just a volume expansion hypertension, as we shall see.

Also in this model of hypertension bromocriptine will lower blood pressure. The effect is considered to be most probably due to a dopamine receptor interaction with bromocriptine.

(Slide)

In this paper it is shown that bromocriptine, when given while the blood pressure in DOCA salt hypertensive rats builds up, will attenuate the development of this pathological situation.

(Slide)

And in this paper the authors come to the conclusion that the model of DOCA salt hypertension in the rat is, in fact, accompanied by an insufficiency of the dopaminergic system and that bromocriptine, in this type of hypertension, is replacing internal dopamine which is not available due to the lack of dopaminergic function.

So in this model everybody is again clear that blood pressure is lowered and everybody seems to be of the opinion that dopaminergic mechanisms are involved.

(Slide)

There is a third model which is considerably used. One uses dogs for it. It is a model where surgical denervation of the area which sends signals to the brain about peripheral blood pressure, sino-aortic denervation, is being done. So the brain is without information about peripheral blood pressure. The consequence is a tremendous increase in Sympathetic neuron activity in the periphery to induce some signals . Therefore, the blood pressure gets up very quickly, within minutes, and stays high.

Bromocriptine in this case also will lower blood pressure or prevent increase in blood pressure and it has been shown that here again it is a matter of attenuation of more adrenaline released from sympathetic neurons.

(Slide)

Now to the last point, the question whether bromocriptine induces seizures of the epileptic type can be answered only on rather few experimental studies that have been published. They are all of the same conclusion. The conclusion is that dopamine receptor antagonists, like haloperidol, will aggravate experimental models of epileptic seizures in the rodent and that dopamine receptor agonists,

like apomorphine or bromocriptine, will attenuate or suppress such seizures.

I have just two examples of two models, namely, the cobalt-induced epileptic seizures, which are inhibited by bromocriptine.

(Slide)

Secondly the audiogenic seizures, which are widely used. These animals are also protected by bromocriptine and bromocriptine-like compounds from these audiogenic stimuli.

So in conclusion, I should like to say that from the laboratory view of the pharmacologist, we have no evidence to suggest that bromocriptine will induce hypertension, hypertensive crises. There is no way known how this could happen. Secondly, it is also evident from animal experiments that there is no suggestion that central seizures would occur with a dopamine or mimetic-like bromocriptine. Thank you very much.

DR. HULKA: Questions?

DR. MCDONOUGH: I just want to ask maybe one or two questions about Parkinson's disease. That is, patients who are taking 50 and 60 mg a day of Parlodel, with respect to the development of hypertension in that particular group of individuals, and whether all models in which you have volume expanded situations, artificially created or in the spontaneously hypertensive rat, whether in any of those instances,

either in Parkinson's disease or in the volume expanded spontaneously hypertensive rat, Parlodel will actually create hypertension in certain situations, maybe due to activation of the serotonin system paradoxically.

DR. FLUECKIGER: Yes, that would be a theoretical possibility. I mean bromocriptine is the ergot compound which has been given in the highest doses ever. Right here in Bethesda, at the NIH, daily doses up to 300 mg have been used with Parkinson's patients. In this respect, no seizures and no hypertensive effects were seen. In the regular Parkinson patient with doses between 15-60 mg, I am not aware, with patients who have taken it for 8 or more years, that there have been such crises induced.

Also I am not aware of such observations in acromegalic patients who are also in the high risk group concerning cardiovascular effects, taking up to 60 mg of Parlodel. I am not aware that hypertensive crises or seizures have been reported.

DR. MCDONOUGH: I think all of us who see non-pregnant patients clinically and use a great deal of Parlodel, of course, see orthostatic hypotension not uncommonly occur. On the other hand, in this situation you are dealing with an individual who is volume expanded initially and then becomes volume depleted. So the model of the experimental rat becomes an important one, even though it is artificially

induced and, in a way, also genetically determined. It is of real concern. We are using a drug here where some very dynamic changes are occurring in the cardiovascular system.

DR. FLUECKIGER: I believe this is the big problem for the experimental pharmacologist to address this situation. We have discussed it many times and we have come to the conclusion that we just cannot do it, at least not with the rat and we have no facilities to, for instance, to try it out in sheep which are today used more and more in physiological cardiovascular studies. But, certainly, in the rat and in the dog there are no such problems occurring. I would not know how to start such a study.

DR. MANGANIELLO: We are being asked as a Panel to more or less look at the biologic plausibility of the fact that Parlodel may be causing some untoward effects in the human female patient, specifically the postpartum pregnant female. As Dr. McDonough pointed out, we are working with a different type of individual, pregnant versus non-pregnant, and individuals who, for instance, are preeclamptic oftentimes are volume concentrated or volume depleted. Possibly adding an agent which may have hypertensive qualities, you may be compromising their cerebral blood flow, predisposing them to a seizure activity.

We do know, however, that Parlodel as a dopamine agonist does have some presser effects. Individuals who are

in cardiotoxic shock will be put on a dopamine drip to maintain their blood pressure --

DR. FLUECKIGER: May I take this point up?

DR. MANGANIELLO: Sure.

DR. FLUECKIGER: It is a very important point, I believe. If you have a shock patient and infuse dopamine, you will have dopamine receptor stimulation in the renal vascular bed, which will keep on renal function, but at the heart dopamine will act through beta-1 receptors to increase Contractility. That is the complicated thing with dopamine. Dopamine is not a pure and simple dopamine receptor agonist. In contrast to the rigid structure of the ergolene moiety, in the dopamine moiety the side chain can go into different angles. The ergolenes do not have affinity to beta receptors, only to alpha receptors, while dopamine is also acting by a beta receptor. Especially in the heart, it is stimulating beta-1 receptors and the effect can be antagonized by metoprolol or atenolol, which both have a higher affinity to beta-1 than to beta-2 receptors. So there you have a combined action with dopamine infusion in shock patients.

DR. MANGANIELLO: Again, what you are presenting here are very complex physiologic responses in the human to a dopamine agonist or the native compound and it is kind of hard for me to sit here and say that a particular person may not act in an exaggerated or paradoxical fashion to dopamine,

or in a given clinical situation where a hypotensive episode may be just as detrimental as a hypertensive episode.

So I think at this point in time, I am having a lot of difficulty in justifying the use of this drug in a benign clinical situation.

DR. FLUECKIGER: Yes. 1 have never been of the opinion that experimental pharmacological evidence does falsify clinical observations. That should be clear between us. The question is only can we have a basis of discussing what the mechanism of such observations could be, what the underlying mechanism could be? There I am not aware that anything else but hypotension has been described with apomorphine or other dopamine-like compounds and bromocriptine.

DR. MANGANIELLO: So again though, hypotension can be detrimental in a clinical situation, such as with preeclampsia.

DR. FLUECKIGER: Yes. I cannot discuss this.

DR. HANEY: Along those lines, you presented models of seizure activity. I do not know how they relate to preeclampsia. Clearly, the kinds of seizures that the neurologist encounters in epilepsy are different from the kinds of seizures we encounter in preeclamptic patients. Are you aware of a model that would be helpful for preeclampsia or are these purely more related to epilepsy?

DR. FLUECKIGER: No, sir. This was the best I could bring with me. We worked once, many years ago, on eclamptic models which involved serotonin and, of course, serotonin antagonists would be active. We gave it up because we can do that just as well on a vascular strip. The model does not bring more.

But in the case of bromocriptine, we have no evidence of serotonin antagonism in this conjunction. Maybe my colleague have such information but I do not know of reports in which bromocriptine would be useful in migraine attacks, for instance.

DR. HANEY: I guess my concern is that preeclampsia or eclampsia is such a unique condition that I have very little faith that an epileptic type model or migraine type model is applicable. What you are telling me, in essence, is that you do not have anything at all relative to an eclamptic model.

DR. FLUECKIGER: Yes .

DR. HULKA: Thank you. I think in the interest of going on, maybe, Dr. Winter, you would introduce your next speaker.

DR. WINTER: Our next speaker is Dr. Philip Wolf. We showed the slide of his credentials. I might make one comment in passing in regard to preeclampsia. That is a contraindication for the use of bromocriptine.

PRESENTATION BY PHILIP WOLF

DR. WOLF: Thank you. Last year Dan Kramer discussed the epidemiology of stokes and seizures. I would like to review some aspects of the neurology of postpartum stroke.

Just as an introduction, I personally reviewed all the possible cases, as well as the definite cases of seizure and stroke in the ERI study. I was blinded as to whether or not the women were taking bromocriptine and I am still blinded. I do not know which one of those women in the ERI study who had a stroke got bromocriptine. But I can present two typical or classical postpartum stroke case histories and then just briefly talk about the ten ERI cases.

Once again, we ought to keep in mind that only 1 of the 10 ERI cases received bromocriptine and I hope that these 12 cases could help put the U.S. adverse experience into proper perspective.

(Slide)

The first case I think is a typical case of a 24-year old, healthy white female, with lifelong attacks of severe headaches. And 8 days postpartum she developed a severe headache which persisted at varying levels of severity. On day 10 numbness and weakness of the right hand appeared, followed shortly by paralysis, loss of speech, facial weakness and generalized convulsive seizures with coma

occurred. She died 2 days later. The autopsy showed longitudinal sinus and cortical vein thrombosis.

(Slide)

The second is a patient I took care of. She was a 32-year old, healthy white woman, with a history of migraines since age 18. She had a full-term infant in April of 1987 by cesarean section under spinal anesthesia. The infant had a cleft palate. She was not nursing. On April 18, which was 8 days postpartum, she began to have a headache which increased daily, interfering with sleep. This was attributed to the trouble she had with this child with the cleft palate. She saw a neurologist and on April 23 a CT scan was done on her head, which was normal. On April 24, which was now 14 days postpartum, she awakened totally blind and dysphasic. Spinal fluid showed 12 white blood cells and 81 percent were PMNs, at the local hospital. She was transferred to a university hospital in Boston.

On arrival in the emergency room, she developed focal seizures, with her eyes turning to the right. Then they became generalized.

(Slide)

A CT scan showed cerebral edema. The ventricles are very small, consistent with cerebral edema.

(Slide)

An arteriogram showed clots in these white areas in

the superior sagittal sinus.

(Slide)

Just incidentally, on the arteriogram -- this is the early phase, this is the carotid artery -- there was a small aneurysm seen, which we took to be an incidental finding in this woman's carotid artery.

(Slide)

The aneurysm of the supracondyloid left internal carotid artery was found and we did not think it was related to her present illness. Clotting studies in some detail were normal. She was treated with heparin and Decadron and recovered. A year later the aneurysm was clipped electively and she has no necrologic residua.

(Slide)

This is the first of the 10 ERI cases. Only 1 of these 10 was on Parlodel, a 24-year, healthy smoker, gravida [1, para I, delivered on August 5, 1982 and discharged on the third postpartum day. Headaches began 6 days postpartum and persisted as unilateral left frontal and occipital pressure, present most of the day and night. Pain increased with position change. By 12 days postpartum the headache was very severe . She was admitted to the hospital. She had right and then left-sided weakness. A cerebroarteriogram showed occlusion of the trans-sinus and internal cerebral veins. She was treated with warfarin and recovered.

(Slide)

The second of the ERI cases, and the last in these series, is that of a 30-year old woman 8 days postpartum following C. section who developed headache, language disturbance. The next day right leg weakness appeared. There were periods of confusion. By 10 days postpartum she was dysphasic; had right-sided weakens. EGG was slowed in the left frontal region. CT scan showed an enhancing area in this region, consistent with an infarct. An angiogram was Ion-diagnostic . She improved and recovered completely and a repeat CT scan was normal. The diagnosis was cerebral venous occlusive disease.

(Slide)

I think all four of these cases are cerebral venous thrombosis, one of the forms of postpartum stroked. From the two-volume text on stroke, published in 1985, the clinical Features outline the initial manifestations as usually severe headache, with maybe a focal deficit, particularly hemi-?aresis. The headache may be severe at onset or increasing in intensity over a matter of hours or days. There is no characteristic site or nature to the headache, other than the narked intensity. I think this would respond to the unrelenting headache that we have heard described. Then the other features are seizures in half the patients, cumulative necrologic deficits, but it is generally seizure that alerts

everybody that something is going on. There cumulative necrologic deficits are with paresis in the limb in which the seizure has occurred and there may be dysphasic or other cortical deficits.

(Slide)

So these four cases I think all fit into that pattern of postpartum cerebral venous thrombosis. The first patient I chose was the patient in whom this was first autopsy verified and was described in 1828 by Dr. Abercombie, in his monograph, "Pathological and Practical Researches on Disease of the Brain and Spinal Cord". This was the first time that this verified what the mechanism of stroke was in postpartum.

The second was my patient who did not receive Parlodel. In cases 3-12 only 1 of the cases got Parlodel. So if 3 did, 4 did not, and so forth. In any case, I thought these were all examples of postpartum stroke with severe, unremitting headache. The syndrome seems to relate to stroke type rather than representing a drug-induced syndrome, to my eye.

(Slide)

The last cases from the ERI study are all manner of mechanisms of stroke. One was a puerperal cardiomyopathy with emboli peripherally to the iliac artery, the lungs and to the brain, occurring 10 days postpartum.

The fourth case in the ERI study was a known, inoperable AVM. The woman had had prior hemorrhages in 1972 and 1979. She had a recurrent hemorrhage 5 days postpartum. Case 7 was a fatal subarachnoid hemorrhage 1-2 hours postpartum, presumably from an aneurysm. Case 6 from the ERI series was an intraparenchymal hemorrhage 12 hours postpartum of undetermined cause. They speculated that it was vasculitis. Another was an intracerebral hemorrhage. Case 10 was a hemorrhagic infarction with a woman with sickle cell anemia, 7 hours postpartum. Case 11 was bilateral watershed infarctions with disseminated intravascular coagulation in a woman with toxemia. The fatal stroke was a woman who was known to have systemic lupus for 3 years. She began to have her trouble 4 days postpartum with seizures. She was found to have multiple infarcts and she died postpartum of renal failure, septicemia, shock, ITP and so forth, thought to be a consequence of systemic lupus.

(Slide)

This gives an example of the wide variety. The first 2 cases from the ERI series I thought were cerebral venous thrombosis. Case 3 was an embolic stroke from a cardiac source. There were 4 examples of intracerebral hemorrhage of subarachnoid hemorrhage. Two were due to stroke due to clotting factors. The last one was vasculitis due to known systemic lupus.

(Transparency)

In summarizing the clinical features, as I said, the syndrome of unrelenting headache may be more related to the stroke mechanism. That is, inflammation of pain-sensitive veins and dura rather than a specific drug. It has been recognized for over 150 years.

Secondly, the postpartum stroke in the adverse experience reports, that you heard about from Wendy Nelson this morning, had a similar wide heterogeneity of variety of mechanisms to the ERI cases. I have 15 of the adverse experience reports here. Our numbers are slightly different but 5 were venous thrombosis; 3 were intracerebral hemorrhage; 1 was subarachnoid hemorrhage; 1 was a middle cerebral artery embolus from a dissection of a carotid artery; 5 were stroke in which it was difficult to determine" the mechanism. But I thought that this was a common experience in postpartum stroke.

I was not clear whether the hypertension in postpartum stroke was the primary precipitating factor or whether it was secondary to the intracranial process since hypertension seems to occur in many of these cases, as you read the histories, to come on after the headaches appear, or at least at the time the patients are seen for the headaches. It is hard to know whether hypertension is the primary precipitating factor or secondary to the intracranial

process, such as the intracranial hemorrhage, subarachnoid hemorrhage or venous thrombosis.

In the ERI series, and I think in many clinical series of strokes, the case fatality rate is about 20 percent.

(Transparency)

This is a slide from a paper in Lancet, in 1967, showing that two-thirds of stroke that occurred in women under age 35 were in pregnant or puerperal states. So the problem of stroke in women, say, 15-44 is probably, to a large extent, a problem of stroke in pregnancy or in the postpartum period.

(Transparency)

I asked Mr. Thomas Tom, of the NHLBI, who is a demographer, to look at death rates for women 15-44, in the United States, over the past 20 years. As you know, there has been a tremendous decline in stroke death rates for men and women, blacks and whites, at all ages throughout the United States, approximating 50 percent in the last 15 years. The women, 15-44, have participated in this decline. There is no evidence, to my eye, of a bump or an increase since Parlodel or even the pill was introduced but, rather, a steady downward trend ever since.

I think these data are difficult to interpret but I guess data reflecting on this are very hard to come by. That

is all I have to say. Thank you.

DR. HULKA: Questions? Comments? If not, thank you. Dr. Hennekens is next.

PRESENTATION BY CHARLES HENNEKENS

DR. HENNEKENS: Well, it seems to me that last year when this Committee met there was apparent consensus that in terms of known or even postulated benefits or risks, bromocriptine, in fact, seemed to be the best of available agents.

On the other hand, there were descriptive epidemiologic data, a series of case reports that raised legitimate scientific questions and concerns. There were, however, also some basic research findings which were largely reassuring, although not ideal in terms of any clear relevance to the experience of postpartum women.

It was generally agreed that the only way to directly evaluate the potential risks of bromocriptine was to do an analytic epidemiologic study, that is, a study of an adequate sample of individuals with an appropriate comparison group.

Since such a study was being conducted by ERI, we were all anxiously awaiting the results. Since last year's meeting, I believe the data which have become available from this study have served to provide, on balance, further reassuring evidence about the true benefit to risk ratio with bromocriptine.

The ERI study provides, in my view, strong and reassuring evidence against the hypothesis that bromocriptine increases the overall risk of seizures. In the subgroup of seizures occurring more than 72 hours after delivery, a positive association was observed. But this subgroup effect, which has little biologic plausibility, was counterbalanced by an even less plausible but very marked and strongly protective effect of bromocriptine on early occurring 5eizures.

Based on the available evidence, I believe these subgroup findings to be far more likely casual than causal, in other words, far more likely to reflect play of chance than any true physiologic difference in susceptibility.

With respect to stroke, the data were largely uninformative because of the small number of endpoints experienced, a finding that is unfortunate but not unexpected.

When viewed in the context of the totality of evidence, the ERI data are far more reassuring than in any way alarming. So I believe the totality of evidence available today to be more reassuring and, indeed, alleviates most of the concerns suggested by the previous interpretations of the uncontrolled data from the case reports.

Now, it also appeared to me that this Committee had taken the position last year that there seemed to be a need for drug therapy to prevent lactation in at least some

categories of women. One year later it appears that the Committee no longer feels this to be the case.

I think it would be useful to consider distinguishing between the biologic need and patient desirability. While pain is certainly a natural process but, as a patient myself occasionally, the desirability of pain relief is certainly not unnatural.

Dr. Syler (phonetic), a neurologist and colleague of mine from the Cleveland Clinic, pointed out to me just last week that while the headache of migraine will abate after a period of time, she routinely considers in selected categories of her patients the possibility of prophylaxis with beta blockers and, based on recently reported data from our randomized trial of physicians, now uses low dose aspiring prophylaxis.

Ken Rothman, a dentist as well as an epidemiologist, pointed out to me just an hour or so ago, that pain is a natural and logical consequence of routine dental procedures but in almost all cases he and his patients desire and, indeed, elect to use Xylocaine as prophylaxis.

I suppose I should preface these brief remarks by stating that while previously I have spoken as an epidemiologist on issues of efficacy and safety, I would like to make just a very few brief comments as a physician and individual.

As a physician, I would hope that need could be an individual clinical judgment between a health care provider and his or her patient. In my view, such individual clinical judgments should include perception of need on the part of both the patient and the health care provider, as well as the health care provider's knowledge of the known side effects of a drug in light of demonstrated efficacy.

It is certainly possible that a recommendation of this Advisory Committee or even an FDA decision that there is no need for bromocriptine could potentially adversely affect a patient, the health care provider or the relationship between them, whether medically, legally or even socially. But whether or not this occurs, to me, is of far less consequence that in this free society we must appreciate, defend and preserve free and informed choice.

So in closing, I would like to ask each member of this Committee, as well as the FDA, to consider their mandate is the primary consideration of efficacy sufficient, or does the mandate rationally include preempting the freedom of choice of either the health care provider or the patient?

Medically, in my view, the latter would surely be the case for any drug of either undocumented efficacy or, conversely, of documented harm. Given that this does not seem to be the situation with bromocriptine, I believe that neither the Advisory Committee nor the FDA should, in this

case, in particular seek to dictate social policy. I only close by adding that these views are my own and do not necessarily represent the views of Sandoz, Harvard Medical School or the Brigham and Women's Hospital. Thank you very much.

DR. HULKA: Charlie, I would like to ask you a question. Will you tell us what we have seen today that documents efficacy of Parlodel?

DR. HENNEKENS: I do not know what you have seen today because I was not at the meeting today. Would anyone want to comment? I can say as an outsider, who has had the opportunity to review the ER. data, as well as other sources of data, that it just seemed to me that there was a several-fold --

DR. HULKA: We told the ERI folks that they did an excellent job but that has nothing to do with efficacy.

DR. HENNEKENS: That is right. Well, the data that I saw, and I am probably not the best qualified to discuss this, showed that women who received this drug had really a several-fold decrease in development of symptoms postpartum and, indeed, the so-called concern about a rebound effect in the women who used it still left them at a far lower frequency of reporting any such discomfort. But I do not know that I am the best person to discuss that.

DR. NIEBYL: You missed the discussion. Let me

just ask you a question about the so-called protective effect in the first 2-3 days. It seems to me that since these patients were not randomly assigned to drug or no drug, and there is going to be a significant bias against prescribing it to any sick patient, that would explain that protective effect. If somebody seized 6 hours postpartum, nobody is going to give them Parlodel by mouth. So that patient is going to be in the no drug group, or any sick patient, for example, a patient who is not taking drugs by mouth.

DR. HENNEKENS: Yes.

DR. NIEBYL: So that would means there would be a bias that the treated group would be the least likely to have any kind of problem.

DR. HENNEKENS: Yes, I do not feel that I am here to really defend that. I thought that had been established before. I feel that I am really on shaky ground. But let me just ask you, is it not true that if the drug gets approved by the FDA, it has to demonstrate some efficacy? How did it get here?

DR. NIEBYL: That is a good question.

DR. RARICK: As they reviewed, and as I reviewed this morning, there are some double-blind studies that show possible effectiveness in the first week versus the other drugs, binders or whatever else was used. I do not know that you can say it is greatly effective. I do not think you can

deny that it is possibly effective in that first week of therapy.

DR. MANGANIELLO: I am assuming most of those drug trials were done with an active drug.

DR. RARICK: Correct. Of the 17 double-blinded studies, as we saw, 5 were placebo studies --

DR. MANGANIELLO: Was that after the fact that it had already been approved for usage in this country?

DR. RARICK: No.

DR. MANGANIELLO: Those were all with the IND?

DR. RARICK: These were all NDA.

DR. CORFMAN: I am willing to say, assuming that the drug was needed, that I do not think Lisa and I would recommend approval based on the efficacy data that have been presented at this time. But we were not here then. So we are just dealing with all the data and having another look at it. But I think that should be put in the context of the whole discussion for both days rather than just focusing on it today.

DR. BARBO: I would like to raise the point that if we are only going to deal with severe endpoints and problems with the drug, we are not talking about all the women who get headaches and hypotension that are not reported and I do not see studies on that. Our nurses on the floor have told me in the past that a lot of women get headaches and a lot of them

get some hypotension and we have no information at all as to the side effects.

DR. HULKA: Dr. Winter?

PRESENTATION BY DAVID WINTER

DR. WINTER: Thank you, Dr. Hennekens. I am sorry they put you on the spot like that on an issue that is quite different.

After hearing the somewhat eloquent comments, I think I will skip part of my conclusions because they deal with somewhat the same subject, at least in part. On the other hand, I will continue with a little bit of it because it may be our last chance to so comment.

We believe there are some patients who for sound medical reasons should have access to therapy in the post-partum period. We believe bromocriptine is an appropriate choice for some of these patients. We also believe that an informed patient should have the option of choosing the type of therapy she desires if she elects not to breastfeed. While we strongly recommend that all women capable of breastfeeing do so, there does remain a small set of women who do not desire to do so and who seek some symptomatic relief in the engorgement and pain that there might result. These women should be counseled and the options should be explained to them fully.

A striking finding in our survey of women in the

postpartum period was that most women do not discuss their newborn feeding choice with their physician or any member of the office staff. Fewer than 50 percent of the women surveyed from university centers had ever discussed this topic at all. It is clear to us that education is an essential but, unfortunately, often missing ingredient in the decision to breastfeed or not.

This education should be aimed at the physician, office and hospital staff and the patient herself. To this end, we are prepared to take two steps. First, to improve physician education, we are proposing to revise the package insert for Parlodel. While this is not the appropriate form for detailed discussions of the wording, I would like to share with the Committee some of the broad outlines of these proposed changes.

(Transparency)

I have picked a few sections here and this is not complete but, nonetheless, this is a section of indications and usage. The underlining on the right indicates some suggested changes.

DR. CORFMAN: Can you read it because we cannot really see it? We are very interested in your indications.

DR. WINTER: Basically, we have strengthened the wording on alternative therapy. As I said, I do not think this is not the forum but we want to show you in broad terms

that we feel that several changes can be made. But we are certainly strengthening the alternative therapies section, which goes in there.

DR. CORFMAN: If you could just read it?

MR. WILKINSON: I will read it: After stillbirth or abortions, number 1; number 2, after parturition when there exists a contraindication to breastfeeing or medical condition on the mother or child that makes breastfeeding undesirable or, (b) when a mother elects not to breastfeed or not to avail herself of alternative supportive therapy. See also information for patient section.

DR. WINTER: If you can slide that over, you can see the previous indication and use section. It does not allude to other alternative therapies and, in fact, is not cross-referenced as this is. The next point I want to make is that this is cross-referenced to information for patients. We have significantly expanded the information for patients section.

DR. HULKA: I am wondering what you are recommending, if you are recommending bromocriptine for routine prophylaxis of breast engorgement of if you are recommending bromocriptine for particular indications.

DR. WINTER: No, it is not for routine prophylaxis, as I think all of us have stated here. It is to be considered as an option and after discussion for those women who elect

not to breast feed. This should be considered as one alternative.

DR. HULKA: Then what are the indications for use?

DR. WINTER: The first indications that we retained from the previous package insert were after stillbirths or abortions. This does not mean that everybody who has this is supposed to get it. This means that this is an allowable situation in which the drug can be prescribed. It may be chosen not to, obviously, because the major emphasis on our program, which I will get to in a moment, is an education program. So if something is listed as an indication, that does not mean you have to use it for the indication.

DR. SCHLESSELMAN: But isn't the effect of the recommendation to say that anyone who wants it ought to get it, and they ought to get it even though they do not have any condition, in evidence yet, that requires therapy because the drug is used before any breast engorgement or pain?

DR. WINTER: Clearly, it is used before but, no, this does not predicate that every patient must use it. Al 1 we are really interested in is having this compound available as one option.

DR. CORFMAN: Dave, you have not specified the indication. Would yOU give us the medical indications? You said it would leave the clinician to recommend to his or her patient that she should use this drug. To me, that sounds

like routine use.

DR. WINTER: It is very difficult without going through the multiple sections and going back and forth to see the whole context of the insert. I mean, here we are really talking about the nature of package inserts rather than the nature of the use of bromocriptine. If anyone has figured out a package insert, please let me know.

DR. MANGANIELLO: Under number 2 it says, medical indications.

DR. WINTER: I said other conditions. Then it lists two situations where this could be considered.

DR. NIEBYL: But we have already said that we did not think there was a need for the drug in a group of women who have selected not to breastfeed. We already discussed that yesterday, that we thought, as a general principle, that women who elected not to breastfeed or had stillborn, or whatever, that there was not a need for a pharmacologic treatment for that physiologic process.

DR. WINTER: Frankly, what we are suggesting is that these are conditions in which such therapy could be considered. Nothing more.

(Transparency)

I think we may go around and around on this because I can show you rather briefly that we have expanded the information for patients section, in which we go into some

detail -- and again I apologize because it is very small type. Fred, would you be able to read some of-that?

MR. WILKINSON: Yes, just the underlined section, which is an addition to what was existing in the package insert reads: Patients receiving Parlodel for prevention of physiologic lactation should be advised of the following: Certain women are not able to breastfeed because of medical conditions in themselves or their infants. Most mothers have a choice. For those who choose not to breastfeed, treatment of the symptoms of breast engorgement can often be accomplished by use of breast binders, ice packs and, if necessary, aspirin or other analgesics for pain relief. Parlodel actually prevents milk production, breast engorgement and pain from occurring but it has certain side effects in some patients. See adverse reactions.

DR. WINTER: Again, this is an expansion. I must say, I am not familiar with many package inserts in which it is suggested to consider other therapies. I think as package inserts go, this is a somewhat remarkable step, at least in my opinion.

In addition, we have revised the wording in the precautions section and also in the adverse reactions section. I do not intend to go through all of those but it is to give you a sense that we have spent some time in trying to give a fuller picture of the situation and cross-reference

all the other sections. We think it is a significant step forward, at least in terms of the package insert.

(Transparency)

In addition, we plan to take a second step, and that is with the consultation of the Agency, to produce and provide a patient information booklet. We would plan to place copies of this booklet in all physicians' offices handling OB/GYN cases and also in all hospitals that have OB services. A very brief outline of that booklet is as follows there. I think that is slightly larger type and I can handle this .

As envisioned at this point in time, we would have four components to it: The introduction, talking about the benefits of breastfeeding and discussing some reasons why some women cannot breastfeed and, of course, reviewing pregnancy and lactation, as you can read, methods of prevention, again starting with mechanical methods, discussing pharmacologic methods and then, finally, analgesics. Again, the wording can be modified. But this is the outline of something that we feel would be very useful and important. As I mentioned, we consider education a very significant element of this and, quite honestly, we were somewhat surprised, at least on our survey results, about the few number of women who really had counseling about this.

We believe these steps will address the issue of

educating further both physicians and patients and we hope it will ensure that if bromocriptine is prescribed in the postpartum period, it is done in the context of examining alternatives and understanding potential risks, as well as benefits.

To sum then, our position is simply this, if a drug has been shown by applicable statutory standards to be safe and effective for its labeled indication, and if a patient and physician together make an informed decision to choose treatment with that drug, that choice ought to be permitted and, indeed, protected. To deny the physician and patient that freedom of choice because of the Advisory Committee's personal treatment preference, however sound, is a real disservice to the responsible medical community that has prescribed the drug safely and effectively for many years, and also to an informed patient population that has the right to exercise a degree of control over their own bodies and to participate in decisions directly affecting their own wellbeing. We ask that this Committee not remove this element of choice. Thank you very much.

DR. HULKA: Thank you. Let's have a five-minute break.

(Brief recess)

DR. HULKA: If we could start again, we had gotten through question 5, except for the latter part of question 5

in terms of bromocriptine. Then we had gotten through question 6, except for 6.4, which again is in respect to bromocriptine. Why don't we start with 6.4 first and then go back to the second part of 5?

Question 6.4 is: What are the Committee's recommendations concerning the following drugs currently in use -. so now what are the Committee's recommendations concerning bromocriptine for the prevention of postpartum breast engorgement ? What are our recommendations? In other words, do you recommend its use for prevention of postpartum engorgement?

DR. NIEBYL: Are you asking for volunteers or are you going around the table?

DR. HULKA: I was wondering if you wanted to have any comments before we vote on whether you recommend its use, yes or no. But I was just wondering if you wanted to comment on that before we vote.

DR. NIEBYL: We have probably had enough comments.

DR. HULKA: Are you ready?

(Several Committee members answer affirmatively)

All right. All those who think bromocriptine should be used for the prevention of postpartum breast engorgement, please raise your hand.

(No show of hands)

All those who think that bromocriptine should not

be used for the prevention of postpartum breast engorgement, please raise your hand.

(Show of hands)

That looks like a unanimous consensus. This is the response to question number 6.4 and the Committee's unanimous recommendation is that bromocriptine not be used for the prevention of postpartum breast engorgement.

Then let's go back to question 5 because this has to do with the treatment of symptoms of postpartum breast engorgement. The distinction here is that now we are talking about symptomatic other kinds of indications for its use, in contradistinction to what we just considered which was prevention. The question here is what might be the indications or what are the indications? Does anyone want to speak to that?

DR. NIEBYL: I do not think we have any data. We have not seen any controlled trials at all about therapeutic use of bromocriptine. So that would require data to be presented to suggest that once the patient is engorged, it would be effective. But we do not have any such data. In fact, it is very difficult to get such data because it is a self-limited condition that goes away in 24 hours. So if you give a drug when a patient is engorged, you are going to have to have a placebo control and look at the patient very quickly because it is going to go away by itself so fast the

drug will not have time to work.

DR. HULKA: Okay. But if one wanted to recommend bromocriptine for some indications or symptoms related to postpartum breast engorgement, then data on that in appropriate trials would be required.

DR. NIEBYL: I would think so.

DR. HULKA: Would that kind of a statement be what you would like to hear?

DR. MCDONOUGH: Yes.

DR. NIEBYL: Yes.

DR. HULKA: Is there anyone in disagreement with that statement? Is everyone basically in agreement? If you would raise your hands?

(Show of hands)

Then I will try a statement and if it does not work out you can tell me. Question number 5 is should bromocriptine be used to treat the symptoms of postpartum breast engorgement? The Committee's unanimous answer to this question is that we really do not have data as to what these indications or symptoms might be; that if there is an interest in using bromocriptine for treatment, as opposed to prevention, then the appropriate kind of clinical trials should be performed so that the data can be obtained as to the usefulness and the efficacy of bromocriptine in such treatment and for such indications.

If we go on then to question 7, it asks if the Committee recommends continued use of any of these drugs for this purpose, and this purpose is prevention of postpartum breast engorgement. So then what are the Committee's recommendations concerning physician labeling?

DR. ROY: It is really not applicable any more since we have already made our position clear on the previous questions.

DR. HULKA: So you are saying that question 7 is not relevant, given our responses to the prior questions.

DR. NIEBYL: Or question 8.

DR. HULKA: We will do one at a time. Question 7, the Committee feels that there is no relevant answer to question 7, given our responses to the prior questions.

DR. CORFMAN: I would like the Committee to address question 8 anyway, even though it may be moot based on your previous answers. I would like you to think in terms of what if we are unable to get concurrence from sponsors to follow your recommendations. We have a long road to go to follow up on your recommendations and what if we are unsuccessful in getting compliance? Would you recommend that we mandate a patient pamphlet? That is my question and I would like you to answer that question.

DR. NIEBYL: Well, if you are talking about labeling, I would like to make two suggestions about the

label, if that should come to pass, as you say, under those circumstances . One is that the term breast binder not be used but breast support. I think I mentioned that yesterday. The second thing is that I would hesitate to recommend in the package insert or in the patient information pamphlet -- I think aspirin was specifically mentioned and I would hesitate to recommend aspirin because we usually do not give postpartum patients aspirin because it has a much more potent effect on platelets than any of the other nonsteroidal anti-inflammatory or analgesic drugs, such as acetaminophen, ibuprofen or whatever else you choose to use. We usually use that type of drug postpartum, not aspirin, because aspirin can increase the risk for bleeding. So those are two comments on the label.

Now, your question about patient information is should it be? "

DR. ROY: Well, before we get to that, I think the other point, just as a follow up on what Jennifer was saying, is that I take exception to "pain killers". I think a more appropriate, less pejorative term could be selected.

But I certainly think in terms of point number 8 that a patient information brochure should be developed and distributed.

DR. HULKA: I think we will note for the record that we object to the term "pain killers" and that use of

aspirin, for the reasons you indicate, and if any reference is going to be made to what kind of mechanical devices might, be used on the breast, we prefer the term breast support rather than breast binders.

DR. NIEBYL: But as to the question should a patient information pamphlet be mandated, I would say, yes, it should.

DR. HULKA: We want a little revision of question 8. I guess what we are really talking about is whatever the indication, related to postpartum breast engorgement that bromocriptine might be used for, whatever those indications turn out to be, we do think that there should be patient information to go with the drug. Is that correct?

All those who agree with a statement of that sort, would you mind raising your hands?

(Show of hands)

Anybody who disagrees?

We have modified question 8 a bit to relate to whatever the indications for bromocriptine in relation to postpartum breast engorgement turn out to be -- whatever these indications turn out to be for bromocriptine, we do believe that there should be patient information to go with the medication.

We did not specifically talk about sex hormones in terms of any patient package insert. If it is okay with you,

e will let the sex hormones ride for the moment so as not to onfuse the issue.

Are there other comments or issues you want to ddress before we adjourn?

(No response)

Thank you all very much. We want to give our best o the "Pauls" whom we will miss very much next year.

(Whereupon, at 3:30●., the Committee adjourned)

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FOOD AND DRUG ADMINISTRATION

FERTILITY AND MATERNAL HEALTH DRUGS

ADVISORY COMMITTEE

Bethesda, Maryland

June 2, 1989

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