thing.

DR. EAGLSTEIN: Right. But in this point, they say -- they do discuss pregnancy. It says, "The possibility that you may be pregnant should be ruled out by you and your doctor." Is that sufficient?

DR. CHANCO-TURNER: That's what we decided, isn't it?

DR. EAGLSTEIN: You don't want to say it should be ruled out by taking a test?

DR. TABOR: Well, that's done on the next page.

DR. EAGLSTEIN: Okay. Anything else on that page?

DR. RASMUSSEN: Yes. They have about the third sentence down, it says, "An effective form of contraception (birth control) should be discussed with your doctor and used during and for up to one month after Accutane therapy."

That statement as it stands now sounds like everybody has got to be on IUD, birth control, diaphragm, jams, jellies, whatever. What about the 16 year old kids who is virginal and isn't having any sex? It sounds like there that you are telling them that they have to go on birth control pills and I don't think that is appropriate. Or even for 25 year old people. What difference does it make how old you are. If you are not having sex and you don't want to take birth control pills or some other form of contraception, why should you have to?

DR. CHANCO-TURNER: Isn't abstention the best form

of birth control?

DR. RASMUSSEN: I agree, but it doesn't say that in there. If you tell a patient that you have to use birth control, they are not going to think of abstention. They are going to think of pills, jams, jellies, foams.

DR. EAGLSTEIN: Well, do you want to propose alternate words? Do you want to start out saying "sexual abstention or an effective form of birth control?"

DR. RASMUSSEN: Sure.

DR. EAGLSTEIN: All right.

DR. RASMUSSEN: I think if you don't, it implies that everybody who uses the drug has to use birth control.

DR. EAGLSTEIN: I hear what you are saying. I don't know that everyone agrees with you.

DR. RASMUSSEN: Well, let's discuss it. If nobody thinks it is an objection, I won't --

DR. EAGLSTEIN: How do others feel? Do you feel that this suggests that a person who is not having sexual activities now needs to take birth control pills?

DR. CHANCO-TURNER: Well, in the discussion with the physician, it will certainly come out and abstention is --

DR. EAGLSTEIN: Is satisfactory.

DR. CHANCO-TURNER: -- satisfactory, I would think.

DR. EAGLSTEIN: Dr. Rasmussen, I'm not hearing support for your view, but you can propose --

(Laughter.)

DR. EAGLSTEIN: -- an alternative; otherwise, we'll go on.

DR. RASMUSSEN: Well, it seems to be saying that everybody who is on Accutane has to use some form of birth control, and this is not the message that is going to the doctor. This is what you are going to have patients read, most people when they see birth control think of the things that I've already mentioned. They don't think of abstention.

DR. EAGLSTEIN: Well, Dr. Turner feels the doctor will straighten them out. Some patients are smart enough to know that.

Okay. I'll be happy to entertain a proposed change, but otherwise we will move on.

DR. POMERANZ: It's indicated.

DR. RASMUSSEN: These documents will have some medical/legal weight. Not as heavy perhaps as the physician's package insert, but this leaflet will have some publicity. I mean, people will read that. And I would prefer that it not be there without some modifier stating that if you are not planning to have intercourse --

DR. EAGLSTEIN: Please make a proposal to that effect?

DR. RASMUSSEN: -- I think you would wind up -- for instance, if people are on birth control pills, I would wager you would have more people getting sick on birth control pills,

who hadn't been on them before than you would from the Accutane.

DR. EAGLSTEIN: Please make a proposal?

DR. HASERICK: If it is possible that you may become pregnant --

DR. RASMUSSEN: Sure. If it is possible that you may become pregnant an effective form of contraception should be discussed with your doctor and used during and for up to one month after Accutane therapy.

DR. EAGLSTEIN: All right. Okay.

If it is possible you may become pregnant.

Second?

DR. KENNEY: I'll second it.

DR. EAGLSTEIN: He is moving that we add these words.

Further discussion?

(No response.)

DR. EAGLSTEIN: All those in favor of that motion, raise your hand?

(A show of hands.)

DR. EAGLSTEIN: Those opposed?

(No response.)

DR. EAGLSTEIN: It's passed.

MR. BOSTWICK: I've got it.

DR. EAGLSTEIN: Okay. Next page. The next page is where there is going to be an addition for females, "Accutane should not be taken until you are sure you are not

pregnant, and you are using an effective form of contraception."

Any changes in this page?

DR. CHANCO-TURNER: You've got the very same problem.

DR. HASERICK: We've already covered that in the previous paragraph.

DR. RASMUSSEN: Yes, I think that's fair.

DR. EAGLSTEIN: Again, a pregnancy test isn't indicated.

DR. BILSTAD: That's one of the things in the FDA proposal.

DR. EAGLSTEIN: And we don't say one month afterwards. It doesn't tell them that they should use it for one month afterwards.

DR. POMERANZ: It had to be in the previous warning. The previous warning says it.

DR. EAGLSTEIN: Oh, for a month after it?

DR. BILSTAD: Yes.

DR. EAGLSTEIN: Okay. All right. Is everyone happy with this?

DR. BILSTAD: I would like to make one additional suggestion for this page. It is not included in the FDA version. The insert doesn't really say that the treatment is meant for severe cystic acne. One of the previous pages does refer to a severe cystic acne, but it may be appropriate

in the first sentence on this page that we were just looking at, instead of saying, you're condition, say, "Accutane is a medicine for use in treating severe cystic acne that has not responded to other treatment." I believe that is a message that is important to get to the patients that this is for the severe disease and not for the garden variety of acne.

DR. GOLDNER: I would agree with that suggestion.

DR. EAGLSTEIN: Would you make that motion?

DR. GOLDNER: And I would make that a motion. That is a perfect place for it, I believe, right --

DR. EAGLSTEIN: It should be used for treating --

DR. GOLDNER: Before treatment. It is under before treatment. "Accutane is a medicine" -- it states, "For use in treating your skin condition."

DR. EAGLSTEIN: Right.

DR. GOLDNER: We should delete that and have it state, "Severe cystic acne" --

MR. BOSTWICK: That has not responded to other treatment.

DR. GOLDNER: -- "other therapy."

DR. EAGLSTEIN: That is Dr. Goldner's motion. Is there a second?

DR. KENNEY: Second.

DR. EAGLSTEIN: Discussion?

(No response.)

DR. EAGLSTEIN: All those in favor?

(A show of hands.)

DR. EAGLSTEIN: All those opposed?

(No response.)

DR. EAGLSTEIN: It passes.

Further recommendations on this page?

(No response.)

DR. EAGLSTEIN: The next page. During treatment, the during treatment page?

DR. KOEHN: Are we in during treatment, are we?

DR. EAGLSTEIN: Yes, the next page.

DR. KOEHN: Could we possibly add about sunburn on that? It is in the physicians' warning, but I haven't seen it in here.

DR. EAGLSTEIN: Okay. A sunburn warning.

DR. KOEHN: There seems to be more than 5 percent. It is certainly more than 5 percent.

MR. BOSTWICK: I can't remember --

DR. EAGLSTEIN: This is a page that doesn't mention names or use scare tactics of diagnoses. Do you think that the symptoms, as outlined, are satisfactory, to alert the patient to these problems?

(No response.)

DR. EAGLSTEIN: Where shall we add the sunburn?

DR. KOEHN: Some other reactions that have occurred

are:

DR. POMERANZ: Exaggerated sunburn and sensitivity.

DR. KOEHN: Yes, increased sun sensitivity, or something like that.

DR. EAGLSTEIN: Would that be one of the ones proceeded by a little dot, severe sun sensitivity, or sun sensitivity?

DR. GOLDNER: Put it right where a headache was -- where headache was stricken out. The rash thing, hair thinning --

DR. POMERANZ: Sensitivity to the sun?

DR. GOLDNER: -- yes. Peeling of the palms.

DR. EAGLSTEIN: Do you want to move that, Dr. Koehn?

DR. KOEHN: I move that we add, "Some other reactions have occurred are: mild nose bleed, aches and pains," and so forth -- "rash, increased sensitivity to the sun."

Does that sound right?

DR. KENNEY: Yes.

DR. EAGLSTEIN: Increased sensitivity to the sun and peeling of the palms, and so on?

DR. KOEHN: Yes, okay.

DR. EAGLSTEIN: All right. Second?

DR. KENNEY: Second.

DR. EAGLSTEIN: Any discussion?

(No response.)

DR. EAGLSTEIN: No question about this.

All those in favor?

(A show of hands.)

DR. EAGLSTEIN: Opposed?

(No response.)

DR. EAGLSTEIN: It passes.

I should point out that now the FDA had several suggestions here for the during treatment section. And they were concerned that this booklet say, "Serious neurological disorders, visual loss." Headache and blurring vision, that is in here?

MR. BOSTWICK: Some of that is included and some of it isn't.

DR. EAGLSTEIN: Some is and some isn't. It seems to be that in this case they discuss a serious neurologic disorder whereas in the booklet, as it stands, it says, "You should be aware and if any of these things happen, you should see your doctor."

DR. CHANCO-TURNER: It says add old print. So, it is in bold print.

DR. EAGLSTEIN: In this case, we are disregarding this suggestion, "It had serious neurologic disorder which may lead to visual loss if undiagnosed and untreated." And the second point in the FDA position paper was that it should state, "Accutane may be associated with severe inflammatory bowel diesease," which again isn't said. It

says severe stomach pains.

DR. BILSTAD: Severe stomach pain, diarrhea.

DR. EAGLSTEIN: The difference, in general, seems to be the word "disease" or the word -- all right. I think we just need to be aware of what we're doing and to knowingly not comply, or knowingly comply.

And the third one is this skeletal thing. "Accutane taken for longer periods," and here it is the same story. They do say severe aches, pains and stiffness.

All right. Anybody, if you change your mind based on this, speak up as we go on through this.

So, any more on that page where we added sunburn?

DR. KOEHN: Just one thing, and that is -- it says, "Your eyes may also feel irritated," under common side effects. That is hard, I think, for a patient to interpret irritation like a conjunctivitis, which is common from the beginnings of pseudotumor cerebri. I am concerned that that's there, yet, I realize we're having a lot more calls, but maybe we should be responsive to those. And I don't know if that should be there under common side effects.

DR. EAGLSTEIN: You think it shouldn't say, your eyes may --

DR. KOEHN: Your eyes may also feel irritated -- under common side effects -- so, I think, well, my eyes are irritated and so you let it go a while and it may be the

beginning.

DR. EAGLSTEIN: Of pseudotumor cerebri?

DR. KOEHN: Yes.

DR. EAGLSTEIN: I thought that was a headache and blurred vision?

DR. KOEHN: Well, blurred vision -- then, you were asking the patient, you know, are your eyes irritated or do you have blurred vision. I don't know.

DR. EAGLSTEIN: Other thoughts on this issue?

DR. HASERICK: The same thing goes about aches and pains. You've got it in one paragraph and then in a second paragraph. I don't hink it is necessary to put them in both. The second black dot, the middle of the paragraph.

DR. KOEHN: There it says, "severe muscle aches and pains."

DR. HASERICK: Yes.

DR. KOEHN: Which would be helpful.

DR. EAGLSTEIN: So, you would think you should delete it from under the common, is that what you want to do?

DR. BILSTAD: Could I make a comment?

DR. KOEHN: I think so.

DR. EAGLSTEIN: Sure.

DR. KOEHN: I would like to hear what everybody else thinks, but it seems misleading to a patient who doesn't know blurring from conjunctivitis, or whatever. I mean, they don't know what to look for. And if they start to have

some symptoms, you know, it will heal, they'll let it go for a while. I wonder if that doesn't deserve a call at least.

DR. EAGLSTEIN: All right. You have a comment?

DR. BILSTAD: I would like to point out in general in this section that I think the difference between the FDA version and the version that the company is proposing is more than simply one of sophistication of language. The intent is to -- rather than to simply list some symptoms that they may occur, it is to indicate that this is some kind of entity that we're talking about. And if you give it a little more meaning, a little more substance, rather than to simply refer to some symptoms without giving them any context. And that particularly is true for the -- in talking about the joint pains and the muscle pains. There are certainly the incidence of muscle and joint pains is, I think, relatively high. As I recall, it is about 15 percent of patients who have those pains unassociated with anything else. The intent of the third part of the FDA version was to point out the possibility that some patients, at least treated for longer periods, have had skeletal changes.

This is quite different. And one of the questions is: should that be mentioned specifically in the package insert. This is quite different from muscle aches and pains not associated with skeletal changes.

Along those same lines, I would like to ask Dr.

Cunningham -- he mentioned this morning that there were 30 patients who had been treated with -- cystic acne patients who had been treated with Accutane with the visual doses on the package insert and did not have any skeletal changes when examined. I would like to ask him how long in fact those patients were treated and when were they examined, I presume with X-rays?

DR. CUNNINGHAM: I would like to respond to that, because it is a very important point. The changes produced by Accutane in long-term therapy I think are unquestionable. You've seen the results of both, as I pointed out this morning, in a retrospective fashion and a prospective fashion the disorders of keratinization patients. I think that the, as I pointed out this morning, cystic acne population that we studied was a population of 50 patients in the Pacific Northwest. They had baseline exams of their skeleton and follow-up exams at end of therapy and will have follow-up exams at one year intervals thereafter.

Thirty of the 50 patients; that is, those who have finished the course of therapy had had no changes on skeletal X-rays at end of therapy with package insert dosing and duration; that is, either 15 to 20 weeks and 1.0 to 2.0 mg/kg/day dosing.

Now, I do question -- there is no question in my mind that this is an effect of the drug in long-term therapy, and

on the other hand, I do question whether a patient understands skeletal changes. Of course, I guestion whether some of us to understood that a few months ago until we went into it in a little more detail.

Furthermore, the signs and symptoms of this disorder in most of the published literature and in our experience, are rather minimal so that I am not sure that we can properly address that even with our statement about severe aches and pains. That does come the closest to it, however, because that makes sense that then one with severe pains who see their doctor. Now, whether that would be due to skeletal pain or muscular pain, that would be for the doctor to determine, I think.

We are satisfied that the wording that we presently have is about as much information as we can give at the present time to the patient. And the rest of it, I think, will have to be developed and given to the physician and the patient concurrently when we have more information.

At the present time, however, we don't see a problem with the cystic acne population.

DR. BILSTAD: I would just like to point out that the package insert, of course, allows treatment for up to 40 weeks and we've been told earlier that with the disorders of keratinization that changes were being seen at about 26 weeks, at least some changes were being seen. So, I think

you need to keep that in mind that this did not include the two courses of therapy, but was simply the one course of therapy.

DR. EAGLSTEIN: Dr. Del Vecchio, very briefly.

DR. CUNNINGHAM: One other point I would like to make is that the mean dose of these patients -- that the patients received who had skeletal X-ray changes was 2 mg/kg/day That is different from the mean dose in clincial practice. Our dose range in the package is 1.0 to 2.0 mg/kg/day and the practitioner in general is staying toward the lower end of that range in our experience. I don't have the figures on that, of course, but --

DR. EAGLSTEIN: Okay.

DR. DEL VECCHIO: I would just like to address a couple of points very briefly.

We would object to deleting the irritation of the eyes. If you wish to change it to redness of the eyes, if that is more clear perhaps, we could do that. But we are -- conjunctivitis does occur and we want to be sure the patient recognizes it. It is different than visual disburbances. This is not simply a listing of symptoms. We have taken out the most important symptoms. We have added the word severe. We have said be alert to these things. They are more serious conditions. They may be permanent if they are not treated. That is already in there. We have been very careful to put that in and separate them out. That's what we took headache

out of the less common symptoms and put it down into the other area because we feel without saying severe, we're just saying headache.

The other point about hyperostosis, let me just ask you hypothetically, what will the patient practically do with that information? Does the patient go into the physician and say, I wish to be screened for that? And then how does the physician screen them? I mean, we are talking about a totally different area now. Certainly, if we are suggesting that they look for serious musculoskeletal symptoms which are more severe than the usual, fine, but the only way that a physician can respond to a patient, in my mind, would be to say well, if you wish to, we can begin to do routine X-rays. And, of course, that is not recommended. And then follow-up X-rays. Practically speaking, what will they do with that information?

DR. BILSTAD: I think one of the purposes of the package insert is also to make the patient aware of things that can happen. In other words, what are the risks of taking this drug and, in turn, I think that may influence behavior and may influence behavior, of course, in one sense, which we wanted to in terms of pregnancy. It may influence behavior, for example, in getting longer treatment. Patients have ways of getting treatment beyond what the package insert indicates. I think this is a way of saying, or this is one place where it

can be said that if treatment is given beyond what is recommended that there may be serious side effects. Simply saying that there are severe muscle aches and pains, stiffness of the joints and that if you have that, you should go see your doctor does not give that message.

DR. DEL VECCHIO: That is true. As a matter of fact, those are not really the symptoms of the early stages of hyperostosis, and I think that is the problem. I think you are raising another issue though in terms of longer treatment. It means you're going back to the dosing issue again if you're talking about shortening treatment, which is another totally separate issue. But I just raised that question as to what practically the patient will do with that information.

DR. EAGLSTEIN: Thank you.

Dr. Koehn?

DR. KOEHN: I would certainly prefer rather than saying your eyes may feel irritated that you may experience some redness of the eyes.

DR. EAGLSTEIN: Do you want to move that change?

DR. KOEHN: Well, okay. Yes, under common side effects.

DR. EAGLSTEIN: All right.

DR. KOEHN: You may experience some redness of the eyes.

DR. EAGLSTEIN: You want to delete the --

DR. KOEHN: And delete your eyes may also feel irritated.

DR. EAGLSTEIN: -- okay. You may see some redness.

DR. KOEHN: Uh-huh.

DR. EAGLSTEIN: And you --

DR. KOEHN: Experience some redness.

DR. EAGLSTEIN: -- experience some redness and delete also feel irritated.

Discussion?

(No response.)

DR. EAGLSTEIN: All in favor?

(Show of hands.)

DR. EAGLSTEIN: Opposed?

(No response.)

DR. EAGLSTEIN: Passes.

Dr. Haserick, you were -- you had some other concerns you were just saying a minute ago in the mild.

DR. HASERICK: I think all of this gets back to --

DR. EAGLSTEIN: Now, do you want to deal with this issue which has just been placed in better perspective for us that as it stands now, the people are being told about muscle pains and aches which may not even be related to hyperostosis. As the FDA position is outlined, the patient would be told that they could have skeletal changes and they also say to see your doctor if you have joint pain or difficulty

in movement.

Does anyone want to either change what we now have as a proposed patient insert by adopting these, or other words? The FDA words, or any other words?

DR. BILSTAD: I might add one further. It could further be qualified if you want to particularly make the point that the hyperostosis has not been reported in acne patients, the second sentence could be changed then. Instead of if you experience joint pain, simply say, "Although these changes have not been reported in acne patients, you should contact your doctor if you develop severe joint pain or difficulty in movement." That would be an added qualification or an added listing.

DR. EAGLSTEIN: Is that added to the FDA?

DR. BILSTAD: That's added to the FDA version. I'm just offering it.

DR. EAGLSTEIN: In place of if you experience?

DR. BILSTAD: That is correct. It is simply making the point clear that these findings have not been reported in acne patients.

DR. EAGLSTEIN: Does anyone want to move to insert some information about hyperostosis in this patient package insert?

DR. KENNEY: I'll so move, Mr. Chairman, and move that we strike the section, "severe muscle aches and pains,"

and so on, and replace it with this new version.

DR. EAGLSTEIN: I hear your motion. I think the contention on the part of the sponsor is that these are not the same. That this is one set of symptoms and it has nothing necessarily to do --

DR. KENNEY: I see what you're saying.

DR. EAGLSTEIN: -- so if you want to strike it, let's hear it as a separate motion?

DR. KENNEY: No, I'll leave it there.

DR. EAGLSTEIN: So you then want to insert words about hyperostosis?

DR. KENNEY: Yes. I would like to insert this section as it already reads here, with the recommended change of the second -- or the last sentence there.

Would you repeat what you said again,please?

DR. EAGLSTEIN: The first sentence would stand.

DR. BILSTAD: "Although these changes may not been reported in acne patients, you should contact your doctor if you develop severe joint pain or difficulty in movement."

DR. EAGLSTEIN: Is that your motion?

DR. KENNEY: Yes.

DR. GOLDNER: Second.

DR. EAGLSTEIN: Discussion?

(No response.)

DR. EAGLSTEIN: Dr. Rasmussen, are you tuned into this?

This is a motion to insert additional words in this during treatment section. The additional words would be the first sentence of the fourth paragraph of the FDA's suggestions on during treatment and the second sentence would be changed to say, "Although not reported in acne, you should contact your doctor if you have pains or difficulty in moving."

Any discussion on adopting this proposal? No one is concerned about the argument that the patient doesn't have something to do with this information except get a -- I guess get a series of X-rays of the whole body.

DR. KOEHN: I'm sorry, could you read it, what the whole thing is? I can't find the fourth paragraph.

DR. EAGLSTEIN: Okay. We're on during treatment --

MR. BOSTWICK: This is the FDA -- this is the memorandum that --

DR. KOEHN: I've got --

MR. BOSTWICK: -- page 2.

DR. KOEHN: -- I don't know where you are.

DR. EAGLSTEIN: Page 2. And then it is called 2(b), the last paragraph that starts with a little box. That's where we were. We're suggesting -- the motion is to accept the first sentence, plus an additional sentence that says, "Although it has not occurred in acne patients, if you have problems moving and pain, tell your doctor."

Are you ready to vote. Okay. All those in favor,

raise your right hand?

(A show of hands.)

MR. BOSTWICK: That's five?

DR. EAGLSTEIN: Not, it's four -- two, four, five.

Opposed?

(A show of hands.)

DR. EAGLSTEIN: That carried.

So, that is the suggestion insertion. Where did you want this inserted? Was that going to be in this -- we've kind of been discussing under the more serious side effects. If that where it is going to be?

DR. KENNEY: I thought it was going to be on this same during treatment.

DR. EAGLSTEIN: Yes, but during treatment has a mild and a common and a less common, but more serious section.

MR. BOSTWICK: Headed by add bold print.

DR. KENNEY: I suppose right after the sever muscle aches or pains is a good place for it.

DR. EAGLSTEIN: All right. You'll move that effect?

DR. GOLDNER: Second.

DR. EAGLSTEIN: Dr. Goldner seconds.

Yes.

DR. RASMUSSEN: With that positioning, you have to accept the fact that you consider this to be a more serious side effect, which is what it says, and yet if you look at

the patients who have been reported, specifically that paper by Ellis, which is unpublished, and which was included in the last portion of the handout, none of the patients were symptomatic at all, and the X-ray changes were so subtle that the radiologist missed half of them at the 20-some week check up. They could only find them by going back and comparing them with the final check up. We are giving the impression that we are talking about a serious problem here. We have no definition of what serious is and certainly by the published results, at least used in acne, to my knowledge, there hasn't been a patient reported who has had a serious complication. The patients who has a serious complication, to my knowledge, are only reported in that article by Uher (phonetic) and his associates in the New England Journal and those patients are taking about 2.0 mg/kg and higher for period of up to two years and none of them had acne.

DR. EAGLSTEIN: So, you voted against its adoption anyway. Now, you would suggest, however, that we call it mild, at best?

DR. RASMUSSEN: Well, I'm not making that as a suggestion.

DR. EAGLSTEIN: Comment.

DR. RASMUSSEN: But if the people who voted for that put it under this heading of "Accutane may cause some less common, but more serious side effects," how are you going to

justify saying that this is a more serious side effect? I can see that potentially it could be a problem, but,to my knowledge, there has not been a patient reported that we have any access to that has had any serious side effects from this.

DR. EAGLSTEIN: So --

DR. RASMUSSEN: It is a radiological change, which is of concern in the future of what will happen, but to say that it is a serious effect is quite debatable, in my opinion.

DR. EAGLSTEIN: -- we are voting where to place now.

DR. RASMUSSEN: That is exactly why I brought up this problem.

DR. EAGLSTEIN: You would say not to place it here certainly?

DR. RASMUSSEN: Yes.

DR. KENNEY: I have no objection, but where would you like to put it?

DR. GOLDNER: It would go in the paragraph then rather than in the bold print which is what you are really saying? In order for it to be considered as the milder of the side effects, we would put it in that paragraph.

DR. RASMUSSEN: In my opinion, this is such an uncommon, rare and completely asymptomatic problem that I wouldn't stick it in this patient handout at all.

(Laughter.)

DR. RASMUSSEN: First of all, the patient isn't

going to have the faintest idea of what the difference is between the acute, mild reactions that a lot of people get with Accutane as opposed to this change, which is what we are talking about, which is something you would hardly pick up on routine studies at all. So, here is a specific radiologist, Sheldon Markel, who knew exactly where to look and what to look for, you're talking about sending somebody out for spine X-rays or tibial -- I mean, medial tibia plateau, wherever they're looking and say, he doesn't seem to be finding anything or just close to zero. So, you are putting this in a patient handout where a patient will not, in my opinion, be able to interpret that at all. I would put that in the physicians' material, and leave this thing about muscle aches, joint pains, and stiffness, that's fine, but that's what I presume these people were referring to, just a common -- that I see in probably 5 to 15 percent of the patients that I put on Accutane which has nothing to do with X-ray appearances that occurs within two to four weeks after you start the patient on the drug. It usually decreases as the patient stays on the drug and that's what I think they are referring to.

DR. EAGLSTEIN: I sense that you prevail in making people thing that it shouldn't go here, is that right? But that is the motion. Do you want to vote on that motion?

DR. GOLDNER: Well, you can. I'm not sure I would agree completely with Jim. I think that the warning does

belong in there even though I agree it is of less significance than what we originally said. I really like the fact that you are alerting a patient that this drug cannot be taken for longer than the prescribed time. I'm sure you all know that patients get drugs whether you prescribe them or not, and once you've prescribed Accutane, it's easy for Joe to go to his cousin, who is a pharmacist and get some more Accutane and to continue taking it. I like the fact that this is in the patient warning and that you are alerting him that longer than what you prescribe is dangerous?

DR. RASMUSSEN: I think it could be solved for us by just having it as a third paragraph. Not common and not too serious.

DR. GOLDNER: Right, I agree. It doesn't have to be --

DR. EAGLSTEIN: So, why don't we vote on whether or not it belongs here with the serious. That's the motion.

DR. GOLDNER: I would agree that it doesn't belong in the serious.

DR. EAGLSTEIN: Okay. All those in favor of adding it to the serious category, raise their hand?

(A show of hands.)

DR. EAGLSTEIN: All those opposed?

(A show of hands.)

DR. EAGLSTEIN: Okay. Now, do you want to move

to suggest where it would fit?

DR. GOLDNER: I would like to move that that paragraph be put in with the side effects, and I guess it would go into the mild ones in that paragraph, in the appropriate part of that paragraph.

DR. EAGLSTEIN: I think Jim is going to say it is not common.

DR. RASMUSSEN: The first is common and mild and the second is uncommon and serious.

DR. EAGLSTEIN: So, why don't we have a not common and not serious?

(Laughter.)

DR. GOLDNER: If you have the last sentence there, it says in clinical studies the side effects were temporary and disappeared when treatment was discontinued.

DR. RASMUSSEN: I think that this is so rare and so asymptomatic that it should not be placed in an insert that patient's are going to get.

DR. EAGLSTEIN: Do you want to move that we strike it. We recommended adding it. Do you want to move that we reverse that vote? Go to it, because you've discussed that.

DR. RASMUSSEN: Okay. Then I would like to move that this paragraph in a box which starts out, "Accutane or any variation thereof not be included in the handout that's provided to patients."

DR. EAGLSTEIN: Can we get a second. He is voting that this warning not be in the patient handout.

DR. KOEHN: I'll second that.

DR. KENNEY: I'll have to call a parliamentary procedure here, sir. In order to vote to reconsider, which is what this this, you have to have been on the favorable side to do that.

(Laughter.)

DR. EAGLSTEIN: We'll let that be a motion even though it is irregular.

We'll vote on this again. All those who favor the motion that we've already accepted, you will not for this motion.

DR. RASMUSSEN: No, we've got to have everybody vote on this.

DR. EAGLSTEIN: I said everyone was going to vote. The motion is that we not adopt -- that we strike the motion we've already adopted, is that right? That we reverse ourselves basically?

DR. RASMUSSEN: Instead of making it a negative, why don't we just say, we not put the paragraph in?

DR. EAGLSTEIN: Good. All right. That we not put the paragraph in.

All those in favor of not putting the paragraph in?

(A show of hands.)

DR. EAGLSTEIN: All those against that motion?

(A show of hands.)

DR. EAGLSTEIN: I think the question of where it goes -- I think we've solved that.

DR. GOLDNER: That's the significant part.

DR. EAGLSTEIN: It has been suggested that we just put it at the bottom.

DR. POMERANZ: Put it in here.

DR. EAGLSTEIN: Do you want to move to put it at the bottom?

DR. POMERANZ: Move that it goes to the bottom.

DR. EAGLSTEIN: Second.

DR. RASMUSSEN: Second.

DR. EAGLSTEIN: All in favor?

(A show of hands.)

DR. EAGLSTEIN: Opposed?

(No response.)

DR. EAGLSTEIN: After treatment. Any suggestions here?

(No response.)

DR. EAGLSTEIN: Any suggestions on after treatment?

DR. KOEHN: Is it true that about one-third of the patients treated with Accutane have needed the second course?

DR. EAGLSTEIN: The question is: is it true that that one-third of the patients treated once with Accutane need

a second course?

DR. GOLDNER: Is it a third? Is the third a correct percentage.

DR. DEL VECCHIO: I believe that was true in the original NDA data. I suspect it is higher now because people are adjusting the dosages better and that it is lower in terms of the need for retreatment. But that is in there to indicate to patients that it may be necessary for them to be retreated. I don't think the number is. We might be able to adjust that to a more current number.

DR. CHANCO-TURNER: Shouldn't you be referring to the recommended dose?

DR. DEL VECCHIO: I'm not sure what you mean.

DR. CHANCO-TURNER: I mean, is it as high as 30 percent? One-third of the patients on the recommended dose require retreatment?

DR. DEL VECCHIO: No, Dr. Strauss' study just showed today that 90 percent did not need retreated with the recommended dose; so, it is actually -- it is actually more negative than is truly the case. I'd have to ask you what your experience has been in treating these patients. I don't know. These were general averages with more studies.

DR. CHANCO-TURNER: I haven't had to retreat anybody.

DR. RASMUSSEN: I think it is going to depend on the period of follow-up. The longer you go, the more patients

who are going to relax. And since we have not had use of this drug for more than a year, I don't know how we can pick any number. Even the protocol patients were very limited, less than 1000, something like that.

I'm certainly starting to see people who aren't getting good results and I'm certainly starting to see people who have been treated and come back for a second course. It's certainly isn't anywhere near a third, but we've only had the drug out for a year.

DR. DEL VECCHIO: Perhaps we should just say that some cases may need retreatment rather than specify.

DR. RASMUSSEN: Yes. I think that's easier rather than trying to to put a percentage on it.

DR. EAGLSTEIN: Marie, do you move that?

DR. CHANCO-TURNER: Yes, I move that we change that sentence to -- instead of saying about one-third of the patients treated, we should say, some of the patients treated with Accutance have needed a second course of therapy.

DR. EAGLSTEIN: Second?

DR. GOLDNER: Second.

DR. EAGLSTEIN: Discussion?

(No response.)

DR. EAGLSTEIN: All those in favor?

(A show of hands.)

DR. EAGLSTEIN: Opposed?

(A show of hands.)

DR. KOEHN: I was in favor.

DR. EAGLSTEIN: Okay. And that passes.

Additional suggestions on the after treatment of patients, entitled, "after treatment." The next page is the page called general guidelines when taking medicine.

Any suggestions here? Alterations, amendments?

DR. KOEHN: This second to the bottom paragraph, it says, "Do not give it to others who have similar symptoms." I wonder if if it should say, "Do not give it to others." It says it somewhere else, too, but I think patients do read about this general medicine being used in psoriasis, and different things, and sometimes people do -- are tempted to to give medicines not only for cystic acne, but for other things that they've read about that it has been used for.

DR. EAGLSTEIN: So, do you want to move to strike "who have similar symptoms?"

DR. KOEHN: I move to strike, "who have similar symptoms" be struck.

DR. EAGLSTEIN: Do we have a second?

DR. KENNEY: I'll second.

DR. EAGLSTEIN: Dr. Pomeranz?

DR. POMERANZ: I agree with that, but I just wonder if it doesn't dilute it a little bit. Do not give it to others. That's just give it to anybody else.

DR. CHANCO-TURNER: Don't share it.

DR. POMERANZ: Don't share it. I wonder if you should say, don't give it to anybody else who has acne?

DR. KOEHN: Well, psoriasis is very common and --

DR. POMERANZ: Yes, I know.

DR. KOEHN: -- and patients do know --

DR. POMERANZ: But all of this is promoted for it.

DR. EAGLSTEIN: Any other discussion?

(No response.)

DR. EAGLSTEIN: Ready to vote. All those in favor of the motion that we suggest striking the words, "who have similar symptoms" out of the paragraph second from the bottom on this page, raise their hands?

(A show of hands.)

DR. EAGLSTEIN: Those opposed?

(A show of hands.)

DR. EAGLSTEIN: Four to three.

DR. KENNEY: Somebody wants to add "may" to that, too?

DR. POMERANZ: Or who has.

DR. CHANCO-TURNER: Suppose you say, "Don't share your medication with anybody."

DR. EAGLSTEIN: That's what passed.

DR. KOEHN: I already lost.

DR. POMERANZ: Didn't it carry?

DR. KOEHN: It failed; we lost.

DR. EAGLSTEIN: That failed to carry.

Other suggestions. The final page, I think. Any desired alterations here?

DR. KOEHN: I've had several patients who read this. I've given them this and they say, you should not take Accutane if you are or may become pregnant. And they say, does this mean that I can never have any children?

DR. CHANCO-TURNER: Yes, I've had that question.

DR. KOEHN: And yet if you go on and read it, it becomes apparent.

DR. EAGLSTEIN: Do you want to add during treatment?

DR. KOEHN: "During Accutane therapy and one month after."

DR. EAGLSTEIN: Okay. During Accutane therapy or during therapy with Accutane?

DR. KOEHN: Okay.

DR. EAGLSTEIN: And for one month after?

DR. KOEHN: Uh-huh.

DR. EAGLSTEIN: Is there a second to that motion?

DR. CHANCO-TURNER: Second.

MR. BOSTWICK: This is in the warning to female patients?

DR. EAGLSTEIN: Yes, the first sentence. "You should not take Accutane" --

MR. BOSTWICK: Okay.

DR. EAGLSTEIN: -- "or may become pregnant during Accutane therapy or the month thereafter."

MR. BOSTWICK: Okay.

DR. EAGLSTEIN: Discussion?

(No response.)

DR. EAGLSTEIN: Do we want to vote in favor of this motion?

(A show of hands.)

DR. EAGLSTEIN: Those opposed?

(No response.)

DR. EAGLSTEIN: Carried.

Others?

(No response.)

DR. EAGLSTEIN: Now, do you want to look at the petitioner's suggestions for this? I think it can be done rather well at this point. Under E, page 7.

DR. CHANCO-TURNER: On the patient package insert, referring that we did not adopt this women of child bearing age should always obtain a negative pregnancy test?

DR. EAGLSTEIN: Right. That was --

DR. CHANCO-TURNER: That was not adopted?

DR. EAGLSTEIN: -- that was not adopted. Okay. The first paragraph, it was suggested by the petitioner, but not adopted. The second paragraph -- if anybody wants to

reconsider, speak up.

The second paragraph, the petitioner wants to amplify much further on the pseudotumor. He wants the words, "serious neurologic disorder," and he wants it to be named, more or less what we discussed.

Page 8, corneal opacities. We did discuss this and adopted the mild statement. The next is the Accutane with the Chron's disease. I think, again, we've discussed this, and opted for a different statement.

The next is Accutane --

DR. CHANCO-TURNER: Hyperostosis.

DR. EAGLSTEIN: -- hyperostosis. I think we did that.

The next is a long statement on the evils of the high blood fats. Does anyone feel that we should consider this further, or ask that this information be placed in the patient insert?

(No response.)

DR. EAGLSTEIN: The next is the shrinking of the testicles and the decreased sperm production and the atrophy in one patient.

DR. CHANCO-TURNER: Do we have any information on that?

MR. BOSTWICK: There's a study going on, but it hasn't been completed yet.

DR. ROFSKY: Mr. Chairman.

DR. EAGLSTEIN: Would you identify yourself, please?

DR. ROFSKY: Dr. Helbert Rofsky, -- planning manager at Roche Laboratories. Regarding that particular comment, the one patient with testicular atrophy, I happened to be on an emergency call and took that one call. That was from a dermatologist in Pennsylvania who had a telephone report from a patient that his testicles became smaller. The patient was never seen, never heard from again.

DR. RASMUSSEN: Maybe he just vanished.

(Laughter.)

DR. ROFSKY: That would have been very small, the report was just small. Regarding the report on the hamsters, the testicular effects by Accutane, that is an incorrect interpretation of the article. The article was on Golden Syrian hamsters, I believe. It was the use of three retinoids, one of which was Accutane. The other two retinoids did have an effect on the Syrian hamster testicles, Accutane did not. We at Roche do not feel that that should in any way be included be it patient or physician labeling.

DR. EAGLSTEIN: Does anyone on the Committee want to comment or move to include it?

DR. HASERICK: If you will recall, I raised this question about the effects of testosterone. I have been running testosterone, serum testosterone for lack of anything better for our laboratory to do. I have found no changes whatever in, I suppose, about 30 patients.

DR. EAGLSTEIN: All right. So, you have not been able to detect.

DR. HASERICK: I'm not upset about it any more. I was at the time. I wonder why they didn't include that information.

DR. EAGLSTEIN: The next suggestion is that the patients be told to ask the doctor to lower their dose of medicine after the first few weeks.

Does anyone feel we should request that be included in --

DR. CHANCO-TURNER: No.

DR. EAGLSTEIN: -- any thoughts on that? Discussion?

And I think that ends the petitioner's suggestions.

Now, we have to go back to the tetracycline statement. Dr. Koehn, do you have that ready?

DR. KOEHN: Yes. I would leave in on page 3 --

DR. EAGLSTEIN: We're back on tab F --

DR. KOEHN: Yes.

DR. EAGLSTEIN: -- page 3.

DR. KOEHN: I would just put in there in the print like it was before the third paragraph from the bottom, "Of 10 cases of pseudotumor cerebri that have been reported, five patients were on concomitant tetracycline therapy." That's the third paragraph up from the bottom. And right now it just says, "Cases of pseudotumor cerebri."

DR. EAGLSTEIN: That's been moved, I think, hasn't it, or been boxed? Wasn't that all changed?

MR. BOSTWICK: Yes.

DR. KOEHN: Well, that part was deleted. My suggestion is to put just plan old tetracycline sentence under there saying, "Of 10 cases of pseudotumor cerebri that have been recorded, five patients were on concomitant tetracycline therapy."

DR. EAGLSTEIN: What did happen to this? Didn't it stay here, but it just got boxed in bold?

DR. KOEHN: No, tetracycline --

DR. CHANCO-TURNER: It got moved up to adverse reactions.

DR. EAGLSTEIN: Did it?

DR. CHANCO-TURNER: Yes.

MR. GOLDSMITH: To warnings.

DR. CHANCO-TURNER: I'm sorry, to warnings.

DR. EAGLSTEIN: I thought it didn't make it?

DR. TABOR: The pseudotumor?

DR. EAGLSTEIN: The pseudotumor.

DR. TABOR: It's a box warning at the head of the warning section.

DR. GOLDNER: Not at the beginning of the insert. It didn't get put at the beginning of the insert.

DR. EAGLSTEIN: It moved up to the warning?

DR. GOLDNER: It got moved up to the beginning of warning.

DR. EAGLSTEIN: Okay. So, this then would be much further back and very much separate?

DR. KOEHN: Yes, where it is now.

DR. EAGLSTEIN: Okay.

DR. KOEHN: Or actually, it got deleted, but just to put that sentence in.

DR. EAGLSTEIN: Let's hear the words. Vote on the words and then vote on the place.

DR. KOEHN: "Of the 10 cases of pseudotumor cerebri that had been reported, five patients were on concomitant tetracycline therapy."

DR. HASERICK: Who have been reported. They are humans, not animals.

DR. KOEHN: Okay, yes.

DR. GOLDNER: Were they all tetracycline rather than minicycline/tetracycline? Just nit-picking, but is that --

DR. KOEHN: That's what he said.

DR. EAGLSTEIN: They were both.

DR. DEL VECCHIO: Yes, they were. The only problem with putting the number in, of course, is that the number is going to change, In fact, five of the first six were -- those five were among the first six or seven. That's why the package insert now says the majority of them were, or most of them were

concomitant tetracycline therapy. The latest ones were not on tetracycline.

DR. EAGLSTEIN: So you would suggest that we say "some?"

DR. DEL VECCHIO: Well, the only trouble with putting a number in is that that's going to change.

DR. KOEHN: How about several cases of pseudotumor cerebri who have been reported were on concomitant tetracycline therapy.

DR. EAGLSTEIN: Several who have been reported.

Is that a motion?

DR. KOEHN: Yes.

DR. EAGLSTEIN: Are you moving?

DR. KOEHN: Yes.

DR. KENNEY: I'll second.

DR. EAGLSTEIN: Discussion? We had a hand down there. Did you want to help us with this?

DR. ROFSKY: I would like to add that we really have no data, and I think the important point here is we would like, as much as you would, to have this insert as meaningful to the physician as possible to help guide him and lead him in the proper use of Accutane and any other drug that happens to be up. The point is, there is no data to support the concomitant use of tetracycline in Accutane therapy for patients. All these patients had failed on previous tetracycline therapy. The

only data that has been done on concomitant antibiotic use is a recently published paper in the United Kingdom which shows no additional benefit from concomitant antibiotic therapy; therefore, the question becomes: shouldn't the physician just be warned in a just manner that there is no data to support the use of additive or concomitant tetracycline or minicycline therapy, and there is the possibility of added risk.

I would also like to suggest that Hoffman-La Roche work out the exact wording with the agency at some time in the future rather than we try to hone out every word here.

DR. EAGLSTEIN: Dr. Koehn, would that be satisfactory to you?

DR. KOEHN: That would be fine.

DR. EAGLSTEIN: Do you want to withdraw your motion?

DR. KOEHN: I will withdraw my motion.

DR. EAGLSTEIN: Withdraw the second?

DR. KENNEY: Yes.

DR. KOEHN: I sure would like to see tetracycline mentioned though.

DR. EAGLSTEIN: Dr. Rasmussen?

DR. RASMUSSEN: I think that even though he has stated that there is not a study showing that the concomitant use of the two is any more effective, what I think is sometimes commonly seen in practice is that somebody comes to you who

has been on tetracycline and is still on the drug, and then you are faced with the decision, do you stop everything and start Accutane and endure two to four weeks of flare, which I think is very common, or do you slowly wind one down and step into the other, and this is, I think, where you are going to get into problems.

I have heard Jim Leyden (phonetic) speak on this subject and I don't want to put words in his mouth, but my understanding was that he suggested that one way to avoid that initial flare was to phase one in and phase the other out. So, that might be a potential problem even though you wouldn't be using them for concomitant effect, you would still have the overlap type of a syndrome; so, I would agree with Dr. Koehn, I think that we should have something someplace in there that tetracycline might be mentioned.

DR. EVANS: I think it is common practice. I was at a meeting earlier this week --

DR. RASMUSSEN: It is in our institution.

DR. EVANS: -- yes. And that it was a wide spectrum of usage. Some people used Accutane alone; some people kept them on tetracycline for a period of two to four weeks and then stopped, and some people kept them on tetracycline altogether through the Accutane period. So, there's a wide variety of usages, of combination.

DR. EAGLSTEIN: The proposal you made might be --

some might be upset that it is more of a -- kind oa a anti-tetracycline statement in a way to say that there's no proof that it helps.

DR. ROFSKY: Believe me, we have no vested interest in either accepting or denying the concomitant use of tetracycline. We just want to have the best current information available to people who have to use Accutane.

DR. EAGLSTEIN: Okay. Well, Dr. Koehn, are you withdrawing it or do you want to submit it again?

DR. KOEHN: Well, if I withdraw it, there will be no mention of tetracycline unless someone else on the Committee has an idea of how to put it in there. I am open to suggestions. I think it should be mentioned.

DR. CHANCO-TURNER: I agree with Dr. Koehn. I think it should be mentioned. I personally stop tetracycline or any antibiotic before I start anybody on Accutane.

DR. EAGLSTEIN: Well, why don't you move it again?

MR. GOLDSMITH: I would like to make a point that looking at the other side effects data that we have, we have no information from the other side effects data, including the general malformation data that tetracycline has any effect in any of those. We don't know the percentages of patients on tetracycline or minicycline, but the pseudotumor data stands out in that there is -- the minicycline and tetracycline

data from the ADR forms. I am aghast, et cetera, there is no such data.

DR. EAGLSTEIN: Dr. Koehn, you better move it again.

DR. KOEHN: "Several patients with pseudotumor cerebri" -- just a minute.

DR. RASMUSSEN: "Several patients with pseudotumor cerebri have been taking concomitant Accutane and tetracycline."

DR. EAGLSTEIN: It wasn't just tetracycline though.

DR. RASMUSSEN: Accutane and tetracycline or minicycline.

DR. CHANCO-TURNER: It's non-judgmental

DR. RASMUSSEN: It just says that it is there.

DR. EAGLSTEIN: Well, we're not saying --

MR. BOSTWICK: Oh, okay.

DR. CHANCO-TURNER: That should be under precautions.

DR. EAGLSTEIN: -- you are seconding it, I suppose?

DR. CHANCO-TURNER: I am seconding.

DR. EAGLSTEIN: Any further discussion?

(No response.)

DR. EAGLSTEIN: All those in favor?

Yes, further discussion?

DR. TABOR: I really think that it dilutes the psuedotumor warning to say that.

DR. KOEHN: We've got it way down here.

DR. TABOR: I think you have no data to support.

an interaction between tetracycline and -- or practically no data between tetracycline and Accutane. The real concern, I think, is on a theoretical basis and if you are going to put it in there, you ought to say that it is on a theoretical basis. Your real concern is based on your knowledge, perhaps in the back of your back, that tetracycline can cause pseudotumor.

MR. GOLDSMITH: I think it is right on your ADR report.

DR. TABOR: You also have five cases that did not have tetracycline. I mean, the argument can be carried, you know, to other things that they might have been exposed to. We have no animal data to indicate that there is an interaction.

MR. GOLDSMITH: There is no data that there's not an interaction. It's never been studied. It is raising a warning. It is not to dilute the Accutane.

DR. TABOR: Well, I'm not saying that you shouldn't raise the warning, but I really think that talk about the pseudotumor cerebri cases is diluting the pseudotumor warning.

DR. HASERICK: Is there a motion on the floor, Mr. Chairman?

DR. EAGLSTEIN: There is. We're discussing that motion, I think. He's discussing points against it.

DR. CHANCO-TURNER: But wouldn't the fact that you're

putting things in two separate places not dilute the pseudo-tumor warning?

DR. TABOR: Well, obviously, it dilutes it less than putting them side by side, but --

DR. RASMUSSEN: I think this is a concise statement of what we know at the present time. It just says that some of the patients have been simply on Accutane and others have been on Accutane and concomitant with either tetracycline or minicyline.

DR. CHANCO-TURNER: I think it should go under precautions just like you tell them they should not take extra vitamin A.

DR. TABOR: I'll rest it there, but I do feel that it dilutes the pseudotumor warning.

DR. EAGLSTEIN: Further discussion?

(No response.)

DR. EAGLSTEIN: We will vote on the motion which is to add the words, "Several cases of pseudotumor cerebri have been in people taking either tetracycline or minicycline concomitantly," something to that effect.

All those who favor adding those words?

(A show of hands.)

DR. EAGLSTEIN: All those opposed?

(No response.)

DR. EAGLSTEIN: Carried.

Now, do you want to propose where we will place these words? Or suggest placing them?

DR. RASMUSSEN: How about just where that sentence was deleted?

DR. EAGLSTEIN: Under adverse reactions?

DR. RASMUSSEN: Yes, under adverse reactions. It was the third paragraph from the bottom on page 3.

DR. EAGLSTEIN: Okay. So, you move that these words be placed in the third paragraph from the bottom on page 3?

DR. RASMUSSEN: Yes.

DR. EAGLSTEIN: Second?

DR. KOEHN: Second.

DR. EAGLSTEIN: Any discussion?

MR. BOSTWICK: I only have a question. It is only going to be one sentence. It's not going to include the second sentence conerning, "This disorder using..."

DR. EAGLSTEIN: No, that was all stricken.

MR. BOSTWICK: All right.

DR. EAGLSTEIN: All those in favor of that placement?

(A show of hands.)

DR. EAGLSTEIN: Opposed?

(No response.)

DR. EAGLSTEIN: It passes.

That completes our question four and brings us to question five, which is: should a required patient package insert be rcommended? Maybe we could get clarification.

I don't know what that would mean?

MR. BOSTWICK: It is worded that way for a purpose. The Food and Drug theoretically can't mandate a patient patient insert, but it is -- the Committee is free to recommend that that the firm issue a patient package insert and make it part of their package with the drug. So, I guess what we're trying to do is wheeze around the idea that even if the Committee does, and the Committee is free to recommend that it be made mandatory. It really isn't a regulation to do that.

DR. HASERICK: That sounds so appealing to me, there must be something wrong with it.

(Laughter.)

DR. HASERICK: What do you say? What is your attitude?

DR. DEL VECCHIO: It depends on what it is you are recommending. If you're talking about packaging this particular brochure with stock packages of Accutane, that's one consideration. The problem in patient package inserts is that unless they are packaged with the unit of use type of packaging, but there is no guarantee whatsoever that the patient will get them. You cannot legislate that. You can't make the pharmacist give them out. The oral contraceptives are packaged in a unit of use and each one of those contains a package insert for the patient.

Accutane and most other medications do not come that

way because the prescriptions vary all over the lot in terms of numbers and, therefore, what you are going to have is a stock package with a series of brochures in them which may or may not be given out by the pharmacists. Some pharmacists, I think would gladly give them out. They feel they should be a source of information with patients about the truck. Others, I think, would totally ignore them. You run into the problems of distribution of parts of a package and whether it will get there or not. And our feeling is that making as much of an impression as we can upon the physician to give that brochure out that there is just as good a chance of the patient getting that information from the physician as it is under such a required format.

The other thing is, of course, that with a mandated one that is given out with the prescription, the patient receives the brochure only after they have the prescription filled and they pay for it and they have it in the bag. They may or may not be on their way home, but they could, of course, request it before then if they knew that. So, the problem is, they've already got the bottle, whereas if they get it from the physician, they have the opportunity to ask him or her questions. They can discuss it with the nurse, and so forth.

I don't think that the -- that this is a totally foreign idea. I think there are some very positive points

to it, but I don't -- our position is that it doesn't really add to the possibility of the patient will get the required information, but we feel it should be between the physician and the patient.

DR. POMERANZ: I think it should be done both places, as a patient package insert and also given by the physicians. I don't think we should miss any opportunities to make certain the patient gets this information.

DR. RASMUSSEN: Perhaps because I know physicians too well and pharmacists not well enough, I have serious doubts that a substantial percentage of physicians will give this out for a variety of reasons. Some, because they are philosophically opposed. Others, because they are not the source of the drug, and consequently, there cannot be a matching between the number of patients who are going to receive the pamphlet and the number of pamphlets you actually have, whereas if you provide it with the medicine as it is sold, as you run out of medicine, you run out of pamphlet; so, you cannot give medicine without pamphlet.

A physician could see somebody, run out of pamphlets, and not have anything else to use. We happen to use almost an identical sheet in the Dermatology Department of the University of Michigan, which we give two copies, one of which we have the patient read and sign and then we stick it in the hospital chart, and the second one which actually goes home

with the patient; so, we would comply with that quite nicely, but I have a feeling most people would not. There would be a problem maintaining the supply and there would be a problem giving it out.

DR. EAGLSTEIN: So, you are in favor of this request that we recommend a required package -- patient package insert?

DR. RASMUSSEN: I think that while it may be difficult to do that nothing will be lost with an attempt to do this. There will be no harm.

DR. EAGLSTEIN: Other comment?

DR. GOLDNER: Well, my pharmacy background makes me object to that because I just feel that -- I object to the concept of mandatory pharmacy package inserts. I believe that that brings the questions back to the pharmacists rather than the physician where they belong. Pharmacists can help with a lot of the questions, but many of these problems he is just not familar with, and I don't really believe that these dangers and these problems belong to the pharmacist. I believe they belong to the physician and I would much rather see the onus be put on the physician to educate the patient than to have this patient folder that was so designed to be dispensed by the physician. I object to the pharmacy --

DR. RASMUSSEN: I don't think it is designed as the sole source of information. I think it is designed as a

check on the patient who may not have been -- who may not have received this in the physician's office. I think the idea is to get them --

DR. GOLDNER: You want them done by both?

DR. RASMUSSEN: -- I didn't mean to imply that this was the only source of information after you paid your $50 and then you get one of these things, because that's terrible.

DR. GOLDNER: Yes. That's correct. I object to that kind of a viewpoint. You are not proposing that, but in general --

DR. RASMUSSEN: No, no.

DR. GOLDNER: -- I really don't approve of patient inserts through the pharmacy.

DR. DEL VECCHIO: I would just like to remind you that all 60,000 retail pharmacists will receive these brochures directly from Roche. Will be able to get more of these brochures at any time whereas getting them with the package they've gotten through a wholesaler, because most pharmaceutical companies sell from wholesalers. They may then be broken down. They do have the opportunity right now, and will have to have that additional input with the patient.

DR. EAGLSTEIN: All three places.

MS. LACHEEN: I'm from the Health Research Group and I would just like a clarification.

It is my understanding that if a patient package insert is mandatory that a pharmacist is required by law to distribute it, and so even if there is no 100 percent guarantee that you still have a majority of the pharmacists distributing it for that reason, and that would be the most successful way of making sure the patients get it.

Is that correct?

DR. EAGLSTEIN: Youare asking if that is correct?

MS. LACHEEN: That's right.

DR. EAGLSTEIN: Can you answer that for her?

DR. BILSTAD: Well, I wanted to clarify that point earlier that if FDA were to decide that patient package inserts were mandatory and if we did not come to an agreement with the firm on that, we can go through the comment rulemaking procedure and require package inserts. That was just a clarification of the point before. I agree with the point you are making.

DR. EAGLSTEIN: And her point is correct that if you were to mandate it; then it would be somehow a law?

DR. BILSTAD: If we go through the rulemaking procedure, which we can do; then, that would be the case.

DR. EAGLSTEIN: Pharmacists would be obliged to.

Somebody had pointed out earlier that if you know the pharmacists is going to do this, you are more likely to in fact spend the time with your patient.

Is there any other comment before we vote on this

question? Any other discussion?

(No response.)

DR. EAGLSTEIN: Are you ready to vote. All those in favor of number five, which is to say that we adopt the resolution -- we suggest a a required patient package insert should be recommended.

All those in favor?

(A show of hands.)

DR. EAGLSTEIN: All those opposed?

(A show of hands.)

DR. EAGLSTEIN: It carried.

That, I think, ends the session on Accutane. It's 3:15. We have a subcommittee report on Lindane, which we might be able to get through very quickly. Shall we give it a try.

MR. BOSTWICK: You've also got on your program a short presentation.

DR. EAGLSTEIN: Oh, do we, I'm sorry.

The representatives for the National Pediculosis Association, do you want to make your presentation, or would you let us --

MS. KENNY: We need five minutes, I know we are very pushed for time and everybody has to leave.

DR. EAGLSTEIN: We have a subcommittee report that you are familiar with, and it was my impression that you were

satisfied with that report?

MS. KENNY: We are, but with one exception.

DR. EAGLSTEIN: Do you want to address that exception, or do you want us to try to deal with the report? You are saying that you can't wait for that?

MS. KENNY: We can condense our presentation and a little bit of discussion.

DR. EAGLSTEIN: Okay. Please come to the podium and discuss the one point that you would like to.

To clarify for the Committee, at the last meeting a subcommittee was appointed by Dr. Arundell. I was the chairman. Dr. Pomeranz and Rasmussen were the other members. Dr. Pomeranz could not make the meeting, which was yesterday, but Dr. Rasmussen and I were there, as were the representatives of the Pediculosis Association and representatives of the sponsor. And you have before you the proposed recommendations. These are proposed by the subcommittee to the Committee and the Pediculosis Association representatives agree with one exception, or seem pleased except in one area, is that correct? I don't want to misrepresent you?

MS. KENNY: Right.

DR. EAGLSTEIN: And in the interest of time, we're going to try to address the area where they don't agree with the subcommittee's proposal.

MS. KENNY: I guess we can live with most of this.

I guess where we differ is on the three part issue of contra-indication for infants and for pregnant and lactating women. And we think that the subcommittee hasn't really gone far enough on their recommendation.

DR. EAGLSTEIN: Where is that now?

MR. BOSTWICK: It isn't in here.

MS. KENNY: It isn't here, because actually --

DR. EAGLSTEIN: We didn't adopt it.

MS. KENNY: -- they tended to leave the warning as it was, which is essentially a caution for pregnant and lactating women, or perhaps not even that strong. And we think that this is just a common sense issue for women, and in addition, it's a bottom line issue.

There was some discussion yesterday that the sponsor was going to voluntarily restrict the product for use on pre-mature infant, but we believe that they are not going to do it for the even more premature infants, who are still in utero and these are the infants whose immature and developing central nervous systems are going to get whatever -- however miniscule amount of Lindane that enters the mother's blood-stream from application to herself. The developing fetus is going to get this and we just can't condone that.

I think we are also asking you to act today as an advocate for infants, and we're defining it for this purpose as babies two years old and under, based on the fact that their

surface to volume ratio makes them more likely candidates for CNS adverse reactions. And I guess that's our main point of difference.

DR. EAGLSTEIN: You would like Lindane contraindicated for those under two?

MS. KENNY: We would like it contraindicated for children under two and for pregnant and lactating women, or at least a strong caution on the package for consumers regardless of whatever is left on the PDR and for physicians. We would like consumers to see it on contraindications or caution on the package.

DR. EAGLSTEIN: Dr. Pomeranz?

DR. POMERANZ: In reading this over under number 3(d), warn anyone. I would put in parenthesis, (particularly anybody that is pregnant assisting in Lindane applications.)

DR. EAGLSTEIN: Okay.

DR. POMERANZ: If that is going in physician package insert, that's one thing I thought might be helpful.

DR. EAGLSTEIN: Dr. Pomeranz was suggesting that under I 3(d), it should read: "Warn anyone assisting, or especially pregnant women?"

DR. POMERANZ: Yes. I warn anyone and in parenthesis (particularly pregnant women.)

DR. EAGLSTEIN: Warn anyone and particularly pregnant women.

DR. POMERANZ: Warn anyone, and particularly pregnant women.

DR. EAGLSTEIN: Does the Committee want to take a minute and read through this yourselves independently?

DR. CHANCO-TURNER: Yes.

DR. EAGLSTEIN: And then we can get to it.

I think a few of our Committee are leaving now and the representatives from the Pediculosis Association --

MS. KENNY: We've got an hour.

DR. EAGLSTEIN: Is that right. We're considering sending everybody home to think this over. I know that it has been an expense to you to come here, but everybody is tired. A few have left. I don't think that a proper evaluation can be made, and I would suggest that your chances of getting through to clear minded people are not good right now.

(Laughter.)

MS. ALTSCHULER: We definitely know we don't need Accutane and Kwell at the same time.

DR. EAGLSTEIN: Is anybody going to be terribly upset if we adjourn at this point and take this up at a future meeting?

MS. ALTSCHULER: By a future meeting, are you necessitating the presence of or --

DR. POMERANZ: How long -- I mean, it seems pretty straightforward to me.

DR. EAGLSTEIN: Does it? It does to me, but I spent all day yesterday working on it.

MS. KENNY: I've read it through and it just seems straightforward.

The only problem I have is the infants under two and absolute restriction against them. As far as the pregnant women goes, I don't have any problem with that.

MS. KENNY: How about the pediculosis, and let it stand on scabies.

DR. CHANCO-TURNER: You mean, under (1) and remove pediculosis as an indication?

MS. KENNY: We just feel that there are safer, less toxic possibilities and alternatives for pediculosis for anyone of any age, and that it is not necessary to use Lindane on really anyone for pediculosis, yet alone infants.

MS. ALTSCHULER: Or any pediculicide on a two-year old or younger.

DR. EAGLSTEIN: The Committee yesterday --

DR. POMERANZ: What do you do with kids under two that have them?

DR. EAGLSTEIN: -- that's the problem that was addressed.

MS. ALTSCHULER: Comb them.

DR. EAGLSTEIN: Comb them. The thought yesterday was they will receive some treatment and it may be equally

unsafe, as it were, unless you believe that combing will be sufficient.

MS. KENNY: Well, that's for babies. Babies with limited amounts of hair.

DR. KOEHN: May I ask a question as a new person and not here last year.I noticed in your write up of the last meeting that you are considering -- that you voted to take the shampoo separately and make up a new -- a different warning for that rather than for the cream and lotion. Has that been done?

DR. EAGLSTEIN: The vote last time, I believe, was to remove pediculosis as an indication for the cream and lotion.

DR. KOEHN: And you were going to change then the shampoo so that it wasn't left on overnight, and so forth?

MS. KENNY: Right.

DR. EAGLSTEIN: That had already been done.

DR. KOEHN: That's done?

DR. EAGLSTEIN: That's done.

DR. EVANS: That was the reason that they elected to use shampoo as the drug of choice because it was only used for a matter of eight to ten minutes whereas the others were left on overnight.

DR. KOEHN: So, we're saying now that we should not even use the shampoo for four minutes?

MS. KENNY: No. I mean if the stuff is going to be

left on the market, you ought to use the shampoo for four minutes --

DR. EAGLSTEIN: But not on people under two.

MS. KENNY: -- but not on people who are pregnant, nursing or under two.

DR. KOEHN: Pregnant, nursing and under two.

DR. EAGLSTEIN: That's the issue. If you agree to this --

MS. KENNY: For pediculosis, there are alternatives that are safer.

DR. EAGLSTEIN: -- if this committee report is satisfactory to you, it is to the committee obviously. The Pediculosis group is not satisfied as regards one point, and that point in particular is that they would like the shampoo, at least, if not all the Lindane preparations to be contra-indicated for people under two, pregnant or lactating. Is that right?

MS. KENNY: Right. I think the numbers you are talking about are huge. There are millions of people who are using just the shampoo and if you could separate the shampoo, I think you would be helping millions of people if we could contraindicate for those populations.

DR. EAGLSTEIN: The committee discussion centered on the fact that in all likelihood, the people will get treatment with shampoo of another sort, or hair treatment and that

that might not be safe.

DR. CHANCO-TURNER: They'll get A-200.

DR. EAGLSTEIN: Yes.

MS. KENNY: There are better OTC options than A-200.

MS. ALTSCHULER: Well, looking at the other side of the coin, there really isn't any great advantage to using the Lindane preparation. It doesn't have anything -- knowing it's lack of ovacidal action, it is not like it's going to be the be all and end all above everything else. It's efficacy is pretty well -- not that much greater than anything else available, if any. So, there's no reason to look to a potentially toxic substance when you can get the same effect nonetheless.

DR. McILREATH: Dr. McIlreath from Reed and Carnrick. If you contraindicate this for shampoo, which is left on for four minutes and allow it for scabies, which is left on for 12 hours -- eight to 12 hours, you're talking of -- saying that something is okay to -- which will produce levels of X level. Something is not okay if it produces levels of less than one-tenth X. We have 40 years experience with never a report of any teratology or any fetotoxicity reporting with the compound and a raft of animal studies, which have shown a lack of evidence of any fetotoxicity even in three generation studies, and it seems to us that there is nothing but an emotional concern about the potential hazard.

MS. KENNY: I think it is clear that the studies go both ways. I think there are studies on both sides. Studies that point out both and that the evidence is not in on this substance, and I think the substance is going to be controversia for a long time.

DR. EAGLSTEIN: I don't think the committee found evidence on both sides frankly, or they probably would have reached an alternate conclusion. The evidence was that the blood levels in utero and the blood levels after shampoo were really quite low. And your view was that it would be better if they were zero and that could be down by combing or --

MS. KENNY: Our view is that most people misuse. Many, if not most,people misuded this substance, and when I say that I am not just going on my own experience with hundreds and hundreds and hundreds of families, but also on the experience to, for instance, Dr. Von Hanson (phonetic) at Allied Health Center in Tucson, and he is also reported as saying that in probably 60 percent of patients, people overuse and misuse this substance so that you get a situation where you may get blood levels on use as directed, but when you get overuse and misuse, you get probably considerably higher blood levels in the fetus.

DR. EAGLSTEIN: I think the committee agreed with you and tried to address the area of overuse and misuse in the ways outlined. Certainly, we all agreed that the sponsor

should take many steps to educate the physicians and the literature should be clarified.

Your concern really is that overuse may still occur and you want to prohibit these people from having the chance to overuse it by prohibiting them from having it.

MS. KENNY: Would the committee consider saying on the package insert, "Pregnant women should consult their obstetrician before using the substance."

DR. EAGLSTEIN: I hope you are getting the sense of this. I am trying to represent this issue as it evolved yesterday that the idea here is that the Pediculosis Association would like to preclude being pregnant, lactating or under two a contraindication so that there would be no choice for them, as it were, and so that they couldn't overuse or misuse.

DR. KOEHN: And that is just for lice and not scabies?

MS. KENNY: Pediculosis.

DR. EAGLSTEIN: Well, they'd like it for everything, but they --

MS. KENNY: We can't talk about scabies, we are really not qualfied.

DR. EAGLSTEIN: -- okay. They're sticking with lice. For lice. And the point especially being that overuse is apparently quite common. And the committee agreed -- the subcommittee agreed, and I think the full committee last time

agreed that it was a terrible state and that there hadn't been nearly enough attempt by the sponsor to make things clear. And we were quite critical of the sponsor. And I think we asked that we adopt a statement to that effect, a general statement, number five, that the firms are encouraged to do much more to educate.

But that was the remedy that the committee was suggesting, the remedy being to give people the information to use it properly rather than saying they can't use it since they were going to use something.

DR. CHANCO-TURNER: But you were suggesting a patient package insert too, weren't you, in number three?

DR. EAGLSTEIN: Number three?

MR. BOSTWICK: Well, we had that example.

DR. EAGLSTEIN: We have it.

DR. POMERANZ: Has the company made any progress in a unit dosage system so that they are not giving it out in large amount, 32 ounce bottle?

DR. McILREATH: As we pointed out yesterday, we can do that. It's been done with several other drugs. Pharmacists don't buy it. They want something that's convenient for them. The unit dose, if you want to call two ounces a unit dose, that is a common package now for us, but pharmacists still prefer a larger one that they can dispense in the appropriate amounts. We believe that we can and will increase -- improve

the directions for use to make it more clear about how much you should use under various circumstances. But I don't think we would come out with a one ounce unit.

MS. KENNY: We suggested a sliding -- we would be satisfied with a sliding scale on the bottle.

DR. EAGLSTEIN: The Pediculosis group actually came out against the unit dose feeling that it might lead to more abuse and hoarding.

MS. ALTSCHULER: And also with the understanding that there would be a sliding scale approach used in the doses; so, that it is not encouragement to use a whole bottle just to wet the hair.

DR. KENNEY: Mr. Chairman, I would like to move the adoption -- that the full committee adopt the subcommittee's report.

DR. EAGLSTEIN: Is there a second?

MR. GOLDSMITH: Second.

DR. EAGLSTEIN: Discussion?

MS. KENNY: What happens with the patient package insert which is voluntary?

DR. EAGLSTEIN: We'll get to that next.

MS. KENNY: Can there be some resolution by the committee that they strongly recommend to the sponsor that they develop such a patient package insert?

MR. BOSTWICK: We had an example. And we thought what we would do -- has gone through the floor -- we thought

we would discuss that and develop the sense of what the committee felt about it.

DR. McILREATH: Perhaps I can save you some trouble. We will prepare a package insert -- a patient package insert.

DR. EAGLSTEIN: Now, is that your question?

MS. KENNY: That's my question. I mean, the question is, is there going to be a recommendation that they use some of our guidelines -- our brochure as a guideline in doing so, or not?

DR. EAGLSTEIN: My feeling as to what happened yesterday was that the subcommittee agreed that this package -- that this information, which is developed by the Pediculosis Association was very good and should serve as the basis for what the company would develop as a patient package insert. And that it would be recommended that there be a patient package insert. And I think that the company agreed and we wanted to -- we felt we would have more time for deliberation and that people might amplfy, but short of that, I think adopting this should adopt the ideas that we are requesting the company or the sponsors to make an insert based on this insert.

MR. BOSTWICK: Right.

MS. KENNY: I don't know if they agreed to that.

DR. McILREATH: Well, I think, it will go beyond that.

MR. BOSTWICK: That doesn't change the fact that

the committee can adopt the recommendations and adopt that package insert as part of them and then we will have to negotiate with Reed and Carnrick over the content. But the committee is certainly free to adopt this insert as its --

In other words, III, since we don't have time, would really be that the subcommittee recommends the sponsor develop a package insert based on the Pediculosis insert and that this be available to the patient. I don't know that that is as far as you want to go.

Did you hope we'd say it would be mandatory?

MS. KENNY: No. Obviously, I understand that it has to be voluntary.

DR. EAGLSTEIN: Okay.

MS. ALTSCHULER: One last thing. On the physician directions inside where you have on Part I, "Emphasize the need for combing out the nits after shampooing to prevent self-reinfestation."

DR. EAGLSTEIN: Right.

MS. ALTSCHULER: Would it read similar to that, or would there be more specifics as to the ovicidal or lack of ovicidal action by Lindane if used safely? Only because in the sense of reeducating the physician, he thinks it does it all. Explicit numbers perhaps?

DR. EAGLSTEIN: Do you recall what was the -- you wrote this as what we --

MR. BOSTWICK: I wrote that as what we recommended. We didn't specifically include the other portion.

DR. EAGLSTEIN: She is saying that since this is a physician insert and it is part of educating the physician, she would like to see it say something like, since Lindane is not 100 percent ovicidal, it is important that the patient be told to comb out the nits to prevent reinfestation.

MS. KENNY: A four-minute application is sometimes less than 20 percent ovacidal.

MS. ALTSCHULER: Right. It's that low.

DR. EAGLSTEIN: Does the committee have any feeling on this particular issue?

(No response.)

DR. EAGLSTEIN: I told you the committee wasn't sharp right now.

MS. ALTSCHULER: That's all right. Well, we're taking our chances.

DR. EAGLSTEIN: Jerry, you seemed tuned in to this. Do you think that idea should be inserted?

DR. POMERANZ: I don't see any reason not to --

DR. EAGLSTEIN: That lack of ovacidal --

DR. POMERANZ: -- at this point.

DR. EAGLSTEIN: Does the sponsor have a problem with that?

DR. McILRETH: No.

DR. EAGLSTEIN: No. So, you would concur?

DR. McILRETH: Yes.

MR. BOSTWICK: So, this statement, we just include --

DR. EAGLSTEIN: Include the lack of 100 percent effect.

DR. KOEHN: Lindane is not 100 percent ovicidal.

DR. EAGLSTEIN: Right.

Include less than 100 percent ovicidal.

Other points of agreement or disagreement?

DR. KOEHN: Just a question, do you know -- does Lindane -- what about Lindane and wearing rubber gloves?

DR. EAGLSTEIN: That was brought up. No one knew. We don't know if Lindane will penetrate the rubber gloves in the time used during wash. We thought maybe in a brief washing time it wouldn't, but in the long run, it would. We didn't really know.

So, there is a motion -- somebody moved to --

MR. BOSTWICK: Dr. Kenney.

DR. EAGLSTEIN: -- accept this as it now stands.

DR. BOSTWICK: The recommendations are amended by adopting the National Pediculosis Association patient package insert.

DR. EAGLSTEIN: Right.

DR. BOSTWICK: And the additional statement is under

3(f).

DR. EAGLSTEIN: Less than 100 percent effective.

MR. BOSTWICK: Which would include the information that Lindane is less 100 percent ovicidal.

DR. EAGLSTEIN: Is there a second to that?

DR. POMERANZ: What about the 3(d) that I suggested?

MR. BOSTWICK: 3(d).

DR. EAGLSTEIN: Right. And the pregnant women, especially pregnant women.

DR. POMERANZ: More than anyone.

DR. EAGLSTEIN: Okay.

DR. POMERANZ: We could say especially pregnant or nursing.

MS. ALTSCHULER: Yes. Yes.

DR. EAGLSTEIN: A second. I'm looking for a second.

MR. GOLDSMITH: Second.

DR. EAGLSTEIN: Now, you understand this does not accept the area where you would like us to change.

MS. KENNY: I understand that.

MR. BOSTWICK: Contraindications for pregnant women.

DR. KOEHN: It says, "Patient package insert, please see the accompanying example." If we vote for this, does it mean that we're voting never use Lindane to prevent lice?

MR. BOSTWICK: Yes.

MS. ALTSCHULER: Right.

DR. EAGLSTEIN: To prevent.

MS. KENNY: To prevent.

DR. KOEHN: Oh, to prevent. I'm sorry.

MS. KENNY: We did this in 20 minutes.

DR. EAGLSTEIN: All those in favor of the subcommittee' report becoming the committee's report?

(A show of hands.)

DR. EAGLSTEIN: All opposed?

(No response.)

DR. POMERANZ: Can we take up again at another point, the question of the under two?

MR. BOSTWICK: Oh, sure. We've been looking at Lindane for seven years and we're not going to stop now.

DR. EAGLSTEIN: Well, I want to thank the committee. You worked very hard. Thank everybody for being so indulgent.

(Whereupon, at 3:45 p.m., the meeting was adjourned.)

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