just going to have to recommend to Reed and Carnrick and see how they react to it.

Follow-up information on the people who have had conclusions.

And I see written in here, Doctor, irritability and sleep disorders. Is that yours?

DR. EAGLSTEIN: No.

MR. BOSTWICK: Which I am sure they have made some effort to do in the past anyway. I don't think this is a great revelation to Reed and Carnrick. Here's the one that I don't know how Dr. McIlreath feels. Sponsor more sensitive studies of neurotoxicity in humans than have been performed in the past.

DR. McILREATH: Well, I don't know how you'd do that.

MR. BOSTWICK: Well, one way you could do it would be to take a group of people.

If you had a proper indication for the use of the drug, say, scabies; therefore, you know you are going to maximize your absorption. Put them into a clinical research center. Get an EEG before. Treat them overnight just like you would if they were going home and perform and EEG and that isn't necessarily everybody's definition of sensitive or sophisticated, but it would give you some idea if there was some potential for having spikes on EEG, even if they don't have convulsions. That is what everybody is concerned with.

Otherwise, I think you'd have a pretty tough time defining what you were actually studying. I mean, most of these psychometric testing things are fairly complicated and require controls.

MS. ALTSCHULER: I think your suggestion before would be quite helpful including in whatever publication you were speaking about that when you are talking to the physicians, to also encourage them to be aware --

MS. KENNY: And to report.

MS. ALTSCHULER: -- and to report. We've got doctors in Boston who are sitting on cases that we can't -- you know, it is not a priority for them to get that information in. And so even in the last hearing, it was thrown out of our testimony or our discussions simply because we couldn't document it because he didn't find it important enough to follow through, but that child ended up in the hospital. So, if they would just be alerted to even think to ask the question about Lindane.

DR. RASMUSSEN: But that wouldn't answer the question of neurotoxicity.

MS. ALTSCHULER: Well, once you -- you have to have a population to test. I would think that would probably be the --

DR. RASMUSSEN: But those would all be retrospective things. What he is talking about is a prospective type of a

study. To really assess, you would have to have some baseline of what was there before.

MS. KENNY: Right.

MS. ALTSCHULER: But at least in some of the stuff we've read, one of the problems is that by the time it occurs to the physician or whoever is looking at the case to think about Lindane is too late. So, if they would be forewarned that way.

DR. McILREATH: But I don't think it would help this though.

MS. KENNY: He means a specific study.

DR. RASMUSSEN: The only way you are going to get any good data is prospectively, not random retrospect. You are still going to have the same problem that you were discussing and you're still going to have underreporting. Even if you blurted it out on the Today Show, you know, you'd still have people who they just don't want to do it because they gave it and the kid got sick. Why refer your own mistakes.

MS. KENNY: Right. I agree.

DR. RASMUSSEN: It's like I go up and say, look what I did.

MS. KENNY: I agree with you. There are so many of those cases that -- you know, we've just heard of so many of them that -- in such a short time that I can't believe there are just not hundreds of them out there.

DR. RASMUSSEN: Well, that type of a study with an EEG is something that could be doable. There are plenty of CRCs, plenty of pediatric neurologists, plenty of people who have treated for scabies. You couldn't get a million patients but like the stuff that Chuck Ginsburg has done is basically good stuff and you've start it on 8, 10, 12 people.

DR. EVANS: In certain parts of the country, they do have that kind of volume.

MS. KENNY: Yes. For instance, my brother-in-law is a doctor with the Apache Indian Health Service and he says he's got plenty of people there.

DR. RASMUSSEN: Does he have a CRC though?

(Laughter.)

DR. RASMUSSEN: That's the problem. You need a fairly sophisticated system. It could be. Those types of things are doable. Whether it would really solve the question, somebody might say that that is not a significant piece of information. Doesn't satisfy all the problems.

DR. EVANS: Well, I am afraid to get any meaningful data would be extremely difficult. You know, we could do it on a small number of patients, but whether is extrapolatable, or what it means, I don't know. If you are talking about longitudinal studies or learning studies, the kind that Dr. Allen was referring to, gee, to get anything that you could make a conclusion about is extremely difficult.

DR. RASMUSSEN: It would be extremely difficult. It would be like trying to prove where high fat diets give you heart disease and people have studied whole communities for 10, 20, 30 years and it is still debated because there are so many variables.

DR. EVANS: That's right.

DR. EAGLSTEIN: I think that would be comforting the encephalographic studies though.

DR. McILREATH: There have been studies done, as I mentioned last time, on factory workers where they were manufacturing Lindane. I suppose we could go back -- one approach would be to go to those people and see if any follow-ups were done and what --

DR. RASMUSSEN: But those were all adults. That's not what you're looking at. those were adults who were manufacturing.

DR. McILREATH: That's true.

MS. ALTSCHULER: Weren't some of those studies done for malathion?

MR. GRANDY: Not in this country.

MS. ALTSCHULER: There wasn't a study done with --

MS. KENNY: Tht is the -- study, you mean?

MS. ALTSCHULER: -- no, no.

MR. GRANDY: No, that was Lindane.

MS. ALTSCHULER: No, no, the study at Boston's Children Hospital.

MR. GRANDY: That was an absorption study.

MS. ALTSCHULER: All right.

MR. BOSTWICK: We can leave it as a recommendation and we're just going to have to see whether it is feasible.

DR. RASMUSSEN: Well, obviously you are going to have to talk to somebody who knows something about neurotoxicity, and I certainly don't consider myself to be knowledgeable in that area.

MR. BOSTWICK: This goes back to the original problem. There are so many reports about neurotoxicity, but we don't have anything hard on it. We have a lot of people who think that it is.

MS. ALTSCHULER: Right.

MR. BOSTWICK: If we could find some way to find out without costing everybody a whole lot of money, it would be great, but I don't think that is possible.

MS. ALTSCHULER: That's why I think it would be better -- you know, if you get that population that is already experiencing some sort of a reaction, you know, catch them while they've got it. But other than to let it make it happen in another population.

DR. EVANS: Well, you are not making it happen. You already know that it is endemic to certain areas and you just go in looking for scabies as well as pediculosis. You can find these kind of populations to do it in.

DR. RASMUSSEN: Well, it wouldn't be an experimental study. You would be giving people Lindane whether you were going to EEG them or not.

DR. EVANS: That's right.

DR. RASMUSSEN: An EEG is not an evasive, traumatic procedure and they just paste little electrodes on your scalp. There is no drug; there is no risk, absolutely nothing at all. And you just go to sleep in a lab.

DR. EVANS: Well, I think all of this is good information to have. I don't know if we can mandate it, but I think the more information we have on this matter, the more comfortable we feel about its being used.

We have pretty much been through the label on pediculosis, the shampoo and pediculosis. Now, were we going to concern ourselves tody with the use of the other forms and other kinds of pediculosis?

MR. BOSTWICK: You mean the cream and the --

DR. EVANS: The cream and the lotion.

MR. BOSTWICK: We decided not to use them.

DR. McILREATH: They are not going to be contraindicated, removed from the --

DR. EVANS: So, we are just going to use it for scabies?

MR. BOSTWICK: Right.

DR. EVANS: Has that been addressed so far, the

directions for use for scabies?

MR. BOSTWICK: No.

I don't know how different it is and how much work it would mean.

DR. EAGLSTEIN: This means that if the committee accepts these recommendations and then the recommendations are passed on to Reed and Carnrick?

MR. BOSTWICK: Right.

DR. RASMUSSEN: No, they would go to the group tomorrow.

DR. EAGLSTEIN: Then would Reed and Carnrick come back with the response, proposed label?

DR. McILREATH: Yes.

DR. EAGLSTEIN: Would that be reviewed by you or by the committee?

MR. BOSTWICK: By us.

DR. EVANS: It would be reviewed by us.

MR. BOSTWICK: And if we think the committee needs another whack at it, if it seems as though some of the issues are more than they're willing to decide on -- I am not guaranteeing this community will see it again, but there's a very good chance it will.

DR. EAGLSTEIN: It seems to me that the real concern of the committee was education. That there has been a failure somehow for all the doctors who prescribe it to learn

the proper way to use it or the proper way to instruct people. And in that sense, I'm leaning to the specific idea of putting a statement in the warning. Well, the more general idea would be that should the committee have as a recommendation that Reed and Carnrick do all that it can to assure that the physicians as well as the public are educated. Should that be a general --

MR. BOSTWICK: That is something you can generally say. The question is: what is all that it can? You know, what Reed and Carnrick thinks all that it can and what we might think are two different things.

DR. EAGLSTEIN: Right. But I just mean as a formal proposition and all these imply that statement that there isn't that statement and, as you said, we are dependent upon the sponsor for developing and trying to get this.

MR. BOSTWICK: I don't see any problem with that at all. I think just a general proposition --

DR. EAGLSTEIN: I think that ought to be a proposal to the committee.

MS. ALTSCHULER: Certainly to pull the contradictory information off the shelves. I mean, they can't continue to have three different sets of instructions out there.

MR. BOSTWICK: Part of the problem with the label recommendation for Lindane in general is that we have not implemented some of the revisions that Reed and Carnrick

has already proposed because we have been trying to hammer it out with the committee. This is not all Reed and Carnrick's fault. Part of it is our fault because we wanted to get as many people as possible in the process and, to be honest, I think it works. It takes longer, but I think we will get a better label. The problem is that it is not as quick the way that we would like it.

DR. EAGLSTEIN: Well, as a general proposition, I would like to propose that the subcommittee propose that the committee adopts a resolution or a statement --

MR. BOSTWICK: Recommending --

DR. EAGLSTEIN: -- recommending.

MR. BOSTWICK: -- that Reed and Carnrick be encouraged to educate both the physician public and the general public in the proper use of the drug, I guess, would be the statement.

DR. EAGLSTEIN: And then a second thought. I did think that in educating the physician something in the warning section should point out that it is harmful or poisonous. I had thought poisonous, poisoning could occur because the -- I don't think the physicians don't really realize that, the general physician who doesn't do dermatology or pediatrics all the time need to know this. They may not realize that you can have a toxic effect through skin penetration. And that that ought to be in the warning section to the physician.

MS. KENNY: How is the PDR revised? How often is the

PDR revised and who has the authority to revise it, and that type of thing?

DR. EAGLSTEIN: This is the PDR.

MS. KENNY: What you are reading is the PDR.

DR. McILREATH: The PDR is approved labeling and when your labeling is refined --

DR. RASMUSSEN: But it is published by a private firm.

DR. McILREATH: -- it is done once a year and --

DR. RASMUSSEN: They send out revisions that are important if there are major errors, but that's about all you ever see.

MS. KENNY: So, whatever --

DR. EAGLSTEIN: -- and we can't change that until it is approved by the FDA.

MS. KENNY: All right. So when the physician insert is changed, it will change --

DR. McILREATH: The PDR.

MS. KENNY: -- in the PDR eventually.

DR. McILREATH: Yes. Except that what was alluded to before has been confirmed that more lay people read the PDR than physicians.

DR. RASMUSSEN: I think that is very good because that's their main source of drug information, whereas with physicians, it is your teachers who tell you about drugs, not the PDR.

DR. EAGLSTEIN: I read the PDR a lot. We read it with our --

DR. RASMUSSEN: You are the chairman, Bill, so you are going to have to.

(Laughter.)

MR. BOSTWICK: Okay. Well, as far as Dr. Eaglstein's proposal concerning a statement that the drug may poison?

DR. EAGLSTEIN: I had -- you know, poison may occur because of skin penetration.

MR. BOSTWICK: In the warning section?

DR. EAGLSTEIN: Right.

MR. BOSTWICK: It does say that Lindane penetrates human skin and has a potential for CNS toxicity at least in current -- so, you have the sense of that there, except it does not say poison.

MS. ALTSCHULER: I thought we said it the other way the other time.

MR. BOSTWICK: The second sentence in the warning section says: "Lindane penetrates human skin and has the potential for CNS toxicity."

DR. EAGLSTEIN: Maybe that should be moved up to the beginning statement.

MR. BOSTWICK: That would be first and then the second --

DR. EAGLSTEIN: Right.

MR. BOSTWICK: -- the second sentence would be -- the first sentence would become second.

DR. TABOR: I think that is a very good idea.

DR. EAGLSTEIN: And I think that would probably satisfy my concern.

MR. BOSTWICK: Just reverse the order of the first and second sentence.

MS. ALTSCHULER: Great.

DR. McILREATH: Something was brought to my attention and getting back to the container label warning. May be harmful or fatal if swallowed or used -- what was the word?

MS. KENNY: Misused.

But I think that word is a little vague there.

DR. McILREATH: Well, fatal if misused, does that mean if I use it twice I am going to die?

MS. KENNY: Right, that's too vague.

DR. RASMUSSEN: But there is a potential for it.

DR. McILREATH: If ingested, it may be harmful or fatal if it is swallowed. I think swallowed would be better. You have to be very careful about it or use too frequently.

DR. RASMUSSEN: Well, the problem with many drug words is that words like that are nebulous, very nebulous. Like the word that Bill suggested about massively, and there was a really gorgeous letter to the editor of the New England Journal where somebody asked a bunch of doctors what their impression of always, never, frequently, rarely, and the numbers

for all of these ranged from 52 percent to 100 percent. I mean, they are completely worthless words, which is also nebulous.

DR. TABOR: I think that is a tricky issue because it's on the package, on the container, and it is probably going to be read more than any of the other stuff that we have been pouring over this afternoon. I think the portion that says, "may be harmful or fatal if swallowed," no one would have any argument with.

DR. McILREATH: No, I wouldn't.

MS. ALTSCHULER: It has got to go one step further though, but I agree maybe it should be a different word.

DR. RASMUSSEN: Why don't you make two sentences out of it. Say, "May be harmful or fatal if swallowed. Multiple applications predisposed to CNS toxicity."

MR. BOSTWICK: Wells, let's take "or misused" for the time being. "May be harmful or fatal if swallowed," is something everybody can buy.

MS. ALTSCHULER: Abused better than misused?

DR. McILREATH: Well, even abused, you know, I can use it three or four days in a row, but I would say it is not going to kill you.

DR. RASMUSSEN: Or daily use may be harmful

DR. EAGLSTEIN: It is going to be limited to harmful. Harmful is overused.

DR. TABOR: What is the purpose of putting this on

the bottle? The purpose is to highlight the worst case.

DR. McILREATH: To me the highlight is don't drink it.

DR. TABOR: Yes.

DR. RASMUSSEN: I think there is probably more toxicity from frequent daily application than from ingestion.

DR. EAGLSTEIN: I think overuse is the problem.

MS. KENNY: That should be in the directions and warnings on the package --

DR. McILREATH: Not serious. All the serious ones have been -- all but one of the serious ones. By serious, I'll say convulsions by getting ingestion.

MR. BOSTWICK: This product can be toxic if misused.

MS. KENNY: I think all that should be in the patient package insert. On the bottle, all you need is to keep people from drinking it. I think that is the point of something stuck on a bottle is to keep people from drinking it.
So they don't leave it on the bathtub ledge. It should be stored away. It's a little tiny bottle, with a little tiny round circle label on it. I mean, what is it supposed to say?

DR. TABOR: What you are really objecting to is whether mild or moderate overuse would result in fatality.

MS. ALTSCHULER: Can you say dangerous of your health?

MS. KENNY: May be dangerous to your heath.

MS. ALTSCHULER: Abuse or misuse, I mean, clearly it can be.

DR. TABOR: May be harmful or fatal if swallowed. Is that --

DR. McILREATH: That's fine.

MS. KENNY: I think that's fine too.

MR. BOSTWICK: Let's go with that for now. I know one thing, the pharmacist should not place a label over these.

MS. KENNY: And you can't put the details of the safety on the bottle, stuck on the bottle.

MR. BOSTWICK: Well, I am pretty satisfied with this. How about you, Dr. Eaglstein? Do you want to get into more specific labeling? And I don't know --

DR. EAGLSTEIN: One thing I wanted to ask is -- the Tappan (phonetic) studies just came out. Are you going to go with six hours? Are you going to try to go with six hours?

DR. McILREATH: No. That came out and we went to 8 to 12 and I think that was a matter of convenience because it is overnight 8 to 12 hours. You put it on; you go to bed.

MS. KENNY: You mean that is the justification? Convenience is the justifcation?

DR. McILREATH: Yes. The difference between 6 and 8 is not that great, but if somebody wanted for convenience to put it on overnight. Now, the six hours was slight less than 100 percent.

DR. EAGLSTEIN: Do you have any further information on what happens? I know their peak blood levels are four hours?

DR. McILREATH: Yes.

DR. EAGLSTEIN: And it keeps falling?

DR. McILREATH: That's right. Even though it is left on -- in those studies it was still left on; so, the peak blood level occurred at 4 to 6 hours and declined even though --

DR. EAGLSTEIN: Is there any difference if you take it off, do you have a lower --

DR. McILREATH: Well, we haven't done the examination of taking it off early. A lot of people say if you try and do that, what you will do is enhance penetration. When you try to wash it, you are going to drive it through.

DR. RASMUSSEN: There is a study that addresses that point from Germany where people put it on and did time blood absorptions and then tried washing it off sooner and actually they got more -- they got a higher peak levels because you hydrate the skin and you pump more of it through. In other words, washing it after 24 hours didn't give you a higher blood level than actually washing it off sooner gave you a higher blood level because you had more moisture while there was more drug on the skin.

DR. EAGLSTEIN: So, washing it off before the four hour peak --

DR. RASMUSSEN: Produced a higher peak level than washing it off at the end of 24 hours. Early washing -- the net -- the end result was that early washing produced a higher

peak level than washing it off at the end of 24 hours. The end result was that early washing did nothing to reduce the peak blood level. It was a study out of German.

DR. EAGLSTEIN: Well, I would think washing after the peak.

DR. McILREATH: Well, see, if you wash it after the peak there is still material in the skin and by washing it at that time --

DR. EAGLSTEIN: That gives you a second peak?

DR. McILREATH: -- you are going to drive that through. So, you could wind up with --

DR. EAGLSTEIN: That is theoretical?

DR. McILREATH: -- that's theoretical.

DR. EAGLSTEIN: It is not factual?

MS. KENNY: Even if you wash with quite cold water it doesn't matter?

DR. McILREATH: That's right. Unless it is on the surface high up enough that you can clean it off. After six hours or four hours, it's going to be into the skin.

DR. EAGLSTEIN: What were the times in the Tappan study?

DR. McILREATH: Two; six to 12 and 24 hours.

DR. EAGLSTEIN: What was the thinking behind the six to 12?

DR. McILREATH: I'm not sure. That was before I

joined the company and I think it was just leeway as to when they get it off. In some cases, they couldn't get it off before 12 hours.

And that was another study where nursing mothers were treated at the same time.

DR. EAGLSTEIN: So, you might think in his studies that he actually caused --

DR. McILREATH: In that two hours, he might have.

DR. EAGLSTEIN: -- in either one of those two schedules.

DR. McILREATH: In two hours maybe he didn't because there might be enough still high on the skin that he was able to wash, but at six hours, six to 12 hours, he probably got more off.

I don't recall if that had soap in that, or just washed.

DR. EAGLSTEIN: Soap.

DR. McILREATH: It was soap, okay.

DR. EAGLSTEIN: And then they rinsed with plain water.

Does anyone have more to add?

(No response.)

DR. EAGLSTEIN: We are going to adjourn if that is all right.

MR. BOSTWICK: You're the boss.

DR. EAGLSTEIN: All right.

(Whereupon, at 4:20 p.m., the meeting was adjourned.)