I believe an accommodation with industry Ohio regulatory officials agreed to a 12-week maximum dosage for the duration of use of these products. I do not believe that the 12-week period was based on any solid scientific footing, but I think it was just basically a political or regulatory accommodation with the industry so far as I do.

DR. JONES: Ms. Culmo.

MS. CULMO: Cynthia Culmo, Association of Food and Drug officials. Mark, what did the translation of the Commission E monograph say about addiction in short-term use?

MR. BLUMENTHAL: The commission E monographs -- it's Commission E -- did mention that the herb ephedra might be addictive. We qualify that and I can give you a quote on that, it did say ephedrine-containing preparations are listed as addictive by the international Olympic Committee of the German sports Association. They noted that in the monograph ephedra preparation should be used only on a short-term duration because all of tactical axis and danger of addiction. We qualified that and I believe that I would differ to Dr. Adams' testimony as an expert in addiction as to whether or not that is bona fide.

DR. JONES: Other questions from the floor?

[No response.]

DR. JONES: Seeing none, thank you very much, Mr. Blumenthal.

And now Paul Rubin is going to provide an introduction to a series of speakers that will start before lunch and continue after lunch.

MR. RUBIN: Good morning. My name is Paul Rubin and I am an attorney in the Washington, D.C. office of Patton Boggs and I am here today on behalf of Metabolife.

I would like to thank the Food and Drug Administration, the Office on Women's Health, the distinguished panel and Dr. Jones for the opportunity to speak today.

I understand that the focus of today's meeting is on the science surrounding ephedra rather than legal and regulatory issues and accordingly I am going to keep my comments brief and focus on the first and third questions posed by the Office on Women's Health.

I would like to first mention that the Ohio law does mandate the 12-weeks duration of use in response to the prior conversation.

I would like to focus on the review of the AERs. FDA's review regarding the safety of ephedra is

based primarily on adverse events reports. This is the case even though the concept of relying upon AERs to draw scientific conclusions and make product or ingredient specific risk assessments has been widely criticized.

The United States General Accounting Office is the investigative arm of Congress and it is both independent and bipartisan. In July 1999, the GAO issued a report condemning FDA's reliance upon AERs to conduct rulemaking and/or make scientific assessments regarding dietary supplements containing ephedrine alkaloids.

I am going to quote the GAO report and I am just choosing three quotations and there are many others that could have been chosen. On page 8 of the GAO report, heading: FDA Analyses Relied on Poorly Documented Reports of Adverse Events. "The agency used AERs as the sole source of support for a specific dosing levels relied on weak information to set limits on duration of use, and did not perform a causal analysis to determine whether ingestion of a dietary supplement containing ephedrine alkaloids caused or contributed to the adverse events."

Page 11 of the GAO report, heading: Adverse Events Reports Were Incomplete and Inconsistent. "The

AERs that we examined often lacked important information and the information that they did contain were sometimes inconsistent. These problems suggest that AERs should be used with caution and their use can contribute to uncertainty in FDA's conclusions."

Page 24 of the GAO report, heading Recommendations. "FDA needs to provide stronger evidence on the relationship between the intake of dietary supplements containing ephedrine alkaloids and the occurrence of adverse events that support the proposed dosing levels and duration of use limits."

I would also like to mention that the GAO focused its comments on the dosing levels and duration of use limits, but I do not believe that should be viewed as an endorsement of other aspects of FDA's proposed rule. If you look at the letter that Congress sent to the General Accounting Office, GAO was only asked to look at those two issues.

Nevertheless, despite the strong comments from the GAO, we are here today addressing the scientific validity of AERs. FDA has added that numerous AERs to the docket and appears to be operating under the assumption that the scientific flaws associated with AERs might somehow be rectified merely by counting more of them. This is not the case. Good

science cannot be based upon faulty underlying data regardless of the amount to faulty data collected.

A large house of cards is no more secure a building block to formulate regulatory and scientific decisions than a small house of cards. We believe rather than focusing on AERs the scientific focus should be on clinical trials and clinical research and that is what our panel will be discussing this morning as well as this afternoon. I should also mention that we applaud and encourage NIH funding of additional research regarding the safety of ephedra.

I would also like to note that Metabolife and regulated industry are proposing and recommending the adoption and enforcement by FDA of all encompassing standards for dietary supplements that contain ephedrine alkaloids, including warning statements, dose restrictions, and claim restrictions that are deemed reasonable by industry and we urge the adoption of the standards.

I would like to thank you for your time and I will now introduce the first of our very distinguished panel of speakers who incidentally cover a wide range of disciplines including, but not limited to, cardiology, pharmacology, toxicology, endocrinology, and clinical nutrition.

Our first speakers are Dr. Carol Boozer and Dr. Patricia Daly. Dr. Boozer has received a master's in nutritional biochemistry from Cornell University, a master's in nutrition from Harvard University and a doctor of science and nutrition from Harvard University. She is currently an assistant professor in the department of medicine at the College of Physicians and Surgeons at Columbia University in New York and director of the energy metabolism core laboratory at the Obesity Research Center in New York.

She has published numerous articles on obesity and weight loss and has recently submitted an article for publication on the efficacy of ephedra and guarana for weight loss.

Dr. Daly is a graduate of the University of Washington Medical School and she completed her residency in internal medicine at the New England Deaconess Hospital in Boston Massachusetts and a fellowship in endocrinology at Beth Israel Hospital in Boston Massachusetts.

Dr. Daly was an instructor in medicine at Harvard University until she relocated to York Hospital in York, Pennsylvania where she is a clinical endocrinologist. Dr. Daly's major research efforts focus on the contribution of insulin resistance and

sympathetic nervous system activity to the pathogenesis of obesity-related hypertension and the role of thermogenic agents in the treatment of obesity.

If it would be acceptable, Dr. Jones, I know that Dr. Daly and Dr. Boozer would prefer to speak consecutively and then take questions from the panel after both of them have had the opportunity to speak.

DR. JONES: We did discuss that end we will allow the two 15-minute presentations to follow one after the other and then we will do ten minutes of questions for simplicity.

MR. RUBIN: Great. Thank you.

DR. JONES: Thank you.

MR. RUBIN: I would also just like to mention that although I am here on behalf of Metabolife, Dr. Boozer and Dr. Daly are not and they will, I am sure, address that in their presentations. Thank you.

DR. JONES: I would ask them indeed to please address that. Thank you.

DR. BOOZER: Good morning. Thank you Dr. Jones and panel members for the opportunity to speak at this meeting today. I have been asked to speak by the Ephedra Research Foundation about several studies that I have conducted for them and they are providing funding for my time and expenses to do so today. They

have also provided funding for the studies that I will discuss. But I have personally no financial interest in any aspect of the dietary supplement industry.

As was mentioned in the introduction, my graduate training was in nutrition. My research interest is in obesity. My research includes a variety of aspects of studies of obesity including etiology, differential susceptibility, and treatments. I think it is important to underline here the importance of the current epidemic of obesity that we have in this country. We estimate approximately 40 million adults in this country are suffering from obesity. This is not a benign condition. The number is increasing and we know that obesity contributes to numerous increased health risks contributing to increased mortality and morbidity.

We also know that conventional weight loss treatments have limited effectiveness. Increasing numbers of individuals are therefore turning to alternative methods for weight loss. Preparations that include ma huang, ephedrine alkaloids are among the most popular.

Ma huang in combination with guarana or koala nut is the herbal equivalent to of the well researched weight loss treatments of ephedrine and caffeine.

Although ephedrine and caffeine combinations clearly produce weight loss in animals and in humans efficacy for weight loss of the herbal combinations have not been previously evaluated in clinical trials. The Ephedra Research Foundation, therefore, decided to fund a six-month, multi-site, randomized, placebo-controlled trial to assess the safety and efficacy of a dietary supplement containing ma huang and koala nut.

I was asked to conduct a separate eight-week clinical trial of Metabolite's product, Metabolife 356. I agreed to conduct these studies with the understanding that we would conduct an impartial study that would be published regardless of outcome. I felt that results from clinical trials would contribute much-needed data to this highly publicized concerns currently based only on anecdotal information.

Both of these studies are now completed. The results from the six-month study are currently under analysis. We will proceed with the usual procedures for peer reviewed publication of those results.

Dr. Daly, who directed the study at the Boston site, will talk more about the protocol.

Results from the eight-week Metabolife study have been presented at the Federation of American Society's for Experimental Biology meeting that was

held here in Washington last year. The manuscript is now in final review by Scientific Journal end we fully expect it will be published this year.

The review process for scientific papers is slow and sometimes frustrating. We ask your indulgence, however, as we go through this process. Because to bypass it is to risk scientific credibility that is so important to bring to this emotionally charged area. While we cannot discuss data from a six month study because an abstract has been already published for the Metabolife study I can provide those results.

This was a standard protocol for clinical trials, double-blind, placebo-controlled randomized two-arm design. The subjects were weight stable men and women, aged 25 to 55 with BMI between 29 and 35. Sixty-seven subjects were randomized, 32 to placebo, 35 to Metabolife 356.

Metabolife 356 is labeled to contain 12 milligrams of total ephedrine alkaloids and 40 milligrams of caffeine as ma huang guarana per ma huang guarana tablet. Although in its package insert, Metabolife recommends a more gradual usage of its product. For this study we decided to start subjects with the full amount, six tablets per day for a total

of 72 milligrams ephedrine alkaloids per day and 240 milligrams caffeine. We did this to provide maximum opportunity to detect side effects.

Forty-eight subjects completed the study, 24 per group. Of these those taking Metabolife had significant -- statistically significant greater loss of body weight which amounted to 8.7 pounds versus a weight loss of 1.8 pounds in the placebo group. There was a greater change of body fat in the actively treated group -2.1 percent versus a gain of .2 percent in the placebo group.

There was a significant difference in triglycerides with a loss of 15.7 versus a gain of 8.5 milligrams per deciliter in the placebo group.

Heart rate was significantly increased over baseline in the actively treated group with an increase of 6.9 versus a decrease of 1.7 seven beats per minute. Mean blood pressure systolic and diastolic did not differ between groups at anytime point nor were they different from baseline in either group at study end. When the rise over baseline for all subjects was compared at each time point, mean systolic blood pressure was significant only at week 6 for active versus controlled. The difference of 4.1 versus -2.6 millimeters of Mercury.

Repeated measures analysis of variance of completers, however, showed that the variability of the change in blood pressure was constant within subjects over groups. And the between group effect was not significant unless weight loss was used as a covariant.

To avoid any possible bias due to subjects who were lost to follow up intent to treat analysis was performed with all missing data imputed by carrying forward the last previous measurement to final observation. This very conservative treatment of the data resulted in changes of the magnitude of differences between groups but did not change the statistical significance of the treatment outcomes.

Eleven of the he 35 subjects in the actively treated group withdrew from the study. Eight of the 32 placebo subjects withdrew. Of the eight placebo subjects who withdrew to had recurring medical conditions that they had previously concealed from us. Six left for what they reported as personal reasons.

Of the 11 subjects withdrawing from the actively treated group, three withdrew for personal reasons, one withdrew for increased irritability, four for self-reported heart palpitations, two for self-reported palpitations and chest pain, and two for measured increases in blood pressure, that is, 140/90.

Of those subjects who withdrew all who withdrew for self-reported palpitations had follow-up EKGs and none of the showed any abnormalities.

Among the subjects who completed the study, there were no statistically significant differences in self-reported symptoms. There were however differences with increased reporting of dry mouth and insomnia. No subjects had any serious or long-lasting adverse event in this eight-week trial.

The measured heart rate, systolic blood pressure and self-reported palpitations, insomnia, and dry mouth side effects observed in the study could be anticipated based on earlier ephedrine caffeine studies and are consistent with a sympathomimetic action of ma huang. It would be expected that these could be minimized by more gradual introduction of the treatment.

In conclusion this trial clearly showed efficacy for loss of body weight and body fat of one herbal product containing ephedrine alkaloids. It could not answer the questions of long-term safety. These questions are better addressed by our six-month clinical trial which Dr. Daly will now address. Thank you.

DR. JONES: Thank you, Dr. Boozer.

Dr. Daly.

DR. DALY: Thank you. Dr. Jones, members of the panel, ladies in gentlemen, I am a board certified endocrinologist and physician. My training after medical school is in the field of internal medicine with subspecialty training in endocrinology and metabolism. During my subspecialty training and in the subsequent 10 years I spent on the faculty at Harvard Medical School and at Beth Israel Deaconess Hospital in Boston, I spent my time doing clinical research, seeing patients, teaching medical students and residents and fellows.

My area of research interest has included the use of thermogenic compounds for the treatment of obesity.

As a physician now in full-time clinical practice I see all of the morbidity associated with obesity. You'll hear later today from Dr. Bray who is an authority in the field of obesity research about the increasing numbers of obese adults in this country and the serious health problems associated with obesity.

In the early 1990s, I and colleagues at Beth Israel Deaconess Medical Center published results of a small randomized, double-blind, placebo-controlled trial of ephedrine and caffeine for treatment of

obesity. This was a pilot study with a small number of subjects participating. But we found no increase in adverse events and found that the combination was effective with greater weight loss in the active group than in the placebo group. This was over eight weeks.

Unfortunately, funding to carry out the planned larger study did not materialize. In 1996, I was approached by Science Toxicology and Technology and asked to design a protocol which will evaluate the safety of herbal mixture of ephedrine and caffeine. I agreed to do so because I felt that this information was important both the field of obesity and from the public health perspective.

I worked with a statistician and two clinical toxicologist to design a study which will evaluate the cardiovascular, neuropsychiatric, liver, kidney and gastrointestinal effects of this combination. This study was funded entirely by the Ephedra Research Foundation.

We designed and agreed to carry out the study was no monetary interest in the study outcome and under the strict understanding that the results will be published regardless of whether they are favorable or unfavorable.

The study was designed statistically to

include enough subjects to be able to detect very small differences in study parameters between the two groups. The statistician determined that to detect these differences we needed to enroll at least 150 subjects.

We have now completed the study and are in the process of analyzing a massive quantity of data. As Dr. Boozer mentioned, we are unable to discuss those results as yet, but when analysis is complete we will be writing a paper that we have every expectation of publishing in a peer reviewed scientific journal.

I would like to review the study protocol for you to clarify the kind of data that we have collected at the time involved in carrying out this study and the analysis.

As you have already heard this was a six-month, double-blind, randomized, placebo-controlled study which took place at two centers, New York Obesity Research Center at Columbia University under Dr. Boozer's supervision at Beth Israel Deaconess Medical Center, Harvard Medical School, under my supervision.

A total of 167 subjects were randomized in the study. Baseline evaluations of the subjects included 24-hour blood pressure and halter monitors, EKGs, and routine lab tests and urine toxic screens.

Subjects with serious medical conditions were

excluded from participation as is typical in clinical research and as is required by each of our IRBs, institutional review boards.

We recruited individuals, men and women, of all ethnic backgrounds, between the ages of 18 and 80 and included those who were mildly to severely overweight. In other words, with body mass indexes ranging from 25 to 40. Subjects received either active compound which was equivalent to a total of 90 milligrams of ephedrine at 192 milligrams of caffeine in three divided doses or a placebo.

This is typical of the dose in over-the-counter herbal preparations and actually includes a slightly higher dose of ephedra than the Metabolife study that Dr. Boozer mentioned. And by way of comparison, in my prior small study, we gave the individuals 150 milligrams of ephedrine and 150 of caffeine.

In this current study, compliance was assessed by pill counts at each of the follow-up visits. All of the subjects returned for follow-up, one, two, and four weeks after randomization. At those follow-up visits they filled out symptoms questionnaires, had 24-hour blood pressure and halter monitors placed and had physical measurements.

After the first four weeks, which we refer to as the acute phase, subjects that returned on a monthly basis and those visits they filled out symptoms questionnaires, had EKGs, and physical measurements. Blood testing was also done on a monthly basis to look for deleterious effects on kidney and liver and pregnancy tests were done monthly on women of childbearing years.

Because the cardiovascular effects of ephedra compounds are more likely to occur when these substances are first consumed, in other words tolerance or tachyphylaxes is thought to develop over time. Our protocol with cardiovascular evaluation was most stringent during the first four weeks of the study when we are most likely to see cardiovascular effects.

So blood pressure and halter monitoring which was used is quite expensive and is actually quite difficult for subjects. The subjects have to wear these monitors with the blood pressure monitor on the arm, taking blood pressures every 15 minutes during the day and every half-hour at night for the full 24 hours. They wear simultaneously a cardiac monitor with EKG leads all of the chest which become quite itchy over time and they wear that for a full 24 hours and are unable to shower during the time that they are wearing

this.

So it is not surprising that we had some dropouts of subjects because they were unable or unwilling to wear these monitors over 24 hours.

While we are not yet able to discuss our results I can tell you that no subject participating in this study suffered a life-threatening event such as seizure, stroke, or myocardial infarction.

As an endocrinologist I see a large number of obese individuals who suffer from diabetes, hypertension, coronary artery disease, hyperlipoidemia, stroke, and other complications. I recommend weight loss to these individuals using diet, exercise, gastric bypass surgery, or pharmacotherapy as needed because I know that weight loss will improve their health and decrease their chance of dying of the complications of obesity. When I recommend prescription drug therapy many of my patients are not able to afford to $100 plus per month cost and most commercial insurers do not cover these prescription drugs. An inexpensive, safe, and effective, over-the-counter alternative for treating obesity would have a tremendous public health impact.

Our study represents a strong first step in answering questions about the safety of these products

but more research in this field is needed. Given the public health interest in these compounds, and the public health -- for the public interest in these compounds and the public health impact of an effective, safe, cheap, over-the-counter-dated treatment government sponsorship of support for additional research is also called for.

Thank you for your consideration. We will be happy to take questions.

DR. JONES: Thank you, Dr. Daly. Questions from the panel? Dr. Philen.

DR. PHILEN: Thank you. I would like to know if these people were on some kind of a specific diet or if you had dietary rules for them to follow?

DR. DALY: Are you referring -- Yes, they were all instructed both the active and placebo groups were all instructed in a low-fat diet and encouraged to exercise.

DR. PHILEN: Was there a specific caloric maximum they were to a hereto or anything?

DR. DALY: No, there was not.

DR. JONES: Dr. Lieberman.

DR. LIEBERMAN: have got a few questions for Dr. Boozer. First I wanted to ask, did you control caffeine intake in the volunteers in your study?

DR. BOOZER: To enroll them or during the study?

DR. LIEBERMAN: During the study.

DR. BOOZER: Yes, during the study, yes we did ask them to -- you are at talking about the Metabolife study, the eight-week study?

DR. LIEBERMAN: Yes, the one that you actually presented the data from.

DR. BOOZER: Right, yes. Yes, we did ask them to limit their intake of coffee, any caffeine-containing beverages.

DR. LIEBERMAN: Okay. The other -- one of the other questions I had was, I think you may have said it and I missed it, how many subjects on the placebo group withdrew?

DR. BOOZER: Eight.

DR. LIEBERMAN: And then, to follow up on that, with regard to the subjects who withdrew in the active treatment group you listed a series of reasons that they withdrew, many of them were side effects typically associated with administration of ephedrine.

DR. BOOZER: Right.

DR. LIEBERMAN: Did the those subjects all withdraw themselves or were some withdrawn because you observed that their blood pressure was higher than

would be permitted by the protocol?

DR. BOOZER: The two withdrew for elevated blood pressure we withdrew. We asked them to withdraw when they reached that point. That was a predetermined cutoff point for our protocol. The others who withdrew, withdrew voluntarily.

DR. LIEBERMAN: Okay, and the final point I wanted to make was we have not seen your FASEB abstract I would suggest that you enter it into the record.

DR. BOOZER: Sure.

DR. LIEBERMAN: Thank you.

DR. JONES: Other questions from the panel? Dr. Philen.

DR. PHILEN: Are you able to tell us, Dr. Daly, how many people completed your study?

DR. DALY: I am sorry, I do not have the number at the tip of my tongue, but I feel it is important not to have any of the data out until --

DR. PHILEN: That's fine. That's fine. I understand.

Also, when you were working with the statistician do you recall the size of your type 1 and type 2 errors were?

DR. DALY: I do not. I know that they were -- it was an important part of coming up with that

number and I know that we used the most stringent measurement we were making was with the 24-hour blood pressure monitor, so we were looking at the smallest difference to be able to detect a difference in blood pressure.

DR. PHILEN: That was what you were using to calculate your --

DR. DALY: Because that was the thing that gave us the largest end basically.

DR. PHILEN: Thank you.

DR. JONES: Dr. Schwetz.

DR. SCHWETZ: Bernard Schwetz, FDA. Do you how an estimate of when the report from the six-month study would be ready to be submitted to a journal for review?

DR. BOOZER: We hope within the next month or two.

DR. SCHWETZ: Oh, the six-month study?

DR. BOOZER: Yes.

DR. SCHWETZ: Thank you.

DR. JONES: Thank you. A question here from the floor.

MR. MOWERY: Daniel Mowery from the American Phytotherapy Research Laboratory. You talked about, Dr. Daly, about the IRB's review of this. Could you

give us a little bit more insight on the concerns the IRB might have had or did not have given what we hear about the adverse effects of ephedrine and so forth, especially as has been brought up here in different sessions.

I have some concern about what is going to happen with future research trials on ma huang at the IRB level. I know that in my own case I am working with a couple of IRBs right now myself that there is some a grave concern based on what happened in 1996 and 1997 about ma huang.

Can you just tell us a little bit about what you have seen, either one of you, on those issues, Dr. Boozer, Dr. Daly?

DR. BOOZER: We go through the St. Luke's Roosevelt Hospital IRB for our study because the Obesity Research Center is located in the hospital and we had no challenges to our protocol from the IRB there.

MR. MOWERY: None at all? So apparently they're not concerned then about some of the things we have been talking about here, you know, the level of adverse effects that might occur in the general population after you've stripped away all of the susceptible people? I mean they have had no concern

whatsoever about that?

DR. DALY: Well, I think that the protocol was very conservative in wanting to exclude individuals with active coronary disease, known pre-existing hypertension, or previous strokes and things. So we addressed the issue that probably would be anticipated to be concerns by the IRB before they had them.

MR. MOWERY: Thank you very much.

MS. MCAFEE: Hi, I have a few comments. I am Lyn McAfee from the Council on Size and Weight Discrimination. Following up on what was just said, you have taken out of huge chunk of the people who would receive any benefit from this drug by removing people with the comorbid conditions. So this is absolutely the best case scenario, with that be a fair statement of that?

DR. DALY: Well I do not think that everyone with a comorbid condition was removed. For example, individuals who have diabetes but are controlled by diet were included in the study. You know, it is difficult, because to do a scientific study if you do include individuals with comorbid conditions those can be confounders. Uncontrolled diabetes would make someone lose more weight and that we're not going to be able to tell what our efficacy is. So we are really

sort of between a rock and a hard place while you do want to know how these things work and whether they are safe in those individuals to include them in a scientific study, you know, it can change the science basically.

So there are two issues. The safety concern And wanting to be certain that you are not including someone who might have a harmful outcome and the efficacy of wanting to know that it is working because it is working but not because there is something else going all get that person.

MS. McAFEE: And diabetes is of particular concern and hypertension. And those are the people who would most benefit.

I also wanted to address the issue of the length of the studies. I mean, one was eight weeks and what was six months. That is a very, very short time in the natural history of obesity. And I know the money issues, but what I am saying is, I do not know that we can extrapolate a whole lot. Weight loss traditionally stops around six months. And what we have seen in the other drugs in the Redux, Meridia, and Zenecalt drugs is a regain and if what we're looking for is health benefits we're not sure to what extent those health benefits will be kept as there's a gain

effect people don't really look at that a whole lot.

DR. DALY: I agree, a longer study would be great and if funding becomes available I am sure you will find some of us who are happy to do that. I think six months is relatively long by the standards of some obesity studies but, you know, two years would be great.

MS. MCAFEE: It is hard for me to extrapolate from that that there is really success there are in a long-term basis; I just wanted to make that point.

DR. BOOZER: There is one additional study that I have not mentioned that may throw some light onto that -- that question. Metabolife did fund a follow-up study to this eight-week study and that was to bring people back 12 to 18 months after completion of the study just to find out what they did on their own. So we will have some results.

MS. McAfee: Excellent. Thank you.

DR. JONES: We had one more question from the panel. Dr. Richardson.

DR. RICHARDSON: Yes, Mary Ann Richardson from NIH. I just have one quick question for Dr. Boozer. You said that there was an upper limit for blood pressure in the Metabolife study, 140/90. But you said in the two groups over all the change in blood

pressure was nonsignificant unless you controlled for weight loss. And when you controlled for weight loss what did that looked like between the groups in terms of increased blood pressure and how high was that?

DR. BOOZER: This is very -- as you can tell, this gets very technical statistically and we try to be as conservative as possible in analyzing this in every way. We did get a significant effect in the active group what we controlled for weight loss, so that there was then a significant difference between the two groups. I do not know how else to answer it.

DR. RICHARDSON: But that did not reach the significant level -- I mean the level for removing it from the study?

DR. BOOZER: It did reach statistical significance for the ANOVA but whether a reach clinical significance is a judgment call.

DR. LIEBERMAN: Just a follow-up on that. When where to two subjects who had high blood pressure withdrawn? Was it before or after that six-week period?

DR. BOOZER: One was early on in the first week and one was after that period. We sort of separated out the first week from the rest. I think the second subject was I believe about week four.

DR. JONES: Very good in no more questions from the floor?

[No response.]

DR. JONES: Doctors Boozer and Daly, thank you very much for presenting your data. We will look forward to publication. Thank you.

Mr. Rubin, I would note that we are right before lunch. You have Dr. Bray, and Dr. Astrup who will be presenting by video and Dr. Patrick whom you and I have discussed has probably even as we speak is just leaving a classroom. We had expressed concern about his ability to get here at 2:05.

Let me just see, are Doctors Hennekens and Soller in the audience? Would you gentlemen be prepared to speak immediately after lunch if we were to take Dr. Bray now? Then we could break for lunch and we would bring you gentlemen back after lunch and then we would go to Dr. Astrup's video and then Dr. Patrick; would that be satisfactory, Mr.Rubin?

MR. RUBIN: Dr. Jones, there is one possible alternative.

DR. JONES: Sure.

MR. RUBIN: I know that in retrospect Dr. Bray was hoping to speak after Dr. Astrup's video.

DR. JONES: I see.

MR. RUBIN: So perhaps we could do to video now if we have 15 minutes.

DR. JONES: If the video is there, is it cued and ready to go?

MR. RUBIN: It should be cued.

If it is, I would just like to make a few introductory comments prior to --

DR. JONES: Can someone either give me a wave in the back, yes, it is cued, and, yes, it is ready to go? Terrific. Okay, thank you.

The lights here are so bright and, you know, if I were used to the Broadway stage it would be different.

[Laughter.]

MR. RUBIN: I would just like to briefly set up the video for everyone. I will provide a little bit of background on Dr. Astrup. Dr. Astrup first apologizes for not being able to be here today but he is in Denmark and the trip was a bit difficult for him.

Dr. Astrup is currently a professor of clinical nutrition at the University of Copenhagen Hospital, the president of the Royal Danish Nutrition Council, and adviser to the national boards of health under the ministry of health in Copenhagen, the Secretary and a member of the executive board of the

International Journal of Obesity and the director of the Research Department at the Royal Veterinary and Agriculture University in Copenhagen, Denmark.

He is a leading researcher in the safety and efficacy of ephedrine preparations and ephedrine caffeine preparations for weight loss in humans and has published many studies on the topic which FDA has reviewed and commented upon.

Dr. Astrup will be discussing his research and responding to FDA's concerns regarding ephedrine and ephedrine caffeine combinations.

I would also like to mentioned that the initial videotape that we received from Dr. Astrup ran approximately 25 minutes in length and due to time constraints we had to edit it. We edited it down from 25 minutes to approximately 13 minutes and we wanted to make sure that our editing process did not alter the content, so we sent the transcript to Dr. Astrup to review to make sure that he was comfortable with it and I would like to read Dr. Astrup's comments into the record.

"Concerning the video recording of my presentation of research on ephedrine caffeine according to our agreement the video has been edited for time purposes and I have had the opportunity to

review the transcript of the edited version. I agree with all statements being made and confirm that the editing has not change the content or conclusions" and it is signed Dr. Arne Astrup, August 8, 2000.

DR. JONES: Thank you for attending to that, Mr. Rubin. Again I would invite you, if you would like to submit the full videotape to the record, we would welcome that as well. I will leave that to your decision but with Dr. Astrup's concurrent statement that you read we are grateful for your 13 minutes --

MR. RUBIN: Thank you and you can run the videotape now.

[Videotape shown.]

DR. JONES: We thank Dr. Astrup for providing that to us.

Dr. Bray are you ready?

DR. BRAY: I have to hook up my computer.

DR. JONES: Okay. And we cannot really ask a question of Dr. Astrup.

MR. RUBIN: Actually, if anyone has any questions for Dr. Astrup I know that he is willing to respond. I mean, we cannot do it now, unfortunately, but feel free -- we can relate any questions you have to him and we can have his responses put into the record if that would be helpful to you.

DR. JONES: That would be helpful. We would just get the questions of the record then and get a -- Dr. Philen.

DR. PHILEN: You probably know this already -- Rossanne Philen, Centers for Disease Control. In Denmark is this caffeine ephedrine combination available over-the-counter or is it a prescription item?

MR. RUBIN: Prescription. It is approved by their board. They operate in a slightly different way than we do.

DR. PHILEN: Right. Because it sounded like he was suggesting that it was a medication that was dispensed through their health-care system. Thank you.

DR. JONES: Were there any other questions to enter in the record from the panel?

[No response.]

DR. JONES: Great that is helpful. I would assume then that we do not really have to forward that to Dr. Astrup since we have -- I mean you would let him know, please, that we did ask.

There is a question here Dr. Richardson or Dr. Schwetz.

DR. RICHARDSON: Did he say how long the treatment was in his study, his formal study?

MR. RUBIN: Six months. Actually, I have the slide that I think I would have here, we were going to load two more slides from our Secretary but you're going to miss those because they are not here but I do have his your trial. He had a six-month forearm placebo-controlled trial which he described followed by six months open label trial and at the end I had hoped to have it on here but I do not. I have most of the other slides but I do not have that point.

Can someone hook up -- oh, I am there look at this. Let's see, this being my first time doing this, there are some real experts somewhere in the back I guess.

So our next speaker is Dr. George Bray. Dr. Bray is a graduate of Harvard Medical School and did his residency in internal medicine, his specialty is endocrinology, diabetes and metabolism and he is currently a Boyd Professor at Louisiana State University and a professor of medicine at Louisiana State University Medical Center. He has received several grants to study dietary, genetic, and hypothalamic obesity and he holds a patent for the treatment of selective weight control and for selective regional fat deposits.

Dr. Bray will be discussing the history of

youth, safety, and efficacy of dietary supplements containing ephedra for weight loss.

DR. BRAY: Good afternoon, Dr. Jones. For those of you usually hear me talk I do not use notes, but because this is going into the record and having edited my own transcripts, today I am going to read my comments into the record so that they will be precise and the poor person who has to transcribe it will not have to edit them.

Dr. Jones, panel members, and members of the audience, thank you for the opportunity to present to you this afternoon.

My name is George A. Bray, M.D. I am a Boyd Professor and professor of medicine at Louisiana State University and was executive director of the Pennington Biomedical Research Center in Baton Rouge, Louisiana from 1989 through 1999.

My appearance at this panel is supported by Metabolife.

By way of background I received my undergraduate education at Brown University where I graduated summa cum laude in 1953 and I continued with my medical education at Harvard University where I graduated magna cum laude in 1957.

Following an internship at Johns Hopkins I

completed my medical residency and research training at a number of institutions including the National Institutes of Health, the National Institute for Medical Research in London and the New England Medical Center in Boston, Massachusetts.

Since 1965, I have been funded continuously by the National Institutes of Health which is where almost all of my funding comes from and I will be funded with my merit award through 2006 and with the show trial through 2009.

As a result of my research on obesity I have contributed more than 1300 publications, chapters, reviews, and abstracts to the medical literature. My central theme for my research program has been to understand the development of obesity and how it can be effectively treated.

I'm here today to argue that the continued availability of over-the-counter products containing ephedra alkaloids is one tool to help combat this problem.

Let us not throw out the baby with the bathwater. Obesity is a major epidemic.

Although the relative weight of human beings has been increasing slowly for nearly a century, sometime in the 1970s the rate of increase exploded.

Obesity is now recognized as a chronic disease that is increasing in prevalence. Both the World Health Organization and the National Heart, Lung and Blood Institute have labeled obesity has epidemic. More than 20 percent of adult Americans are now obese and the prevalence for obesity in children and adults has increased by nearly 50 percent in the past decade.

The progress of this epidemic in the United States is shown on the next two slides. The slide down by my artwork taken from a paper in JAMA in October 27th of last year, shows the prevalence of those using BRFSS survey with less than 15 percent, less than 10 percent, 10 to 15 percent, and more than 15 percent reporting 30 percent overweight in their states.

Note that there are four states were 8 percent of the reporting states having obesity by these criteria in 1991.

Note that by 1998, all but 10 of the states, 80 percent, were now in this category with 30 percent of a BMI of 30 in 15 percent of the groups. So it has been a major increase within even this decade and there is no evidence that it has slowed down.

Obesity is also a stigmatized disease. The common view is that obese people are lazy and weak willed. It is also believed by many that if the fat

people just had the willpower to push themselves away from the table they would not be obese. I reject this view, although it is widely held by the public and by health professionals alike.

The stigma of obesity is supported by the clamoring of women to be lean and by the more than $30 billion spent in health activities related to obesity.

A recent report emphasizes the impact of quality of life in this problem.

The next slide will show this data published in JAMA late last year on 40,000 women in the Nurses' Health study. In this group they divided them into those who gained more than five pounds, those who were stable within five pounds and those who lost more than five pounds. Among those who gained more than five pounds in the four years of this follow-up between 1992 and 1996 there were a number of problems that you can see that were significantly worsened in this group of the 38 percent of the women.

Their physical function was lowered, their vitality was reduced and they had increased bodily pain.

In the group that lost weight all of these same quality of life functions improved.

So obesity is a stigmatized disease with

significant impact on quality of life. Obesity also poses major risks to health. One major consequence of obesity is an increase in mortality.

One major consequence of obesity is an increase in mortality. In this same JAMA issue that had those maps that I showed you a moment ago, Allison, et al, working with two previously published studies showed clear evidence that between 280 and 325,000 extra deaths could be accounted for each year by obesity.

The relationship of excess mortality to obesity is best described by a J-shaped curve; and I do not have the slide here, but I have published one like its many times.

As body weight increases there is a curvilinear increase in mortality. This relationship exists for men, for women, and for all ethnic groups. Obesity also increases the risk not only for mortality but for a variety of diseases particularly diabetes melitis, heart disease, hypertension, gallbladder disease, and some forms of cancer.

The ails that obesity brings both social and physical are reversible with weight loss. For most of the markers of ill health care is a proportional improvement with each unit of weight loss. To obtain

significant benefits may require as little as five to ten percent weight reduction. The longer the weight loss lasts the greater the benefits; that is, you shifted to appearance of the risk associated with obesity to a later time frame even if weight is regained.

The basic cause of obesity has been recognized for centuries. It results from an intake of energy as food that exceeds with the body needs. The excess is stored as fat. We reach our peak energy needs in her late teens and early 20s thereafter energy needs gradually decline at about 10 kilo calories per day per year.

If we do not make our adjustments in energy expenditure our weight gain is about a pound per year or a little less over most of our adult life.

The current backbone of therapy for obesity for the stigmatized and risky problem is diet, exercise, and behavior therapy. And I will deal with these treatments one at a time.

The first popular diet book was published nearly 150 years ago by a man named Banting and new diets appear almost every month. It must be obvious to anyone who thinks about the problem that if any of these diets lived up to their claims people would

throng to them and there would no longer be a problem of obesity.

Quite the contrary is true. Obesity is at epidemic proportions leading to the inescapable conclusion, at least on my part, that none of these and diets meets their claims.

Exercise is the second part of the -- of obesity treatment. As modern society has become ever more mechanized few humans have been willing to maintain the activity levels of their forbearers. Few of us would want to go back into the field to harvest sugar or rice as we grow it in California -- Louisiana.

We must conclude that in part there's something aversive about exercise. Few people want to do it although those who do exercise can maintain a lower bodyweight. It is noteworthy that exercise that is effective increases heart rate and this is indeed one of the ways to evaluate if it's effective on cardiovascular fitness.

Exercise also increases blood pressure, one of the things we've been talking about, since it is needed to move increased quantities of blood to peripheral tissues.

The third element of weight control is behavior therapy. Its principals were put into

practice more than 30 years ago at the onset of the current epidemic of obesity. Although there are many reports of successful weight loss, programs with behavior therapy, while it is being actively pursued, like any treatment that is stopped, fewer than five percent maintain more than half the weight that they lost.

Given this epidemic of obesity the fact that obesity is a stigmatized condition in a world that prizes thinness and youth, not weight and age, it is no wonder that Americans spend more than $30 billion annually on diet-related products and services.

Since I cannot yet prevent the epidemic of obesity it is incumbent on us to offer what support we can with therapy. At present the pharmaceutical industry, as many of you know, is actively working on new strategies for treatment, but even if they had drugs in the pipeline now it would be the late this decade before anything would be available.

If they could, we would have ideal an medication which would be effective, inexpensive, and safe. What you heard Dr. Astrup say a moment ago is that the combination of ephedrine and caffeine that he has been working on comes as close as anything we currently have to meeting those criteria.

I would thus submit that over-the-counter herbal preparations when used judiciously and according to recommendations meet these criteria.

The initial reports of an effective ephedrine caffeine preparation for the treatment of obesity came from the Danish pill called the Elsonor pill that was used to treat asthma, but that also produced weight loss. It contained 40 milligrams of ephedrine and 100 milligrams of caffeine and was given three times daily. From this initial lead Astrup whose work you just heard described pursued the use of ephedrine and caffeine and used several different combinations to develop the one that he tested in his protocol which I will show at the very end. It was 20 milligrams of ephedrine and 200 milligrams of caffeine given three times daily.

With this combination there's a small increase in thermogenesis of about 8 percent and a small increase in blood pressure -- systolic blood pressure of 9 beats per minute which gradually declines as the beta one, beta two receptors are down regulated with exposure to this sympathomimetic drug.

It should be noted that exercise too increases heart rate and blood pressure to levels similar to those seen with this a acute response to the ephedrine caffeine combination. With continued

treatment in his trial there was a four to 11 millimeter drop in blood pressure and a one to two millimeter drop in heart rate in the first 12 weeks, again reflecting this adaptation to beta one and beta two receptors.

During their 24-week double-blind placebo-controlled trial subjects lost about 17 and a half percent of their bodyweight compared to about 14 percent with placebo. The efficacy would also appear to be supported by the rapid growth in the use of the over-the-counter products that we have been discussing in the last day and half. If these compounds were not meeting the needs of consumers there would be no momentum for the sale of the 3 billion doses that we heard described from the survey yesterday.

Costs. The second need in a product for the public is low cost. The over-the-counter route has real advantages here. By making products available directly to the consumer the costs will be substantially lower than if consumers must go through the prescription route and involve physicians.

The herbal over-the-counter preparations were meet this goal.

Safety. The major thrust of the hearings that we have had yesterday and today have been on the

safety of these preparations. During the pass day and half I have listened to a number of experts review the available information and have listened to them come to divergent conclusions. I am also old enough to have lived through the rainbow bill pill problem more than 30 years ago, the poor quality of protein that in very low-calorie diets that led to the problems of the 1970s and Fen-Phen problem of the 1990s.

In all of these cases there was a clear relation between the health problem and the product that was implicated. As I looked at the chart with the logarithmic growth in the use of herbal ephedrine caffeine preparations presented yesterday and the few reports of adverse events which do not seem to have risen, it seems clear to me that none of the issues that surrounded the other problems when the FDA took action in these early events are in place now.

The experience with ephedrine and caffeine in Denmark provides additional reassurance. As Dr. Astrup said, it has been on the market for ten years there and that an estimated 2 percent of the population or more than 60,000 people have had an exposure of some period of time with few significant adverse -- with no significant adverse and events and a few minor ones.

This experience needs to be added to the

database that we are evaluating when deciding on the effectiveness or use of these products by the public as over-the-counter products.

Caffeinated beverages have been consumed by humans for centuries and there is nothing to suggest that they need to be regulated. Ephedrine has been used in the treatment of asthma since I was a house officer more than 40 years ago. From the data I reviewed I must conclude that over-the-counter preparations of ephedrine caffeine are safe when used according to the directions.

If I may, I will show the Astrup slide. Thus, in summary I would argue that the balance of the risk benefit fulcrum is clearly on the side of benefit. I would thus urge the panel to allow those people, particularly the individuals who would not qualify for the use of agents in the prescription category to continue to have access to herbal preparations. It will improve their quality of life. Again, let us not throw out the baby with the bathwater.

DR. JONES: It was Dr. Bray who had responded to some of the earlier questions about Dr. Astrup's studies and now he is showing a slide.

Dr. Bray, if you would briefly describe?

DR. BRAY: This is Dr. Astrup's data. He has

two separate papers, one showing the parallel arm trial, the yellow is the placebo group, the white are the caffeine, the red the ephedrine and the blue are the ephedrine --

DR. JONES: Can you turn the lights out on the stage, please?

DR. BRAY: -- for six months. Then at 24 weeks the subjects of whom there were 45 initially in each group, I believe there were about 120 complete -- he said 40 dropped, so there must have been 140 completed.

They were given the opportunity for all of them to go on an open-label, six-month extension to examine continuing (a) effectiveness, and (b) safety.

The colors are coded for the groups on which they were originally treated to show you what happened in each group. At the end of the six months of follow-up that is 50 weeks the groups were not significantly different in any of the four treated groups; all had maintained or improved their weight loss over where they had been at the end of the six-month double-blind randomize placebo-controlled trial, and there had been no significant adverse events in that second six-month treatment.

DR. JONES: Thank you, Dr. Bray. Questions

from the panel?

DR. BRAY: Thank you for the opportunity to present.

[No response.]

DR. JONES: Seeing none, from the floor? Dr. McLaughlin.

DR. McLAUGHLIN: Yes. Jerry McLaughlin from Nature Sunshine Products. I am sitting here stewing about this cardiac affect of the ephedra in caffeine canceling out each other on the tachycardic because mechanistically this doesn't make sense. I am wondering if he have an answer as to how mechanistically this could take place? I mean this is different in all of the pharmacology texts that I have ever read on these.

DR. BRAY: Actually, you should be addressing that question to Dr. Astrup, because it is his beta that shows the affect is there. One of the beauties of science is that we sometimes find things that we don't expect to find from our mechanisms.

Astrup is one of those very, very careful investigators and if he's made the observations I'll have to revise my my theories to fit the observation. I don't have a mechanism for you either but I don't think that he does.

DR. McLAUGHLIN: I would like to ask him about the mechanism because it doesn't make sense. And I think the panel should realize that that's going to be a tough one to really validate.

DR. JONES: Thank you. Ms. Wood.

MS. WOOD: Doctor, the only other country that you compared with here was the doctor who said in that country, Denmark I believe it is under prescription that this is used by the public. are there any other countries you have compared because the argument hear is you say it has to be over-the-counter and we believe it has to be at the FDA approved prescription? Have you compared your statistical research with other countries where the success rate was good as Denmark on which is under prescription?

DR. BRAY: You have essentially seen all the data that exists.

MS. WOOD: Thank you that's all.

DR. JONES: Thank you. Any further questions?

[No response.]

DR. JONES: Very good. I thank you, Dr. Bray. We appreciate your flexibility and I will call it for round figures 12:45. If we return at 1:45 this will be the order of the presentation, Dr. Soller and

Hennekens, I believe I spoke with you and that was the order you wished to go in? Soller. Okay, thank you. Not only are the lights bright but the hearing has quit too.

Dr. Soller then Dr. Hennekens and then Dr. Patrick should have arrived by that time and we will hear from him and then we will continue with the schedule with Dr. Huber. One note as you go to lunch and return, please return through the Independence Avenue entrance. These badges for this meeting do not get you in through the other entrance for visitors. There's a whole lot of rigmarole there. So, please come back around, a few extra steps is probably good for us all -- back in through the Independence Avenue entrance, please. And we will see you at 1:45.

Thank you.

[Whereupon, at 12:45 p.m., the meeting was recessed to reconvene this same day at 1:45 p.m.]

A F T E R N O O N S E S S I O N

[Time noted: 1:45]

DR. JONES: Welcome back from lunch. We have changed the afternoon just slightly. We will start with Dr. William Soller, then Dr. Hennekens and then we will hear from Dr. Patrick. So if we can, are we ready?

We will have 15 minutes and five Q&A as this continues our abstract session as we were during earlier. Dr. Soller, thank you.

DR. SOLLER: Thank you very much. It will take me a moment just to set this up. Thank you very much, Dr. Jones, members of the panel, ladies and gentlemen. I am Dr. Bill Soller, senior vice president and director of science and technology for this Consumer Health Care Products Association, a 119-year-old trade organization representing manufacturers and distributors of dietary supplements and non-prescription medicines.

The issue of ephedra safety as raised by this meeting affects CHPA members who market of ephedra-containing dietary supplement products as well as other members of CHPA who market certain over-the-counter OTC nasal decongestants and weight control products.

By my introduction the core issues

surrounding the consideration of ephedra safety relate to the use of adverse experience reports or AERs as a foundation for public health decisions about products availability and labeling. CHPA manufacturers take very seriously the financial report about their product safety and we certainly feel compassion for those who believe that they have suffered from the use of dietary supplements or OTC medicines.

As scientists, however, we have the obligation to view data objectively and often in the abstract so as to come to a deliberate decision about the quality and strength of the underlying data that might be the basis for public health decisions about ingredient safety.

Fortunately, there is an accepted process of how to undertake the scientific regulatory decisions.

Scientific regulatory decisions on ingredient safety are made case-by-case in a weight of all evidence data-driven, dialogue-driven process that includes all the relevant data and information. Such public health decisions that may affect ingredient availability or labeling must be based on data that are scientifically documented, clinically significant, and important to safe effective use of product by the consumer.

This is a logical, long-standing policy of FDA as it relates to consumers product issues. The ensures that all the evidence is brought to bear on the issue and that the ultimate public health decision is based on scientifically-documented data. This accepted scientific regulatory approach should be used by FDA to exert its ample enforcement authority to ensure safe and beneficial dietary supplements remain on the market.

It is by using this approach that we consider a ephedra to be safe when formulated, manufactured, and labeled according to the industry's voluntary program and when used according to label directions.

However, FDA's approach in this matter has been fragmented and inconsistent with this accepted scientific regulatory process. It undermines this particular process, FDA appears to have selected information to include in the docket, blurred the case-by-case assessment by introducing irrelevant information on other sympathomimetic and asked it consultants to come to a public health judgment based on partial data.

Let's take these one at a time. FDA appears to have selectively included information in the docket. The correct issue here is the weight of all the

evidence, the incorrect issue is the selection of some of the evidence.

FDA reopened the ephedra docket only a week ago requesting comment on the epidemiologic hemorrhagic stroke project study which addresses phenylpropanolamine or PPA. FDA entered only this study into the docket and not even by reference included the voluminous information that we have submitted on PPA over the last 10 to 15 years into the PPA docket for the OTC review.

And, in fact, FDA's review on the pharmacology review of ephedra did not include most of the pivotal information on PPA that we submitted to the Agency. And given that FDA has entered only selective information on PPA into the ephedra docket I would like to emphasize that as with every ingredient safety issue each individual AERs and study must be considered in the context of the totality of the evidence on the ingredient.

For PPA the totality of the evidence overwhelming supports the safety and effectiveness of PPA when used as directed on product labeling and this conclusion is based on approximately 40 clinical studies and well with 3,000 subjects including healthy volunteers, obese and hypertensive patients in single-

and multidose regimens as well as two supportive epidemiologic studies all of which are detailed in our submissions that we have made to the agency.

PPA-containing products have been used literally by millions and millions of consumers over the past 50 years with a very low incidence of serious side effects.

But should the ephedra docket include certain safety information on other sympathomimetic, let's remember that it is a case-by-case evaluation that should be the basis for public health decisions on ingredients safety.

FDA's review of published literature includes about 50 plus cerebral and cardiovascular-related references, 34 percent or so which relate to ephedrine the others sympathomimetic. The inclusion of a large amount of information out of the sympathomimetic agents and the HSP, the hemorrhagic stroke project study in the ephedra docket implies that evaluation of a safety profile of other marketing sympathomimetic is important in the context of ephedra's safety.

We do not agree that this is the cases since the intended use of an ingredient is fundamental to its safety evaluation and different marketed sympathomimetic have different intended uses based on

their very well-known pharmacological structure activity relationships.

The fact is while ephedra may include several sympathomimetic agents with different relative ratios with Alpha and Beta receptors -- activities it is the mixture of these agents in the final ephedra product, not the activity of any one ingredient, per se, that is relevant to the intended use or misuse of the product and consideration of its safety.

Hence, notwithstanding the fact that PPA is a minor component of ephedra a partial review of PPA in FDA's report is also of limited value in the review of ephedra and potentially misleading. Likewise, introducing the hemorrhagic stroke project study in the ephedra docket is also of questionable value. Even if the study were of a quality to enhance our understanding of the safety of PPA.

On this latter point there is serious limitations to the HSP study but is important to note that the HSP study did not established a causal relationship between hemorrhagic stroke and the subsequent ingestion of PPA and the subsequent development of hemorrhagic stroke and collected no information on ephedra.

As Dr. Charles Hennekens will directly follow

me with the more detailed review of the strength and limitations of the HSP study it should suffice for me to say that chance bias and confounding are each plausible alternative explanations of the findings from the study.

Thus as a stand-alone study the data from the HSP are not sufficiently informative to draw any conclusion either about the PPA or ephedra.

Another concern relates to FDA instructing its consultants to review selection of AERs and determine whether ephedra is safe; that is, to make an overall public health assessment based essentially on selected AERs. This direction from the agency was inappropriate.

First, it is well-recognized that in general AERs are individual reports often lacking in important details or presenting details giving more likely explanations of the reported events.

As such, they are considered mainly as hypothesis generating and not hypothesis testing data sets certainly not rising in and of themselves to the level of scientific documentation needed for an overall public decisionmaking.

The AER database on ephedra is inadequate and only a small subset of reports have sufficient detail

for appropriate causation analysis. Different reviewers -- FDA reviewers saw different sets of AERs and among the reviewers there were wide differences in opinions about the causation judgments relating to individual AERs showing the highly subjective nature of this database and their analyses. A careful review of the AERs as we think was done by the Ephedra Education Council shows the great limitations to these data as a basis for any causality assessments supporting significant or unreasonable risk attributable to ephedra.

Second, in this regard, as mentioned, an important hurdle in coming to a public health decision about ingredient safety is the scientific documentation phase of the scientific regulatory process. In this phase all the relevant information must be gathered and evaluated for credibility and completeness before a public health judgment can be made. Therefore, FDA should have either given its consultants all the information and ask the overall question on safety, or asked the consultants only about the nature of the scientific documentation of the AERs.

As a result the conclusions reached by these consultants are necessarily limited if not frankly in question.

Parenthetically, I might add that at least one of the FDA's expert reviews of AERs reportedly associated ephedra place pharmacological plausibility as top criterion of the attributional assessment. This bias is the review against ephedra since nonephedra-related health problems can have an endogenous sympathomimetic component by first deciding if the AER has a sympathomimetic-related course of events sympathomimetic mediated conditions can falsely be attributed to ephedra and there is a tendency to not look for other more plausible explanations.

These concerns are important. FDA has approach its assessment on ephedra in a fragmented way undermining the accepted scientific regulatory approach that evaluates each ingredient on its own merit, focuses on the scientific documentation first, and relies on the weight of the evidence.

Important information on ephedra is still being developed by the industry and we have heard this from other speakers at this meeting and this should be included in any assessment of ephedra for regulatory decisions are taken.

Finally, CHPA members' companies that market ephedra-containing dietary supplements have adopted a voluntary program for their ephedra containing problem

products relating to formulations of labeling. This was the first adopted by the American Herbal Products Association and subsequently by CHPA, the National Nutrition Foods Association and the Utah Natural Products Alliance.

The industry voluntary program was reviewed by previous speakers and I just highlight some of the elements of that including serving limits, standard constituent identification, quantitative listing of actives, a stipulation for no synthetically derived ephedrine alkaloids, no claims relating to an altered state of consciousness, euphoria, or as a legal alternative. And then special warnings that have as components age restriction, pregnancy, nursing warning, warnings regarding contraindicated indications conditions, drug, herb, interaction warnings, and warnings regarding exceeding recommended serving and finally in-use precautions concerning emergent side effects.

On balance then, in the context of the significant and legitimate concerns about the quality and strength of the AER data set, the nature of FDA's method of review and the estimated usage of ephedra we can come to no other conclusion then when formulated, labeled, and used according to industry's voluntary

program, ephedrine-containing dietary supplements are safe. CHPA recommends that FDA adopt these industry recommendations into regulation.

Thank you very much. And, Dr. Jones, I am happy to take questions or to turn it over to Dr. Hennekens and then we can take questions together. Whatever your pleasure is. Thank you.

DR. JONES: If the panel has no objections, the two presentations do good together, and so if the panel is agreeable, and I would ask the audience but I think we will just go ahead. Pragmatically do your two together and we will to 10 minutes of questions and answers.

DR. HENNEKENS: Thank you, Dr. Jones. My name is Charles Hennekens. I reside in Boca Raton, Florida. On November 4, 1999, the first draft of the hemorrhagic stroke project or HSP became available. Since that time I have served as a paid consultant to the consumer health care products association or CHPA, who also paid my travel expenses.

I received my M.D. from Cornell University Medical College. Had clinical training a internal medicine at the New York Hospital, Cornell University Medical Center. I served two years as an EIS medical epidemiologist with the CDC. Later had research

training in epidemiology in public health at Harvard including receiving a doctorate of public health in epidemiology.

I was the chief of preventive medicine at Brigham and Women's Hospital, and of course, John Snow, and Eugene Brownsald professor of medicine at Harvard Medical School. I have written or edited several textbooks including one entitle Epidemiology in Medicine which is widely used in medical schools and schools of public health.

I am currently visiting professor of medicine and epidemiology in public health at the University of Miami School of Medicine. I wish to comment on the findings of the HSP or hemorrhagic stroke project on phenylpropanolamine or PPA in view of FDA's request for comments on the study's relevancy to the safety evaluation of dietary supplements containing ephedrine alkaloids.

Yesterday Dr. Love of FDA emphasized the dietary supplements containing ephedrine alkaloids were the focus of this meeting. I was concerned however by her slide entitled "published clinical investigations on ephedrine alkaloids" on which the HSP on PPA was the first she described. There are clear and important differences in structure and activity between PPA and

other ephedrine alkaloids. These are actually outlined in a letter for my colleague, Professor Brian Hoffman, of Stanford, a world-renowned molecular pharmacologist who concludes, "I would encourage you to not paint all sympathomimetic with the same brush."

I would also like to point out that the principal investigator of HSP, Ralph Horowitz, has not yet submitted his manuscript to a peer reviewed journal, although a study report was submitted to the FDA Center for Drug Evaluation and Research several months ago. I understand that the study is currently being evaluated by this Agency.

Since November 4th, 1999, I have had a series of communications and discussions with the researchers conducting the HSP so there is nothing I will tell you today that has not been communicated either orally or in writing to my colleagues and friends at Yale including Ralph Horowitz and Larry Brass as well as their colleagues, Walter Kernan and Catherine Viscoli.

The views I am presenting here today also are virtually identical to those of an independent panel of five world-renowned academic experts in epidemiology who reviewed and commented on the report in detail to CHPA and then finally one other well-known epidemiologist and two neurologists have also offered

virtually identical views.

So overall, based on my analysis of the available data, I conclude that HSP has numerous methodologic issues that limit this interpretability. The results of this study are not sufficiently compelling to drive any public health decision regarding reported PPA use either as cough or cold suppressants or as appetites suppressants with the subsequent development of hemorrhagic stroke.

I would like to summarize to you briefly the reasons for these conclusions, focusing on confounding bias and chance all of which are likely to affect the findings.

Now, these investigators used best efforts in the conduct of this large study, and indeed assembled approximately 700 cases and 1,400 controls. Nonetheless, as I said, numerous methodologic issues and concerns limit the interpretability of the study findings. As regards confounding, for example, despite matching on gender, ethnic group, and age, there remain marked differences in the characteristics between the cases and the controls. Cases of the study differed from the controls in socioeconomic status or SES.

For example, 39 percent the cases with 62 percent of the controls were college graduates. In

cigarette smoking habits 51 percent the cases and 30 percent of controls; history of hypertension, 39 percent of the cases and 20 percent of the controls. Family history of stroke, 9 percent of cases, 5 percent of controls, as well as alcohol consumption, 14 percent of the cases, and 7 percent of the controls and history of caffeine consumption, 7 percent of the cases, and 3 percent of controls; inadequate or inappropriate control for these confounders could easily explain any observed association with PPA use.

It needs to be emphasized, however, that although the study was large, there was a very small number of exposed cases and this simply does not allow for appropriate control of any, if not all of these variables. For example, SES differences alone may explain the differences in who gets the disease as well as who uses PPA.

Several sources of bias could also have influenced the results including selection and observation. Selection bias was present due to the low-end unequal participation rates, about 42 percent among the cases, 30 percent among the controls. Observation bias was present because cases had experienced a catastrophic event, hemorrhagic stroke, and controls were selected by random digit dialing.

Persons who had an event such cows hemorrhagic stroke could be far more likely to have made a stronger effort to recall what products they had used. This may have led to differential overreporting in PPA by cases.

Further, 44 percent of the cases had some degree of aphasia, possibly limiting validity and reliability.

As regards chance, the small number of exposed cases limits the ability to statistically control for even the available confounding variables in this study. This situation also greatly increases the possibility that chance alone could be a plausible alternative explanation for any apparent association between use of PPA and subsequent development of hemorrhagic stroke.

Having said that, it should also be emphasized that in the study overall there was no significant association between use of PPA and hemorrhagic stroke based on 27 users among cases and 33 among the controls yielding a 2-sided P value of .17.

Statistical significance can be achieved in this study but only in the subgroup of women who use PPA in appetites suppressants where the comparison here is six cases versus one control, yielding a two-sided P value of .03.

Curiously, one of these women, also used PPA in a cold remedy and had she been so classified, even the remaining extreme relative risk would no longer be statistically significant. Since the overall findings for the primary hypothesis was null, selective emphasis on particular subgroups with even smaller numbers may well be misleading.

Furthermore, even if real, the population risk associated with PPA and hemorrhagic stroke would be exceedingly small. One might even question the clinical implications of such a relative risk even if they derive from a randomized trial, not a retrospective case controlled study because the numbers were so small.

Thus, these data are not sufficiently informative to draw any definitive conclusions, it is quite possible that all of the observed effects could be attributed to confounding, bias, or chance, due to selected emphasis on particular subgroups.

Thus, my colleagues and I believe that the results of the HSP are not sufficiently compelling to drive any public health decisions regarding reported use of PPA in cough or cold suppressants or as appetites suppressants and subsequent development of hemorrhagic stroke.

Lastly, and perhaps most germane to the deliberations of this meeting, there were no direct questions concerning ephedrine and other dietary supplements asked in the HSP, so all of these considerations lead me to include a lack of relevance of the HSP to ephedrine alkaloids.

I thank you very much for your attention.

DR. JONES: Thank you, Dr. Hennekens.

Are there questions from the panel?

[No response.]

DR. JONES: Seeing no questions from the panel, any questions from the floor?

[No response.]

DR. JONES: Dr. Soller, if you would, and I was shuffling papers myself as you were booting up and making your initial remarks, and I'm sure you did state the Consumer Health Care Products Association, the nature of it again, please? I just did not get that.

DR. SOLLER: The Consumer Health Care Products Association or CHPA is a 119-year-old trade organization representing the manufacturers and distributors of dietary supplements and non-prescription medicines.

DR. JONES: Very good. Thank you.

Are there any other questions from the floor?

Dr. Philen.

DR. PHILEN: Just a very small question. I could not hear you very clearly when you were referring to a doctor from Stanford. What was his name?

DR. SOLLER: Brian Hoffman, Professor Brian Hoffman.

DR. PHILEN: And one more detail. There were 27 users among the cases, and how many in the controls?

DR. SOLLER: Thirty-three.

DR. PHILEN: Thirty-three. Thank you.

DR. JONES: No other questions from the panel?

[No response.]

DR. JONES: Thank you Dr. Soller.

Dr. Hennekens.

DR. HENNEKENS: Thank you.

DR. JONES: Are you Dr. Patrick?

Mr. Rubin, I guess you're going to do another introduction?

MR. RUBIN: Yes, exactly. Thank you.

I just want to introduce the last of our speakers today. Dr. Graham Patrick. Dr. Patrick received his B.S. in pharmacy and a Ph.D. in pharmacology from the University of North Carolina. He is currently a professor of pharmacology and toxicology

at the Virginia Commonwealth University Medical College of Virginia.

As a pharmacist, Dr. Patrick has observed patient reactions to ephedrine alkaloids and other alkaloids and as a professor, Dr. Patrick has studied sympathomimetic amines such as ephedrine as well as the drug dependence and motor effects of stimulant drugs. He has been involved in reviewing FDA's adverse event reports for ephedrine for the last five years.

Dr. Patrick will be discussing the safety profile of dietary supplements containing ephedra and ephedra-caffeine combinations including his review of the adverse event reports compiled by FDA.

DR. PATRICK: Dr. Jones, panel, and guests, I would first like to acknowledge that my review of the adverse event reports and my appearance here today is sponsored by Metabolife. Other than that, I have no financial interest in ephedra products or other dietary supplements.

First, as an overview of the positive and adverse physiological actions of ephedra I would like these describe the pharmacology of ephedrine. Ephedrine is a sympathomimetic agent that mimics the effects of sympathetic nervous system stimulation and produces effects similar to those of adrenaline or

epinephrine. It does so both directly by stimulation of adrenergic receptors and indirectly by promoting release of the neurotransmitter norepinephrine from sympathomimetic nerve endings. Excuse me, from sympathetic nerve endings.

Also included in many ephedrine products are the alkaloids pseudoephedrine and norephedrine or phenylpropanolamine or PPA. These compounds are pharmacologically similar to ephedrine itself in most respects but they have proportionately less cardiac stimulant effects relative to their vasoconstrictor effects.

The effects of all three of these ephedrine alkaloids are dose-related and increase in magnitude as the dosage is increased. And that is unimportant pertinent point in relation to evaluation of the effects.

Potential positive effects of ephedrine alkaloids include therapeutic applications of ephedra, topically as a decongestant, orally as a bronchodilator in treating asthma. Ephedrine has been used intravenously to raise blood pressure and to treat shock and hypertension, particularly that associated with anesthesia.

Ephedrine has been used orally as an appetite

suppressant and to increase energy. Potential adverse effects of ephedra at appropriate doses are typically minor. These include in the use of ephedrine-containing dietary supplements, increased blood pressure, particularly systolic blood pressure associated with beta adrenergic stimulation of the heart, increased heart rate, associated with the same effect, urinary retention and constipation associated potentially with alpha adrenergic stimulation, nervousness, dizziness, insomnia, anorexia, or loss of appetite, tremor presumably associated with effects on adrenergic receptors in the central nervous system.

These side effects are no more serious than those that will be expected from any over-the-counter products that contain pseudoephedrine or norephedrine or PPA and some of these side effects are similar to those that will be expected for over-the-counter products containing caffeine or in caffeine-containing beverages.

In appropriate doses ephedra dietary supplements are highly unlikely to cause serious adverse events. For several decades the FDA has approved ephedrine sulfate as an over-the-counter bronchodilator at a dosage of 25 milligrams with a maximum daily dosage of 150 milligrams. The UST for

U.S. -- dispensing information or USPDI, an official compendium of drug information recognizes single doses of 25 to 50 milligrams as appropriate for bronchodilator effects in healthy adults.

The dosage of ephedrine alkaloids in most ephedra supplements is significantly lower than that in over-the-counter products. For example, a typical ephedra supplement contains approximately 12 milligrams of ephedrine alkaloids per serving and the label recommends a maximum daily intake of 96 milligrams.

Some products do include us much as 20 milligrams of ephedra per does or ephedrine alkaloids per dose and those recommend no more than 100 milligrams per day. Again, below the approved dosage levels according to the FDA and to the USP dispensing information.

Moreover, on a milligram-per-milligram basis ephedra which contains the multiple ephedrine alkaloids may be safer than synthetic or pharmaceutical ephedrine because ephedrine itself is the most potent of those ephedrine alkaloids. So to the extent that other alkaloids are included in the preparation the potency will be diminished.

In addition, it has been suggested, that the rate of absorption of ephedra alkaloids from herbal

preparations is slower than from pharmaceutical preparations which may lead to a later and lower peak effect and thus a lower incidence of acute adverse effects. Although this hypothesis has not been adequately tested.

In addressing some of the specific potential adverse effects, doses of 60 to 90 milligrams of ephedra per day do not elevate the blood pressure of healthy adults to clinically significant levels. According to an extensive literature review of by Jewel and Binramache the pressor effects of sympathomimetic amines a single dose of 60 milligrams of ephedrine is required to cause a significant increase in blood pressure in healthy adults. The magnitude of this increase was 10 to 15 millimeters of Mercury pressure, no greater than would be seen with moderate exercise.

Single doses of 20 to 25 milligrams of ephedrine alkaloids are equivalent to doses of 60 to 90 milligrams of ephedrine per day have caused heart rate increases of approximately 8 to 12 beats per minute. This again is not clinically significant and will be insufficient to trigger cardiac arrhythmias in healthy individuals. A heart rate increase of 8 to 12 beats per minute is far less than will be seen with moderate exercise.

Severe adverse events such as the cardiomyopathies bear no relationship to the appropriate use of herbal ephedra products.

The rate documented cases of dialadicordimiomthy have involved extremely high doses of ephedrine a minimum of 400 and to a maximum of 2,000 milligrams per day over a period eight years or more.

The occurrence of stroke bears no relationship to the appropriate use of ephedra dietary supplements. Given that several studies have shown that a 20 milligrams dose of amphetamines administered intravenously does not cause a significant decrease in cerebral blood flow and keep in mind that not only is it a more potent but given by a route that gives a more pronounced affect it is unlikely highly unlikely that ephedrine in oral doses of that same magnitude could cause any ischemic type of stroke.

To my knowledge, there have not been direct measurements of effects of ephedrine on cerebral blood flow. Given the 20 to 25 milligrams of ephedrine does not significantly affect blood pressure is highly unlikely that ephedrine and recommended doses could cause a hypertensive stroke. The best documented cases of stroke associate ephedrine alkaloids have been attributed to excessive dosage and abuse of these

compounds.

The preponderance of these cases have actually involved norephedrine or PPA rather than ephedrine itself and PPA does remain freely available in OTC appetite suppressants.

In addition, according to the USP dispensing information, a history of stroke is not a contraindication to the use of ephedrine. Incidence of psychosis bear little or no relationship to the appropriate use of ephedra dietary supplements.

My review of reports of psychosis associated with ephedrine alkaloids is revealed that the majority of these cases, more than 80 percent, involve usage of ephedrine alkaloids for a year or more, in some cases up to 25 years with an average daily consumption of 510 milligrams of ephedrine per day. So this is more than five times the dosage recommended on dietary supplements.

The minimum reported dosage of these cases was 125 milligrams per day still in excess of the dosage included in herbal dietary supplements and in many cases the dosage was more than 1,000 milligrams daily. The reviewed literature does not contain a single case of seizure where use of ephedrine is clearly causal. Also, note, the USP dispensing

information does not list the history of seizures as a contraindication to the use of ephedrine.

There's little or no evidence that duration of exposure to ephedrine is related to the incidence of any serious adverse events at the dosage of ephedra alkaloids that are contained in herbal supplements. FDA's adverse event reports provided insufficient data to conclude that ephedrine alone or in combination with caffeine at the dosages in herbal products cause any series adverse events.

My review of these reports indicates to me that the FDA's adverse event report do not provide a sound scientific basis for establishing a causal relationship of ephedra to the adverse events for the following reasons: First, the sampling was not randomly selected from a representative population, a but rather was self-selected.

Secondly, the reports often lacked information essential to evaluating causation such as dosage, duration, and the temporal relationship between consumption and adverse event.

Thirdly, very few of the reports contained information regarding the magnitude of exposure that is reliable information regarding that; the quantity of ephedrine alkaloids contained in the product; and the

dosage or the frequency with which they consumed.

Fourthly, they often lacked any medical corroboration such as medical histories, objective professionals evaluations, diagnostic tests or quantitative measurements.

And finally, many of the cases involve confounding factors such as pre-existing disease or concurrent use of drugs which were as likely own more likely to be the precipitating cause of the event than the ephedrine alkaloids.

The adverse event reports in the categories and FDA labels supportive often lacked information critical to the determination of whether of ephedrine alkaloids were a contributing cause to the reported adverse event.

Of the 260 adverse event reports that I reviewed from the FDA docket there was only one serious event where ephedra could possibly have been the causal factor. Even in that case, however, there was insufficient information to clearly establish causation. The alleged psychosis in that case was not consistent with the published relationships of ephedrine, in that the dosage were only about two-thirds that reported as a minimum in the medical literature. And the subject had a family history of

bipolar disorder.

Of the 260 adverse event reports previewed there were only 12 nonserious events such as anxiety, increased heart rate and insomnia, for which there was sufficient evidence to evaluate causality. There were also 30 or 40 nonserious events that could plausibly be related to the use of ephedra. But the reports of these events lack sufficient information to evaluate the likelihood of causality. These events do not appear to differ in type nor in magnitude from those that might occur with over-the-counter products containing ephedrine, PPA, pseudoephedrine or caffeine.

My conclusions regarding this safety profile of ephedra-caffeine combinations are the dietary supplements containing ephedra and the recommended dosage appear to be safe for healthy populations when used as directed.

There is no evidence that herbal preparations of ephedra are more dangerous than pharmaceutical preparations of ephedra. In fact, as mentioned earlier the herbal ephedra alkaloids may be less potent than pure pharmaceutical ephedrine to the extent that the alkaloids contained in the herbal products are alkaloids other than ephedrine itself.

The scientific literature and FDA's adverse

event reports failed to provide evidence of any serious or unreasonable risk associated with ephedra caffeine combinations. There is no epidemiological evidence that any serious adverse event occurs significantly more frequently among users of such combinations than among users of ephedra or ephedrine alone among users of over-the-counter ephedrine alkaloids preparations or for that matter among nonusers of these products.

There's no difference between taking a dietary supplement that has a combination of herbal ephedra and caffeine and taking an over-the-counter asthma medication containing ephedra and along with coffee or other caffeinated beverages and the dosages that are included in such products. To the extent that minor side effects from ephedra alone or from ephedrine caffeine products combinations in the dosage of these compounds that are encountered in dietary supplements occur they are not much greater in magnitude than the side effects of caffeine and quantities that may be consumed in dietary beverages or in over-the-counter preparations.

Concerning the populations that may use these products, the two main groups of user of ephedra products appear to be young to middle age, overweight individuals, and young individuals who are engaged in

programs for exercise. Neither of these group should exhibit inherently greater sensitivity to a ephedrine alkaloids than healthy individuals unless obesity is sufficient to constitute a cardiovascular risk.

Most ephedra preparations like many other dietary supplements and over-the-counter products for weight reduction do include labeling and warning that medical advice should be sought prior to using such products for weight reduction. This warning should preclude use by individuals who may be at an increased risk.

Finally, it is possible that there may be rare individuals who exhibit extreme sensitivity to the effects of ephedrine alkaloids. But ephedra containing products are no different from other OTC products containing ephedrine or other ephedra alkaloids nor any different from many other readily available products in this regard. Thank you.

DR. JONES: Thank you very much, Dr. Patrick. Are there questions from the panel? Dr. Lieberman.

DR. LIEBERMAN: Dr. Lieberman, U.S. Army. I had a question about an analogy you made. You suggested that it would be one of the factors which suggested that ephedrine would not be a factor in causing strokes was the fact that a fairly high doses

of amphetamine did not reduce cerebral blood flow, are there other areas where you think it might be possible to use data from amphetamine to make a judgments about to ephedrine? For example, with regard to risk of heart attack.

DR. PATRICK: With regard to heart attack. My point was that amphetamines is a more potent drug, and if it does not produce an effect that is unlikely that ephedrine caused that same effect. Amphetamine as a more potent drugs will be more like to induce any serious event that is associate with sympathomimetic effect. For example, the history of amphetamines induced psychosis is much greater than -- far greater than anything that has been seen with ephedra alkaloids.

DR. JONES: Other questions? Dr. Philen.

DR. PHILEN: Rossanne Philen, Centers for Disease Control. You keep commenting that natural ephedra is more likely to be less potent because of the mixture of alkaloids than synthetic ephedra. I'm wondering if you can address the issue of is natural ephedra a racemic mixture or is it a DNL? Or is it D, or is it L, or a synthetic racemic?

DR. PATRICK: This is going back to my basic pharmacology. I'm not certain that I remember. I

believe that be naturally occurring ephedra is L ephedrine.

DR. PHILEN: Has there been any work done like in laboratory animals to compare the L ephedrine versus a racemic mixture ephedrine?

DR. PATRICK: The active isomer would be mor active than the racemic mixture, or would assume to be more active.

DR. PHILEN: So, then is the natural ephedra is L and L is more active, then it's probably more active than a racemic synthetic mixture.

DR. PATRICK: That would make sense. I honestly don't recall the potency ratio between the two.

DR. PHILEN: Well, then that contradicts your earlier statement that tbe naturally occurring ephedra might be less potent.

DR. PATRICK: To the extent that the -- I'm not quite certain what the composition of the pharmaceutical ephedrine is either.

DR. PHILEN: Thank you.

DR. JONES: Other questions from the panel?

[No response.]

DR. JONES: Questions from the floor?

MR. CARTILINA: John Cartilina, the Council

for Responsible Nutrition. I just want to make a point about synthetic ephedrine stereo selective synthesis L-ephedrine is readily available so that not all synthetic ephedrine in the marketplace is necessarily racemic. The advances in stereo selective and stereo specific synthesis now make available those kinds of compounds in the single are desired. Thank you.

DR. JONES: Thank you.

Question, Dr. Philen?

DR. PHILEN: Do we know then though if the Primateen Mist or other synthetic ephedra you buy is D or L or racemic? I mean, how can the consumer know?

MR. CARTILINA: I can't answer that question specifically for the any given product unless it is labeled on the product but I do know that in the last ten years these specific kinds of compounds are now very readily available by stereo specific synthesis.

DR. PHILEN: Thank you.

DR. JONES: Thank you.

Other questions? Other questions from the floor?

[No response.]

DR. JONES: Very good. Thank you very much, Dr. Patrick. I am glad you made it here safely from Richmond. Going 55 miles an hour, we know.

[Laughter.]

DR. JONES: Okay. Let's see where we are. Dr. Huber, is here and then his remarks and then Q&A.

Now, let me just ask you, sir, I believe you have brought three of your patients, three clients?

DR. HUBER: That's correct.

DR. JONES: Do you want us to do your 15 minutes, then Q&A of you and then have the comments as shown in the agenda from the folks who came with you, or would you prefer that we hold the Q&A until you're all finished?

DR. HUBER: How ever you wish.

DR. JONES: We will follow your presentation then, and then we will invite your patients to come forward.

DR. HUBER: Thank you.

DR. JONES: Thank you, Dr. Huber.

DR. HUBER: I am Gary Huber. I'm here soley as the founder and director of the Texas Nutrition Institute. I am an internist by training I graduated from the University of Washington and then went and spent nearly 14 1/2 years at Harvard. I was trained in internal medicine and pulmonary subspecialty in Boston and spent ten years as chief of the pulmonary services for two of the Harvard hospitals.

I spent 11 years on the faculty of the University of Texas Medicine and the last five or six years directing the Texas Nutrition Institute which is a not-for-profit entity in East Texas.

I have board certification in internal medicine and I have also passed my boards, written and oral in the American Board of Geriatric Medicine.

The problem has been much more clearly outlined by Dr. Bray then I can emphasize. Approximately one in five or 20 percent of Americans are now obese in this country; we do have an obesity epidemic and perhaps as many as 100 million or more Americans are overweight the obesity epidemic continues at enormous cost to our economy prevention and treatment have remained very elusive.

This is a patient mine and every patience seen over the past five or six years at the Texas Nutrition Institute has been enrolled in one research protocol or another with informed consent and initially he came to see us as a part of Fen-Phen clinical trial and that's his picture on he left. An then he left, he lost some weight and he came back about years later, and he's actually here today and will talk to you. And I did not recognize him and he said, "Doc you've got it all wrong you're doing the wrong thing. Let me tell

you about these herbal products." And that led us to think about what we were doing and to design some studies and conduct some studies which we've done almost now exclusively with our time over the past two to three years. All tolled we have studied over 300 patients.

We have three studies that I will mention today and the very extensive, I obviously can't present all of the information, but I will submit to you as much as I can with the written addenda. Some of these are already in the public domain and we can submit that as well.

The first study was a six-month trial of three herbal products. This study was totally self-funded by the patients, the only support we received were the herbal products themselves from the manufacturers.

It was an open-labeled study, the patients were randomized to the different herbal products and it was prospective in nature. This study should be really viewed as a series, I believe of case history collections. The dietary supplements all contained herbal formulations and they were commercially available. We compared the results of the outcome of the six-month study, retrospectively, the data that we

had accumulated on patients that were matched for weight and age and everything, who had taken Fen-Phen or pharmacologic agents as I'll mention in a minute.

The second study has two phases. Initially six-week study which we have completed for the most part and a six-month phase which is still in progress. We received a very small amount of funding through the American Nutrisutical Association for the study and they in turn have been support supported by one herbal manufacturer. But the amount of funding is very small. This study is double-blind it has a placebo-control and the patients were randomized. It evaluated four dietary supplements herbal products and a placebo. One of the dietary supplement products was the same product to products with the same products in different doses. This study had about a 9 to 10-week observational period, where the individuals were untreated before they were initiated either on placebo or one of the herbal containing products.

The third study again more of a case history analysis retrospectively of patients that had taken and then prescribed compounded USP pharmaceutical grade caffeine or ephedrine for one reason or another. A tolled, we have somewhere between three in 400 patients.

The studies are very extensive and you can ask the patients about that. To enroll in the studies the patients have to be overweight or obese and the degrees of obesity are graded. There are three pages of absolute and relative exclusion criteria and inclusion criteria so in that way the patients are not our subjects are not representative of the general population that could walk into a store and buy a product.

We did include, however, patients with comorbid obesity-related diseases if they were controlled. For example, if patients had hypertension and they were under control they could be included in the study. The same is true with patients with diabetes whether or not they were on insulin if their comorbid disease was controlled they were included in the study.

They had extensive monitoring they received a comprehensive physical examination and a 60-page medical history all tolled they ended up filling out about 150 pages of questionnaires. We used various questionnaires and tools that had been recommended by various NIH committees. The Institute of Medicine, the American Society of Geriatric Physician. They were evaluated by a physician every two weeks until stable

and then followed up at 4- to 6-week intervals thereafter throughout the 6-month period of studies.

They have had extensive metabolic analysis including biochemical analysis and metabolic heart studies. Each patient received an exercise -- graded exercise tolerance test before entry into the study and while they were on the herbal products in follow-up. they received a number of physical -- including anthropometric measurements, hydrostatic weighing, they received fasting insulin levels, 24-hour urine collection and the like.

We have placed an emphasis on evaluating potential adverse events.

I'm only going to mention this in passing actually the protocol that we adapted I received from one of Dr. Bray's protocols at the Pennington at a meeting a couple of years ago in Colorado. And these were compounded caffeine ephedra capsules prepared by a pharmacist who was certified in compounding these medications. They were prescribed in the patients were followed as they were in the herbal dietary supplement protocols. The only thing I really want to say about it and only because of the limitations in time, is that we had -- they were less efficacious than the herbal products in terms of weight loss and they had a higher

adverse risk profile, particularly in terms of gastrointestinal acid secretion and the like.

This is the first study. This was the open-label, sort of series of case collections. There's about 30 to 40 patients in each of the herbal product groups which I have labeled Nutri1, Nutri2 and Nutri3 and we've compared these two patients that were weight and age matched and sex matched for Fen-Phen, in our phen fen trial in amphetamine alone trial and I've listed here the cost per day -- is there a pointer? No pointer?

The cost per day each of these products. We identified individuals arbitrarily whether or not they responded to the product and it was just an obituary definition of a half a pound.

A responded was defined as a half a pound per week old greater sustained weight loss over the six-month period of trial. The herbal products compared favorably with the existing available pharmaceutical products. This value is perhaps a little bit low because one other things, I think, that we observed as we conducted the study is that patients who previously receive the Fen-Phen and were less responsive to sibutramine than patients who had not. We observed that in retrospect.

Amount of weight loss to in this slide is expressed as the amount of excess weight above a body mass index of 25 that was lost over a six-month period of time.

So, in this open labeled study the product seemed to compare favorably cost-wise and were effective. The second study had a nearly 10-week observational period over which time the patients gained on the average about a half a pound a week. Some of those patients lost weight but the amount of weight loss was very marginal. There was a placebo throughout the period of observation and those patients lost about three-tenths of a pound a week. And then there were four different study groups; product A and product B are the same product just in a different dose. This group received 36 milligrams of ephedra per day, this group 72 milligrams.

The maximum amount of a ephedra in any of these products is 72. Procut C had no caffeine in it and the maximum amount of caffeine that was in this product was 200 milligrams a day. And again the taking of these products appeared to be efficacious in losing weight at a more significant level than placebo-controlled.

We at every visit and in the observation

period, and for the placebo group as well, on their presentation to the clinic each patient filled out a questionnaire that contains all total above 150 questions. And I obviously can't provide all that information today, and I just picked a couple things to share with you. Most of this, for the first study, is already in the public domain. It was presented as a poster assessment in Charleston last year the NSAO meetings and it was presented more extensively at the American Society of Geriatric Physicians and the second study will be presented this fall in part at the meeting here in Washington in September of the American Obesity Association and in October here in Washington at the American Society of Geriatric Physicians meeting.

We intend to submit both of these studies for publication within the next month or two and I want to include as much of the data as I can which is really quite extensive end our report to you. The 150 questions I think it is really important to remember to include some kind of observational period in the placebo because it was remarkable to me how there was a diminution which I did not expect and complaints of blood pressure and these are self questionnaires by the patients. Some of the patients indicated they had

edema but we were not able to confirm that by physical examination so they did not have it at the time of presentation.

And this is presented as the frequency within each group during the period of the study and then we've expressed these data as a ratio to the untreated group giving this a value of one and then some relative risk of ratio for each section.

I was the most surprised person in the world, that blood pressure did not go up. Blood pressure was monitored on each visit with an appropriate measured cuff, size cuff. It was measured in the supine and upright position, apical pulse rates were checked by oscillation over a two-minute period of time, and there were no significant change to my surprise in any of treatment groups in any of the studies.

Two patients were dropped from the second study because of increased blood pressure and when the code was broken both of them had receive placebo. One of the patients had gained 14 pounds over the period of the study and her blood pressure had gone up. Another patient was dropped because of prostitutism and urinary tract obstruction, and to my surprise he to was on placebo.

One patient on active product presented to

the emergency room and I was called that the patient might be having the heart attack. I turned out she had arm pain and a bruise from hitting her arm on a table and her cardiovascular status was not significantly altered.

There was a dropout but the dropout was primarily in the long washing period as patients were tired of waiting for the products.

Just mention a couple of other things; I was also surprised that there was a not more anxiety and nervousness and sleep disturbance. Again these were expressed as relative ratios for the treatment group relative to the observational period and was remarkably free of side effects from anxiety, depression, insomnia, and sleep disruption and the like, again to my surprise. Not all of the patients, but the selected patients had received a battery of psychometric testing prior to initiation of the herbal products and then while they're on the herbal products I have not included those analyses today but when they are available we will submit them to you.

I brought this slide along because about 30 percent or more of the overweight or obese patients complained of some problem of sexual dysfunction on the presentation. And again a bit to my surprise there was

a marked diminution in that over the period of treatment which I do not necessarily attribute to the herbal products themselves but rather to the significant loss of weight that these individuals have had, but these are one of the things that we followed and then had to a very positive responsive pattern.

DR. JONES: If you could move to wrap up, Dr. Huber, your 15 minutes are up.

DR. HUBER: My summary is that these assessments were comprehensive, the dietary supplements appeared to be effective, they appear to be safe they are cost effective, they have a relatively low adverse profile the studies remain in progress.

I had these reservations about these studies, patients were very carefully screened, they were relatively short duration no longer than six months, the number of subjects studied was limited 30 to 40 in each of the herbal groups, the number of products evaluated out of those available was limited, more information more research is needed, thank you.

DR. JONES: Thank you, Dr. Huber.

You did state that the first study that you reported on was self-funded by patients, the second study you had a small award from the American Nutrisutical Association, I believe you stated, if my

notes are correct and I can read my writing.

DR. HUBER: All of these studies were self-funded except for the one study we received about $10,000 from American Nutrisutical Association. They in turn have received, I think, a grant from TeleBrands which is the manufacturer of one of the products.

DR. JONES: And, just for the record, we've asked all presenters the source of their support today to be here today in addition to your work?

DR. HUBER: I came, at this point, at my own expense. I've requested that Ephedra Education Council pay for the cost of bringing my patients and they've agreed to do that. I will ask them for reimbursement for my travel expenses, as well.

I came to your previous meeting at my own expense.

DR. JONES: Very good. Thank you, Dr. Huber.

Questions from the panel? Dr. Philen.

DR. PHILEN: Thank you, Rossanne Philen, Centers for Disease Control. Can you tell me how many patients were in these last tables that you were showing us?

DR. HUBER: 136.

DR. PHILEN: And in this particular part of the study where you were showing us to tables was very

any caloric restriction on the patients?

DR. HUBER: That's a really good question because when I presented the first data last fall to the NASO and to American Society of Geriatric Physicians that question was asked about both physical activity and dietary; because initially we did that. I mean it was a comprehensive weight loss program. So we deliberately in this study deemphasized any kind of nutritional dietary counseling in the initial six-week phase as well as any prescribed physical activity. We encouraged people to exercise, told that was a good thing, but didn't prescribe any. We did a dietary analysis and generally shared the results of that with patients to emphasize what maybe good eating habits are, but we deliberately went out of our way. We wanted to see just what the effect of taking these products was. And then, of course, as you add as we did later in the study we added dietary counseling it became more efficacious.

DR. PHILEN: Thank you.

DR. JONES: Other questions, Dr. Richardson.

DR. HUBER: There were two things that sort of stick in mind as surfacing as side effects that I'm not fully understand. One is the patients feel very warm and they sweat a lot. We measured metabolic rates

and they did not increase as much as I had anticipated. It was very small, or not at all.

But the other thing, several of them, about 10 to 15 percent have had nocturnal leg cramps, and I can't explain the reason for that. It's not anything I can detect in terms of calcium, magnesium, potassium, or other metabolism.

DR. JONES: Dr. Richardson, you had a question?

DR. RICHARDSON: I was just curious about the washout period the nine an a half week to washout period. Were they excluded from for taking any sort of caffeine or products during that period?

DR. HUBER: They were evaluated and then recall at different periods of time when they were initiated on the products. So there was no intervention whatsoever after their evaluation; they weren't excluded at that washout period from doing anything they didn't do otherwise in the life before then.

When they were initiated on a product whether it was placebo or one of the products did not contain caffeine. They were advised that the product may contain caffeine and they were -- it was suggested to them and documented in the chart that they should be

aware of that and if they consumed a lot of caffeine that they needed to be aware of the side effects of caffeine and titrate their caffeine intake downward.

DR. JONES: Other questions from the panel?

[No response.]

DR. JONES: Questions from the floor?

Ms. Wood.

MS. WOOD: Doctor, of the 136 patients that you mentioned you evaluated did they receive the same equal psychiatric evaluation before they went through your program?

DR. HUBER: Yes and no. In terms of the questionnaires in terms of depression scales and other things like that, yes, they all received those, as well as other evaluations of readiness for weight loss, emotional status, stress and like in terms of administered psychometric tests we could not do that for all patients, it was just a manpower thing, but on that we did short-term memory recall, we did a battery of about 15 tests and about a third of the patients received psychometric testing objective psychometric testing before and after they were replaced on the herbal products.

MS. WOOD: But not all 136 patients?

DR. HUBER: No.