1980s.

So we have no information and we didn't -- we can't go back and find the patient today.

CHAIRMAN BONE: Was that a response to your question?

DR. SHERWIN: Yes.

CHAIRMAN BONE: If there are no further questions or comments from the Committee, I think we could resume with the presentation by the sponsor.

DR. SANDAGE: Right. I'd like to introduce Dr. Gerry Faich.

DR. FAICH: Good morning, ladies and gentlemen. You have heard earlier this morning from Drs. Van Itallie, Manson, and Bray, highlighting the high and increasing prevalence of obesity and its mortality and morbidity consequences.

It is in this context that I would like to review the risks and benefits of Dexfenfluamine, talking particularly about the international primary pulmonary hypertension study, then talking about the overall risks and benefits in a model.

And I will add a few comments about post-marketing or post-approval studies.

In talking about the international primary pulmonary hypertension study, you will be hearing from

Drs. Abenhaim and Dr. Rich. Dr. Abenhaim is the principal investigator of this international case control study. Dr. Rich was on the expert panel reviewing cases.

So consequently, I will not go into detail about either the study methodology or all its results. Instead, I'd like to just touch on some highpoints of it and then move to our interpretation of it.

Firstly, where did the international primary pulmonary hypertension study come from? In the mid-1960's, there was an epidemic of Aminorex-induced primary pulmonary hypertension, Aminorex being a sympathmometic anorexigen.

That epidemic involved 400 to 1,000 cases in Switzerland, Austria and Germany. It had a rapid onset within six months of the marketing of the drug. And the rate observed, and I would ask you to keep these in mind, was estimated to be or can be estimated to be 2,000 per million exposed with an odds ratio of greater than 1,000.

So no question, this was a drug-induced epidemic of primary pulmonary hypertension.

Then in the early 1990's, particularly in a report published in The British Medical Journal, there was a cluster of ten to 15 cases of anti-obesity

associated drug cases that were reported. And it was a combination of these two things that led to a concern about whether Dexfenfluamine and other anorexigens could be -- could we be on the cusp of a new epidemic?

As a consequence of that, the IPPHS was designed and carried out. This is, as you know, a case controlled study. I would suggest that it was a state of the art study.

It was done very carefully. Tremendous efforts were made to minimize bias and its conduct and to analyze for both bias and confounding.

The investigators are excellent. It was truly an extraordinary effort. Five countries, two years, 300 tertiary care centers involved, 100 actively participating.

It was an effort to locate all primary pulmonary hypertension cases in those five countries over the two years. So the intent was to make it a population-based, as much as possible, case control study.

And my focus here will be to discuss the limitations, not only of that study, but perhaps of all case control studies, particularly in pharmaco-epidemiology.

Firstly, the results as an overview, the study found 95 cases. Twenty-one percent of them of them were exposed to anti-obesity agents involved and obtained 355 controls in whom 6.5 percent were exposed to anorexigens.

The overall conclusions contained in the written submitted first report from the study, which is what I accessed to analyze it, is that anorexigens, obesity and systemic hypertension are independent risk factors for primary pulmonary hypertension with odds ratios of for systemic hypertension, 25, BMI greater than 32.4, Dexfenfluamine and fenfluamine overall 3.8.

And for all anorexigens combined greater than three months exposure, 10.6. So these are the numbers I would have you be mindful of. For this presentation, I'm going to assume that Dexfenfluamine and fenfluamine have a 10.6 odds ratio with exposure of greater than three months, in part because it accounted for the bulk of the defined anorexigens in this calculation.

Although I should point out that this calculation also involved amphetamine-like agents as well.

Well, I have three concerns, as I've said, and I would class these as inherent limitations to

case control studies in general, and in particular case control studies involving pharmaceuticals.

Those three concerns are diagnostic and referral biased, recall biased and confounding by indication. Let me discuss each of them separately.

By diagnostic and referral bias, what I'm referring to is if referrals are made from the periphery of the health care system based on a supposition or based differentially on whether a patient had or had not been exposed to anorexigens, then in fact, the observed odds ratio will be distorted by that differential referral in the direction of a higher elevated odds ratio for the exposure of interest, in this case anorexigens.

Put another way, what happens to individuals who are at the periphery that is not in tertiary care centers who present with shortness of breath, or as the case may be here, angina. Recall now 15 percent of the cases presented with angina.

What happens to them? I would contend that many of them, in fact, do get misdiagnosed or it's quite conceivable that they would get misdiagnosed as chronic obstructive lung disease or coronary heart disease.

Why would such differential referral

happen during the conduct of the study from '92 to '94. And the answer is there was a considerable amount of publicity about this issue.

Recall 300 centers were solicited. There was an article in Lancet. There was an article in The British Heart Journal. And so consequently, this issue of diagnostic and referral bias is important.

Now I would hasten to say that as you read the conclusions of the study, that doesn't necessarily change those conclusions. It says, "These are the conclusions related to diagnosed primary pulmonary hypertension."

All I'm suggesting is that the entire spectrum of biologically present primary pulmonary hypertension would dilute those results and lower the observed odds ratios.

Somewhat similarly, the issue of recall bias is an issue that does play retrospective collection of data in case control studies.

Recall that one has to see cases and controls, interview both about prior exposures, in many cases going back many years.

Great care was taken in the interview of cases using photographs of pills, using calendars and the like to capture these data.

But despite that, it's perfectly clear that cases who have been interviewed multiple times by care providers seeking participants, are much more likely to have full recall than our controls. And that's of concern.

Now how big a concern is that? I mean, why do I make this point?

If we suppose for a moment that only 40 percent of the cases were not detected, and if we also suppose those undetected cases had the background rate of exposure of controls, because otherwise they would have been referred if you will, that fact alone would drop the odds ratio for Dexfenfluamine/fenfluamine from 3.8 to 2.6.

If eight of the 355 controls had not recalled an exposure, the odds ratio would further drop to 1.8.

Now this is obviously a sensitivity-type analysis. The only point I'm making is that relatively small changes due to biases can have considerable impact on calculated odds ratios.

What about confounding by indication? Confounding by indication can be defined quickly as if a treatment is associated with an outcome, in this case an anti-obesity agent associated with primary

pulmonary hypertension, and the condition being treated is also so associated, that is if obesity is one of the risk factors for primary pulmonary hypertension, it should be no surprise that a treatment will also be associated.

That is, it's sort of the innocent bystander effect. And I would note right away that the investigators have carefully looked at this. They did stratify the analyses. They found the effects persisting.

So it's not that I'm negating the association. I would just point out that when you stratify the data at 30, you find an odds ratio -- this is a matched odds ratio of five. And if you go below 30, it's 2.9.

The suggestion here is that the more obesity you have, the higher the odds ratio, which would sort of go along with the notion that you're more likely to be treated with anorexigens if you're more obese.

And that seems to fit into a confounding by indication model.

The other thing I'd like to point out is that once you get into the individual strata, the numbers actually do get fairly thin, which just speaks

to the statistical robustness and the confidence limits that one needs to be mindful of in analyzing these data.

Well, what are my conclusions? My conclusions are that the association with obesity and hypertension in the IPPHS is very important. And I would like to emphasize, despite millions of exposures, only a handful, all told perhaps 30, cases of the 95 were exposed to anorexigens.

And recall the situation with Amenorex. There is no epidemic here, despite intense case searching. We're talking about a handful of cases.

I would quote the investigators in saying the exact role of the anorexigens and the risk of primary pulmonary hypertension cannot be definitively established due to the lack of knowledge of pathogenic mechanisms, the lack of specificity of the fact within the class of anorexigens.

And then the part I would emphasize is the non-exclusion of all potential confounders and the low absolute risk.

So that's an overview of the IPPHS. Let me now talk abut risk benefits a bit and recap again that the odds ratio found overall for Dexfenfluamine/fenfluamine was 3.8. I'm going to use

the 10.6 for the odds ratio of more than three months of exposure.

One of the major contributions of this study made is that it did carefully quantify, with some careful additional studies in Belgium, the background incidents of primary pulmonary hypertension. And it reaffirmed that that number is between one and two, two is probably the right number to use.

That would suggest that the maximum excess risk from anorexigens is two times the odds ratio minus two, this is just arithmetic, or 19.2 per million exposures to anorexigens.

And I would submit that this is a small number, particularly now if we apply a five year case fatality rate of 50 percent in cases so that this number becomes about 9.6.

And what I would like to do with the 9.6 possible deaths induced by anti-obesity agents is balance that against the potential benefits because we've been hearing a lot about the mortality consequences of obesity.

First of all, how big a number is this? How does this compare to risks for other pharmaceutical agents?

I've prepared this. This shows drugs risks per million exposures or per million person years, depending on the particular agent.

What it shows is for oral contraceptive induced MIs or pulmonary emboli in non-smokers, that risk is about ten per million in person years.

For Metformin-induced lactic acidosis, that risk is estimated to be between 12 and 40 per million person years.

Penicillin anaphylaxis, these are deaths now, is about 20 per million exposed. Accutane-induced congenital defects, that number is 98.

And if you put those numbers -- and by the way, Phenformin-induced lactic acidosis was estimated to be between 250 and 2,200 deaths per million exposed, depending very much on which age group it was.

Put those numbers in perspective. All cause pregnancy risk is 100 per million, pregnancies. Motor vehicle accidents, yours and mine, are 200 per million per person years.

Recall now, we're talking about nine in this situation, nine or ten.

These are data you've seen now before this morning. It comes from Manson and the Nurse Health

Study. It is a multi-varied risk. And it shows, as we talked about before, that risk begins to take off quite markedly at about 27 and accelerates as one goes up the BMI curve.

What I did was I took this and translated it into excess lives per million person years, and this is a simple transformation, so that as BMIs go from 27 to 32, that's an increase of 80 percent which translates, because we know the baseline, to 860 excess lives lost per year -- as per million person years, rather, as weight increases over this range.

As weight increases from 28 to 32 in BMI change, that translates into 645 lives; 29 to 32, 430; and even 30 to 32, 110 excess lives lost per million person years.

The reason I did this was to be able to put it into a model. This model, as all models, is perhaps overly simplified, but I think demonstrates the benefits of the drugs in terms of mortality savings. And we've been hearing about this earlier this morning.

This model suggests that if we treat a million women with a mean BMI of 32, and I would point out that a mean BMI 32 means that they, on average, are women let's say five foot five and weighing 191

pounds. Obviously the range around this would be 28 to 34.

If we treat them with Dexfenfluamine for a year, we can anticipate achieving the following results. And I'm going to assume that they'll persist for a year. And this is based on index results, actually conservative. These are less than the figures shown by Bobby Sandage earlier.

We can expect 200,000 women or 20 percent will lose 15 percent of their body weight. That reduces their BMI from 32 to 27.

And applying that to the data I just showed you, that would suggest that 172 lives will be potentially saved.

Now the driving, underlying assumption here we know that mortality goes up as BMI goes up. The assumption here is if BMI comes down, that the lives saved will track with that.

And I'll come back to that point and tell you why I think that's a valid assumption.

Two hundred thousand women then will have weight loss of ten percent. That translates into 86 lives saved or deaths avoided. And 200,000 will have a weight loss of five percent or 22 lives avoided -- 22 deaths avoided.

In total then, we could expect in this model that per million women treated per year, we would save 280 lives per year. How does that compare then to the excess deaths from primary pulmonary hypertension even taking a worse case scenario.

And it looks like this. Using INDEX study effectiveness, that's 280, as I've just mentioned, against 9.6. And taking INDEX, now talking about the four pound in the first month selecting responders, which captures most of the benefit and lessens exposure. Then the excess deaths would drop to 8.1.

What about this model? I would contend that it's conservative because it doesn't include morbidity. As you've heard, there's a ratio of about four coronary events per death.

It doesn't include quality of life issues. I have used conservative estimates of lives lost. As you correctly said, Dr. Bone, these nurses are probably healthier than the general population.

If you used general population figures, the numbers in this model would go up in terms of lives saved because of the differential between the starting point and the ending point.

As I've indicated, one can anticipate reducing risk by continuing the treatment in

responders only. And then I'd like to emphasize this model is a one year model. It is quite conceivable that primary pulmonary hypertension risk is a risk in susceptibles, that all of that risk then gets incurred in the first year, whereas benefits may be serial benefits in future years.

So you would have multiples in the number of lives saved as long as weight remained reduced, as opposed to incurring further risk from primary pulmonary hypertension.

That's really an issue of what would be the mechanism. Is it a dose-dependent mechanism or is it a selection susceptible? And I think we can't resolve that.

But if it is a selection of susceptibles, then one would anticipate they would be depleted in the first year or so of exposure.

Going back to the core assumption in this model, why is it reasonable to assume that if weight is lost, that mortality will be reduced? Well, you've heard earlier this morning that we know that there are prompt improvements in glycemia, lipids, hypertension and quality of life with weight loss.

We also know from Colditz that there is -- actually this is Williamson. There's a 20 percent

reduction in all cause mortality versus that found even at levels of 28 in the American Cancer Society data following any reduction of any intentional loss of weight.

Colditz has demonstrated a 50 percent reduction in non-insulin dependent diabetes with a loss of only five kilos. And the Swedish study using surgery in morbid obesity shows cure rates, high cure rates, 69 percent, for diabetes and for hypertension.

So this again supports the concept that if you reduce weight, you ought to be reducing fairly drastically the excess mortality associated with obesity.

My conclusions then are that the IPPHS results may have been affected by publicity referral patterns and recall bias that obesity is an important independent risk factor for primary pulmonary hypertension, that the absolute risk of primary pulmonary hypertension, if present, is quite small and below that of the risk of many commonly used medications.

Dexfenfluamine is effective and will prevent excess obesity-related deaths. And lastly, the benefit to risk ratio, particularly considering morbidity is probably well over 50-fold.

Now let me just make a few comments about post-marketing or post-approval studies. The challenges in the conduct of post-approval studies are intertwined with what the purpose of such studies might be.

I think it's fair to say that the purpose would focus on, or could focus on, what is the effectiveness in actual practice. You might call that clinic ethicacy as opposed to clinical ethicacy. That is, how will these drugs, how will this drug, actually work in free-living populations that are not governed by -- if you will.

What will compliance be with labelling, both on the part of physicians and patients? What are long-term effects and what kind of further safety assurance is necessary and can be derived from such studies?

The design issues are size, how big, duration, how long? What are the critical endpoints? Is a mortality a reasonable endpoint to build into a study and can it be practically studied?

And what's the control population? One can envision using drop-outs or using a before and after. One of the problems with randomizing a double blinding is the drift away from studies.

We've heard about drop-outs. Moreover, if it's going to be a real-world effectiveness trial, the ability to actually blind because of practitioner acceptance or lack of acceptance in patients, is a real problem.

It's fair to say that Interneuron and Wyeth are quite interested and willing to work with FDA and quite willing to conduct appropriate post-marketing studies.

But these are the challenges, and there is a great deal of willingness to work through this and decide what would be best.

Now I'd like to turn the podium over to Ted Cicero, who is going to address abuse issues.

DR. CICERO: Thank you very much. The bad news is my talk is about ten to 15 minutes. The good news is I'm going to abort it very quickly. We've already used our allotted time.

And there is a joint meeting tomorrow of the Endocrinologic and Metabolism Committee, the Drug Abuse Advisory Committee, at which time we will consider the issue of abuse liability.

A number of members though may not be able to attend tomorrow and I wanted to just give you a very brief overview of the current scheduling status.

Let me give you a bit of the history of this. I'll go right to my conclusions slide.

(Laughter)

DR. CICERO: Back in 1973, both fenfluamine and its isomer -- and I think it's important for us to point out that although we're discussing the effects of fenfluamine, the Controlled Substance Act reads that compounds, either scheduled compounds and their isomers and metabolites, are scheduled if in fact there's any evidence of abuse. And in fact, they should be then, accordingly descheduled.

So although I'm only considering Dexfenfluamine, the petition is actually to deschedule both fenfluamine and its isomers which would include Dexfenfluamine.

In 1973, fenfluamine was in fact scheduled in the United States under the Controlled Substances Act as a Schedule IV drug pending the acquisition of some data.

I think it's important to realize fenfluamine at that time was scheduled not because of any evidence of abuse liability, but that it bore a striking structural similarity, as you heard from Dr. Wurtman, to amphetamines.

Thus, there was a real fear back in 1973 that perhaps like amphetamines, it might have abuse potential.

Since that time, there has been an enormous amount of pre-clinical studies, that is studies in animals, clinical studies, control studies in patients that had a history of abuse, and most importantly wide-scale epidemiological studies.

As you've heard earlier today, over 30 million people have been exposed to fenfluamine around the world since 1973. And this drug has a remarkably low level of abuse.

Indeed, since the mid-1970s, there hasn't been a single published report in the world literature that documented abuse of this substance.

There have been no case reports reported since 1980. And I think as one other point, the Drug Enforcement Administration actually surveyed its regional offices in a period from 1988 to 1993 and found that 40 of the offices could report not a single incidence of a seizure or a theft of fenfluamine, whereas two reported a single theft during that period.

The Drug Enforcement Agency, in its own analysis of these data, concluded that there really is

no current or past incidence of abuse of this substance.

We would certainly concur with that decision. And in fact, the Controlled Substances Acts require that we look at this essential point. Is there, in fact, any evidence of past or current abuse of fenfluamine?

The evidence is quite clear on that point. There is no evidence to support that conclusion.

And as we're making this -- recommendation that fenfluamine and its isomers should be descheduled from the Controlled Substances Act.

I appreciate that's a very brief review, but in interest of time, and I know we've taken quite a bit of your time already, I'll pass this along to Dr. Lasagna to close off for us.

DR. LASAGNA: Thank you. This Sunday marks the anniversary of a publication of an editorial I wrote 15 years ago, largely ignored at the time. But it might be worth referring to briefly.

I started applauding the hypertension detection and treatment program that was initiated by the Government, and which permitted the identification of a physiological abnormality with predictably deleterious consequences for millions of Americans if

ignored, and a predictably improved prognosis for those afflicted if corrected.

And I went on to suggest that there was a parallel between that program and another possible program aimed at obesity which was another important physiological abnormality.

And I said at that time that no one who knew the available data would doubt that there was a relationship between obesity and hypertension, diabetes mellitus, heart disease, mental distress and orthopedic disorders.

I went on to mention that I thought anorexian drugs could play a significant role in a total weight control program, but that the proper use of these drugs would require a change in the foolish beliefs held by a lot of people, the effect that anorexian drugs were always trivial or transitory in their impact on obesity and furthermore, were extremely dangerous.

And I also mention the fact that I thought it was silly to treat a chronic disease with drugs for only short periods of time as the labelling indicated.

And I ended with a call for a serious and substantial and national effort to attack this problem.

I'm happy to say that there's been a sea change in attitude towards this problem. And as you've heard, this is chronic disease of increasing prevalence affecting one out of every three adult Americans.

It's a cause of serious morbidity and mortality. So it's not only a chronic disease, it's a chronic life-threatening disease. And there are a lot of deaths that seen to be attributable to obesity.

Furthermore, recent research, for example on the genetics on obesity, have I think begun to alert people to the notion that obesity is not just a reflection of a contemptible lack of moral fiber, people who just can't watch their diets or who are lazy or sloth-like. But that it's much more complicated than that.

As you've heard, there is a lot of clinical evidence that even moderate weight loss can reduce obesity-related morbidity and mortality. And there is now, thank God, a growing appreciation of the need for long-term use, not brief use but long-term use, as would be appropriate in a chronic disease of effective appetite suppressiveness.

For those patients, and there are many of them unfortunately, who just cannot lose or maintain

a weight loss by diet, exercise and behavior modification; that is, non-drug approaches.

Have I missed a slide? Well, okay. There's a slide that I used to have which referred to the long-term satiety of things, just trying to remind us all of the point that we're not talking about sympathomimetic stimulant agents of the old variety.

And I will repeat the material you've heard on how broad the experience is with regard to the clinical trials and marketing of this compound.

So I would conclude by pointing out that there is compelling clinical evidence that this drug is safe and effective and that it can reduce body weight and maintain that weight loss with a favorable effect on co-morbidities.

I would submit that the benefits accruing from proper use of this drug are not trivial. They are not small effects. The numbers of people who are helped to achieve target goals, the numbers are very respectable. They are substantial. They're not small.

Furthermore, I would point out that in fact, the good benefits that you've heard described are, I would submit, an understatement of the benefits possible from the proper use of this drug.

Why? Because all out-patient studies are plagued by imperfect compliance with prescribing directions. And on those occasions where it's been possible to measure compliance by studying the level of the drug in the blood of subjects in a trial, one has found mirabile dictum that people taking the drug lose more weight than people not taking the drug.

So I would submit that what you've heard is a minimal benefit picture, not a maximal benefit scenario.

And therefore, I would urge an approval, prompt approval, of this compound, because approval of it will add a significant treatment for obesity to the armamentarium of U.S. physicians.

This drug, by the way, is, I believe, the most thoroughly studies anorexia in the history of the world.

And not only will it add a significant treatment to the physicians' armamentarium, but it will make it possible to achieve a substantial increase in both the quality of life and the longevity of millions of obese Americans.

Thank you for this opportunity.

CHAIRMAN BONE: Thank you to the speakers. I think we now will have questions and comments from

members of the Committee, followed by an intermission. Dr. Borhani and then Dr. Colley?

DR. BORHANI: Thank you very much. I am grateful for Dr. Lasagna's comments and reminding us of HDFP. I have a question to my dear old teacher. Is do you anticipate to recommend a clinical trial in this country like HDFP later on if this drug is approved and therefore, to test the hypothesis that HDFP demonstrated in terms of control of hypertension?

DR. LASAGNA: I'd love to see a parallel to the old hypertension approach, which as you know was initiated actually by -- what was that called -- the Department of Health, Education and Welfare.

And it was truly a national effort, Government-led and a superb milestone in how to do things properly.

If we could mobilize a national effort like that for obesity, it would be a great achievement.

DR. BORHANI: Thank you. I hope someday it will be done. I am very grateful because at the time they started HDFP, we ran into quite a few very strong and vocal oppositions. It wasn't easy to launch that, but I'm glad it was done.

I have a question to Dr. Faich, in fact

two questions.

CHAIRMAN BONE: Maybe we could come back, okay? I'll get back to those, but a couple of other people have questions in between. Dr. Colley I think had a question now.

DR. COLLEY: Just actually two questions, one briefly just to confirm was there no dose relationship between the anorexigens and the primary pulmonary hypertension?

DR. FAICH: Well, firstly on all of the details of the study, I would rather you saved those for Dr. Abenhaim. It was his study. There is a detailed analysis of it.

There is some suggestion that duration of therapy increases odds ratio. So in a sense, that's a dose response phenomenon. But the question of how long that persists and what does it mean in traditional dosing sense and can you extrapolate to Dexfenfluamine I think is a more difficult one.

All of the issue of sub-analyses within the IPPHS run into issues. You can use multi-varied techniques, but the issues really are: what does that do to confidence limits and how far down can you push down towards specific issues of -- I want to talk about a specific age group, a specific gender, a

specific drug over a specific period of time.

I think those are difficulties in analyzing the study.

DR. COLLEY: The second question has to do with any toxicity of the drug in the situation of hyper-compliance. What I would be concerned about is the patients that are taking this drug are ones who have been frustrated by non-drug means of controlling their weight.

And if they begin taking the drug and are aware of the fact that it is probably going to be discontinued if they don't achieve that four pounds of weight loss in the first month, what happens if kthey start advancing the dose on their own?

DR. SANDAGE: In our dose response study, we doubled the dose for the high dose group. And as you saw, the discontinue rate also doubled. It was 16 percent.

Although the side effects are somewhat self-limiting and disappear, the high dose is clearly not easily tolerated by a fair amount of the people who take it.

CHAIRMAN BONE: All right, Dr. New and then Dr. Borhani.

DR. NEW: Does the drug cross the

placenta?

DR. COOPER: Dr. Campbell can answer that question.

DR. CAMPBELL: Yes, we've looked at this in radioactive studies and in pregnant animals. And like all drugs which are lipid soluble, it expectedly crosses the placenta.

This is good because in fact, the teratological studies and the Section I, II, III studies are completely clear. And so this means that because the drug gets there, we can extrapolate that to mean that there is no teratological problem.

I guess there is -- your question is in pregnancy?

DR. NEW: My question was, in fact, the interest in teratology. My second question is I've been sitting here as a pediatrician trying to think whether this drug would have any effect on growth, development and puberty.

And I can't think of any and I wonder if anyone has looked into this.

DR. CAMPBELL: It is not recommended in children.

DR. NEW: Why?

DR. COOPER: I think the issue is that the

drug has not been studied in children. Our entire clinical database is with adults. So I think we simply have to say that the drug has not been studied.

And therefore, well don't recommend it because of unknown issues of safety or ethicacy in people below 18.

DR. CAMPBELL: I can add, where it has been used in adolescents like Prayder Willi Syndrome and others, it doesn't produce any difficulty or problems.

CHAIRMAN BONE: Does it work?

DR. NEW: Does it work?

DR. CAMPBELL: Yes. In the Prayder Willi Syndrome, where it has been used recently, there is a reduction in body weight. So yes, it does.

CHAIRMAN BONE: Dr. Borhani and then Dr. Kreisberg.

DR. BORHANI: Yes, thank you. I had a question about this pulmonary hypertension study. Would you like me to hold it until later?

The simple question I had was I take it the study was done only on women. And also given BMI as I recall, is 30 and over.

My question is was there any relationship between the weight of the patient, let's say lower BMI

since you brought up the issue of hypertension in this group appropriation, and the fact that you saw primary pulmonary hypertension?

DR. FAICH: Well, firstly it was not only conducted in women. It was an effort to collect all cases of primary pulmonary hypertension regardless of gender.

It turned out, of course, that most of the cases, because this is known from primary pulmonary hypertension, whether exposed to anorexigens or not, are in women. The gender ratio is on the order of two or three to one or thereabouts.

And again, I am going to refer this to Dr. Abenhaim. The issue of interactions with other morbidities I did not see detailedly analyzed in the first report.

There will be a series of reports. Again, I think that should be asked of Dr. Abenhaim though.

CHAIRMAN BONE: The investigators and representatives will be speaking, so we'll get to that.

DR. BORHANI: Thank you.

CHAIRMAN BONE: Dr. Kreisberg?

DR. KREISBERG: I'm still a little bit perplexed on why the ethicacy seems so limited. I

mean, I'm not denying the fact that the drug is effective.

But it seems to me that the amount of weight loss is not as large as one might expect if there was always a difference between caloric intake and expenditure, and yet the weight seems to plateau fairly early.

And so the question is, if they are still on a limited caloric intake, is this a compensatory response and a reduction of energy expenditures? Are there now in a steady state or why don't we continue to see continued weight loss?

I think the layer of consumption of calories in excess of need is probably more than the layer that appears to be attacked by this drug.

DR. COOPER: Dr. Kreisberg, there are several answers to a very important multi-factorial question. I think one point that I think we can highlight is the issue of compliance. And Dr. Campbell, I think, can make some comments about the magnitude of weight change seen in compliant versus non-compliant patients.

Because really what we're talking about is a drug that enables one to comply with dietary instructions.

Clearly patients in either the placebo group or the drug treatment group are either complying or not complying based on their ability to control appetite.

DR. CAMPBELL: I think it is one of the problems in the control of food intake, and that is that it is one of the most important things in our life, and that there are many controlling mechanisms which will make us eat. It's fundamental to living.

And perhaps unlike other controlling influences, even hypertension, I think there was a lot of feedback control on continuingness to eat. And it's very difficult to maintain the weight loss.

If you look at other pharmacological agents, the sort of weight loss reported here is not unexpected.

Another thing which we did look at is why, perhaps, after six months, there appears to be a flattening plateau. And we did this by measuring the drug levels and large majority of the INDEX 12-month study.

And what we found was a gradual stopping of taking the pills. Something like 25 percent of people were clearly not adhering to the protocol.

And when you reanalyzed those people who

were actually taking it at a certain blood level, the weight loss continued to fall.

And so clearly, if the doctor can maintain the patient's taking the drug -- in the same ways, they can't maintain them to keep to a diet or to exercise, this is a problem with this group of patients.

The drug, I think, will continue to work. And I think that's something which we have to address in the use of the drug in the future.

So I don't think the drug actually does stop working. I think it reaches a new steady stage. And those people who are actually taking it do continue to lose weight even up to the 12 month period.

DR. VAN ITALLIE: One explanation that has been given for this sustained effect at the plateau level is that Dexfenfluamine lowers the set-point for body weight and lowers it to a certain level.

And that level, that new set point, is reached and the body defends that by the various physiological mechanism.

DR. WURTMAN: It's a research question. It's a question I think now we'll confront because we have the opportunity, I hope we'll have the

opportunity, to do the testing.

But one can come up with many theories. For instance, there was an article in the Lancet about two months ago from England that indicated that the act of weight loss, the act of dieting by itself, diminishes the availability of tryptophan to the brain.

Perhaps you saw that. It was discussed widely.

And if that's the case, we know that tryptophan levels are the primary factor limiting serotonin synthesis. So one could imagine that there would be such a mechanism operating.

I'm not sure I would give that a 100 percent vote at the present time. I think it's really a research question. But my strong suspicion, for what it's worth, is that as we learn more, we will learn about ways of amplifying and maintaining some of the effects we've seen.

CHAIRMAN BONE: Right. Dr. Illingworth and then Dr. Sherwin.

DR. ILLINGWORTH: One brief question. In the follow-up of the studies that are being conducted for say six months or a year, have you had the opportunity to do follow-ups based on active therapy

after drug use stopped to find out how many patients get back -- basically regain their weight?

In other words, to divide the need to continue this kind of therapy on an indefinite basis?

DR. COOPER: Dr. Sandage?

DR. SANDAGE: As I mentioned, we've only followed the patients following the completion of the trial for just a few months. You do see a trend for regaining, but that's the only information we have.

As Dr. Campbell pointed out, as long as the patients in the study continue to take the medication, the weight seems to stay down. But we don't have any long-term follow-up after being off the medication.

DR. COOPER: But clearly our expectation and the experience in use in Europe would suggest that when a patient discontinues the drug, if they haven't made any significant modifications in their dietary habits or their lifestyle, that there will, in fact, be weight regain to baseline.

DR. SHERWIN: I have a question about primary pulmonary hypertension. One, are there any animal data, and two, if they are not in the clinical arena, has anybody looked at, let's say, -- to look at the right ventricle just as an example?

DR. COOPER: Right, two people I'd like to help answer that question: Dr. Campbell and then Dr. Taylor Thompson from the Pulmonary Department of the Mass General Hospital who has reviewed these cases for us.

DR. CAMPBELL: Ever since there was the possibility of a relationship between the drug and pulmonary hypertension, the company invested quite a large effort in trying to see whether we could understand it.

And we've investigated a number of different animal models, long-term treatments in pigs, dogs, and also in isolated tissues and also isolated human tissues where we've incubated the drug.

In none of these, except at doses or levels which are something like 1,000 times the therapeutic levels, have we found any vasoconstriction.

In fact, there are some studies, particularly in the pig, where when we've activated the system with serotonin, the drug actually protects against it.

So the end result is that we've found nothing that could even be suggestive of the pharmacological means.

But saying that, nor has this been shown, for example, for a minor -- or other. It doesn't seem to be a model that one could use. But again, I would suggest this sort of question you might like to address to Professor Rich afterwards. He's more of an expert than me.

DR. COOPER: Dr. Thompson?

DR. THOMPSON: A very little to add to that, and we will get an up to date, state of the art discussion about this rare disorder from two international experts in the field.

The animal data, some of which were done in a model that I'm very familiar with in addition to not altering vascular reactivity, de novo or in fact decreasing vascular reactivity to serotonin, does not appear to cause pulmonary hypertension with chronic administration to dogs or to rats.

And in the model that I'm familiar with, hypoxia as a stimulus to produce pulmonary hypertension does not tend to exaggerate pre-existing pulmonary hypertension or the structural alterations in the lungs that follow.

So there really isn't a mechanistic hypothesis that emerges from the animal data. I've reviewed the cases. These are isolated case reports

of what looks to be primary pulmonary hypertension in patients who have taken Dexfenfluamine.

And fortunately, the International Primary Pulmonary Hypertension Registry puts that rare association in some perspective.

DR. SHERWIN: There are no echoes in patients on this chart for example, I assume?

DR. THOMPSON: The primary pulmonary hypertension has not emerged as a complication in the prospective studies, but I'm only aware of the electrocardiogram being the endpoint in looking for that.

And perhaps those involved with the studies with echoes could comment on that. I'm not aware of that.

CHAIRMAN BONE: To a certain extent, we're anticipating the next section of the program, I think if Director Rich had a comment he wanted to make, and then we'll take a break and come back and actually discuss this as our main item.

DR. RICH: To quickly put things in perspective, if you believe that there is a susceptibility issue, irrespective of the species, and with using aminorex as an example, have to treat 1,000 humans to get one case of PPH, if a dog had the same

susceptibility, then you would have to treat 1,000 dogs to get one case of PPH.

And those who do animal research don't have the funding to take 1,000 dogs and -- so it's not surprising that animal studies have no shown the production of pulmonary hypertension given the low susceptibility of the average species.

DR. SHERWIN: Right. No, I agree, but that's an extreme disease. I mean, there are gradations of change that one might expect to see a more subtle --

CHAIRMAN BONE: I think -- yes, Dr. Sherwin's question I think is addressing the -- asking the company whether they have done special toxicology studies to look at not overt primary pulmonary hypertension in animal models, but changes in pulmonary vascular resistance.

DR. FAICH: There's a somewhat related echologic issue and that is, anywhere where echoes have become increasingly available as a non-invasive procedure to move your towards this diagnosis of exclusion, are you seeing non-anorexigen related increases in the diagnosis?

And the answer is probably yes. That's certainly true in the diagnosis and the elderly in

France. And it probably relates increasing echo.

The reason that has some significance in interpreting this study is you have to ask what the availability of echo does to considering the diagnosis and the referral as well.

So it does have implications. Exactly what they are or what the results of the study might be is a little tougher. But I actually think it has probably increase the apparent incidents of the disease because it's increased the ease of diagnosis.

CHAIRMAN BONE: Thank you. If there's no further information from the sponsor, we'll take an intermission. I have 11:05. We will start at 11:15.

(Whereupon, the proceedings went off the record at 11:06 a.m. and resumed at 11:21 a.m.)

CHAIRMAN BONE: We have a rather late lunch scheduled, and it's getting later. And that means it's absolutely essential for everyone to sit down so we can start.

The next speaker is one of the invited guest expert speakers invited by the Food and Drug Administration to speak on a topic of considerable importance about which we've already heard a little bit in anticipation of this talk.

This is the description and discussion of

the International Primary Pulmonary Hypertension Study, which will be presented by Professor Lucien Abenhaim from McGill University, Montreal.

DR. ABENHAIM: Thank you, Dr. Bone, members of the Committee. I will try to quickly review the study that we conducted, which is called the International Primary Pulmonary Hypertension Study.

Can we have the lights down, please? Thank you very much.

And now I'm speaking on behalf of the International Primary Pulmonary Hypertension Study Group. This group was composed of a number of scientists: epidemiologist, cardiologists, pulmonary physicians, pharmacologists, geneticians and of course the statisticians who belong to McGill University, NIH, France, the United Kingdom, the Netherlands, Belgium. And there were local research in each country.

And all cases were reviewed as I will say later on in more detail by an expert of your panel, which was mainly a North American review panel chaired by Dr. Rich, who will present just after me.

This study was sponsored under the auspices of the Medical Research Council of Canada

with the funds provided by Servier. And we also received some financial support from the Minister of Public Health and Environment of Belgium.

So I think we will go quickly into the introduction. Dr. Faich already presented this data. We started this study after the report of the cluster of cases of fenfluamine-associated primary pulmonary hypertension in France.

And the background was this epidemic of -- related PPH in Switzerland, Germany and Austria, and there had been also come case reports in the literature in the last 15 years of fenfluamine or Dexfenfluamine-associated PPH and also a fenfluamine associated PPH.

The issue was are we facing a new of epidemic of PPH-associated to anorexigens? And so we started a survey of PPH cases in France and Belgium. We wanted to do incident studies at least in Belgium and to be as exhaustive as possible in France.

And to help in the quantification of risk association with other risk factors, we also added the United Kingdom and the Netherlands which are countries where the drugs, the anorexigens, are very -- are on the market, but are used at very low levels.

So the objectives were to develop an

epidemiological understanding of the disease and to investigate several suspected risk factors, anorexigens of obesity, systemic hypertension, recent -- and --. I will not present on the other risk factors.

I will mainly concentrate on the anorexigens ability here and also to a certain extent, thyroid extracts.

So quickly, this is a case controlled study in nature is we identified cases in clinical centers not only by reporting, but also by systematic searching the case.

The cases were varied internationally and they were interviewed by a set of specially trained interviewers blind to the objective of the study.

And we found four properly matched controls per case through the case GP or alternative -- another general practitioner.

Inclusion criteria includes age 18 to 70, both genders, resident for more than six months in the country. Interview possible, consented to participate and not suffering from active chronic disease at the time of the interview.

The cases were screened by a pulmonary physician or a cardiologist extra -- from the

reporting team, and this is very important.

At this occasion, all the cases of pulmonary hypertension and possible primary pulmonary hypertension seen by this center were the general review in order to control for their reporting bias.

And cases were reviewed all by an international expert review panel which obtained copies of medical extraction forms, X-rays, -- scans, a cardiogram. This panel was blind to exposure and classified the cases into A, B and C in order to control for a possible diagnostic bias.

One hundred and six centers participated in this study in one way or another, among which only 35 of them could include a case. And this is, of course, due to the rarity of the disease.

Here is the distribution of the cases and controls per country. France was obviously the country where we had spent much more efforts financially and in terms of human power because of the major concern that country and Belgium. The two other countries, the United Kingdom and the Netherlands, where the drugs are used buy a very small proportion of the population.

We have spent much left efforts. We really wanted to have as complete as possible

recruitment from France and Belgium.

Interviews, as I said, were blind. I think it's important to say that we have spent a lot of time and efforts trying to elicit the use of drugs, but not on the anorexigens. We have used 80 drug trade marks in order to be able to -- not on the other drugs, but also to be blind on the exposure to anorexigens.

The median and mean age is basically what is expected for this disease, and as well as the female to male ratio after -- series that we have collected.

The --, as Dr. Rich will talk a little bit more after. I will just comment here on the mean pulmonary arterial pressure and cardiologists and primary physician with whom will recognize the disease, exactly what is expected in this disease, all the other characteristics of the disease are actually met.

There was no difference between cases and controls in hundreds of diseases that we controlled for. And I think this was very important to the case in -- series was quite similar in many respects.

There are small differences that have now been studied further for this report.

For the results, very quickly, we found four cases with cirrhosis, four -- of IV drug use, intravenous drug use, three with HIV. And we had to control for these in the analysis because they are possible confounders.

So we had to withdraw those sets from the model because it was not possible to conduct a -- modelling due to the small number of --. But that -- seems to -- IV drug use and HIV in this disease.

Now we will spend the time left on mainly the appetites of persons. We studied fenfluamine derivatives, Colditz F/DF and also amphetamine-like agents such as amfepramone, clobenzoex and so on.

We also looked at compounded preparations. And if I think I should spend some time on it, in France and mainly in Belgium, doctors prescribe appetitive suppressant as mixtures of different products which could contain anorexigen, thyroid extracts, diuretics, phototherapy.

And in general, the patient doesn't know what is the content of the mixture. They know that they have to get an appetite suppressant, that it had had an effect on their, if you would, appetite.

But they don't know what the exact content, so this is an important phenomenon on which

I will be able to comment a little bit better later on.

We did not -- detail bulking agents, phenylpropanolamine and others, appetite suppressants in this report.

So this is the exposure to fenfluamine and Dexfenfluamine that we found in our case and controlled series. Nineteen percent of the cases had used at least one defined product contained fenfluamine or Dexfenfluamine.

And 20 -- and about 5.6 percent of the controls that use such -- that define products. Among the products, the main products where obviously Dexfenfluamine was obviously the main product in this series.

You had also uses of amphetamine-like agents. To a certain extent, those drugs are not used at -- in this country. I will use this slide to -- just for the fact that the exposure that we have based on our calculation of sample size on, we have expected five percent of the controllers to be exposed to an appetite suppressant.

And all together, we have 6.5 persons. So if anything, we don't think that we have underestimate the exposure of controls in this study.

I could comment on this later on if needed.

So when controlling for all possible confounders, that is obesity, systemic hypertension and all the other risk factors, suspected risk factors, in the study.

We found that and exposed you a defined product, and that was mainly for the purpose of -- here fenfluamine and Dexfenfluamine was associated to an outreach to a 4.1

If you were taking into account the exposure, all part exposure is 22 years before the development of the disease.

If you would look at the Moore appropriate-time window, it's recent exposure. We found that the odds ratio was closer to six.

For these different products, as I said fenfluamine or -- and also -- agents.

Now if we look at the effect of duration of use for these defined products again, we have another issue which is small for the people that used the drug for less than three months, but which clearly increases with duration of use.

People had used -- defined anorexigen for more than three months having a odds ratio of 10.6.

This is the 10.6 that Dr. Faich used in his model as far as I know.

Now if you look at compounded preparations, we found that seven cases and zero controls out of the 355 controls had used a compounded preparation, and in one case only where we would go to find a -- of this compounded preparation by obtaining a copy of the prescription.

In all the other cases, the doctor refused to give us a copy of the prescription of --. There were liability issues in Europe at the time around the issue of compounded preparation.

And in that compounded prescription, we found in the same compounded prescription, there was a prescription for amfepramone, a prescription for fenfluamine, a prescription for two diuretics, three phototherapies and thyroid extracts in the same compounded preparations.

So if we do a sensitivity analysis in which we consider that all past exporters, that is the definite products, the possible exposure and the compounded preparations -- or anorexigens, we have in that list eight for all past exposure, and there is no change in the -- index of 2.3. We'll come back to that later.

And when we look at the duration of use in this sensitivity analysis, we found that people had used anorexigen, an appetite suppressant, considering again, you know, this worse case analysis where all compounded preparations will be actually anorexigens.

For less than three months, the odd ration would be 3.5 And for more than three months, the odds ratio would be 23.1.

When we go to -- so just in conclusion to this quick presentation, we found a consistency of -- between anorexigen use and PPH. There were people who had recent exposure had a higher odds ratio.

I didn't show the result, but after discontinuation of the drug for more than a year, those ratios were dropping to non-significant levels.

And the longer the duration, the higher the odds ratio, that is the relative risk for the disease.

So this was the study confirmed the association between PPH and AIDS and HIV infection. We found -- cases of AIDS which were not included in the study. We found additional -- which was expected and we found the association with anorexigens which was expected also.

We have had new insights on obesity. The odds ratio for obesity for obesity was 2.5 approximately and it was significant. And we found an odds ratio of 2.5 approximately for systemic hypertension, which was not significant in the models.

And we -- further -- would be the association between IV drug use and PPH and definitely of HIV.

So the conclusions of the task force were that the study shows that the use of anorexigens and a BMI greater or equal to 30 are indefinite risk factors for the disease.

In addition, it is suggested that treating systemic hypertension is an independent risk factor for the disease, although it did not make a significance in the -- analysis.

The magnitude of the association with anorexigen use, the temporality of the association, the relation with the duration of use as well as the consistency of the results with previous observations -- hypothesis of the cause of --.

The exact role of the anorexigen and the risk of PPH cannot, however, be definitively established if we talk about the physiological role due to the lack of knowledge of the pathogenic

mechanism, the lack of specificity of the effect within the class of anorexigen and the non-exclusive of all potential confounders and the low absolute risk.

From this study, the factors of individual susceptibility could not be identified. And also the study -- a role of -- as a risk factor for PPH, the role of obesity and systemic hypertension are important in the observation which may require further investigation.

In a substantial number of PPH cases, no risk factors were identified. Thank you very much.

CHAIRMAN BONE: Thank you very much, Professor Abenhaim. If we could have the lights up for a moment?

Are there questions from the members of the Committee? Dr. Borhani has a question.

DR. BORHANI: I may have missed it, but forgive me if I did. What was your definition of case ascertainment for this case controlled study? And also did you test the interaction between the hypertension and the PPH?

DR. ABENHAIM: Thank you. So the case ascertainment was done through three stages. We visited the major centers. We visited all the centers

actually who participated in the study who reported a case.

And we reviewed all the files. And at that occasion, we also looked at all other possible primary pulmonary hypertension that the center might have diagnosed in the last two or three years.

And we had an algorithm where we used primary pulmonary hypertension as the first. So this was the control for diagnostic -- for reporting bias.

If you wish, I have some data on this here with some slides. And then these forms were sent to the International Review Panel who decided that this was a case or not.

And if I can use some more slides, Dr. Bone, I can maybe show -- can I have the lights?

Maybe we need some validation studies. And we did some validation studies on the selection information and other bias. So this is what we did. We revisited all major centers. And we reviewed all the pulmonary hypertension cases.

And, just to give you some data on this, when the National Reference Center in France, which was the major center, looked at the past exposure to definite -- in cases reported for that center, for which we have a complete ascertainment without

equation and all the other French centers, we found that the exposure to anorexigens is quite similar and in the same range.

When we look at included cases, the exposure to anorexigen, if we can't hear all past exposure, including after the index data, because we look at the reporting bias when people wouldn't know what the index is, similar proportions in the included and non-included cases, whatever the reason for non-inclusion.

And we also did a verification of the selection bias because we think that we have the complete or as complete as possible ascertainment of cases in Belgium. So we applied this to France.

And on the basis of the Belgium study we found that we should have had about 108 cases in the French study. We included 64 in France. We find seven others which were identified but not included.

The authorities or Servier have five more spontaneous reports of PPS exposed to anorexigens that we had not in our study, which shows that we didn't receive all the exposed cases. So altogether over 2 years we might have missed about 32 cases. That is 16 cases per year, which is probably not a very big number. If this was applied to our other ratio of 10

or 20, I don't think it would change a lot, even if all those cases were not exposed.

Now, for the question of interaction, we did test the interaction between anorexigens and obesity and found that it was statistically significant, although it was certainly present. And, as you know, with small numbers like this, it's very rare that interaction would be statistically significant, but it was certainly present.

We tested it with hypertension, and we didn't find any interaction there. And it's very unlikely that it would be present.

DR. BORHANI: Thank you.

CHAIRMAN BONE: Thank you.

One of the questions or one of the comments that was made as you went along had to do with the increase in risk with duration of exposure. And obviously it's a question of considerable interest.

After three months, does the risk continue to increase with duration of exposure? And is there a point at which the risk does not appear to increase further with additional exposure?

DR. ABENHAIM: Sorry for the quality of the transparency. I have heard that I would be asked

this question only recently, and I was in Europe.

If we look at all appetite suppressants in France and Belgium, where actually most of the exposure is, this counts the definite products and also the compounded preparations and also the possible exposure in order to have some statistical, if you wish, power here. So I don't know to what extent this would apply exactly to the FD/F, although I have a slide on this if you want.

What you find is that for less than 3 months, we had 13 percent of cases and 6 percent approximately of the control. That is, if you would apply it to another ratio, it would be around, let's say, 2. or 3.

For 3 to 12 months of use, we had 6.5 percent of exposure in cases and 1.4 percent of exposure in controls. So that would give you a ratio of about 10 or 12. Of course, this is small numbers. And I think we have to be very careful when interpreting those small numbers, as you can see.

And for more than 12 months, we had 15 percent of the cases and less than one percent of the control. That is another ratio. That would be probably around 20 to 30. So yes, it does increase until up to a year.

After that I don't have the data here obviously. The numbers are very small. And I think we should be very careful in interpreting these results. But we do have the impression that there is a dose-response relationship in that. But now it's very difficult to come to an absolute risk measure with those numbers.

CHAIRMAN BONE: So it looks like there are two issues here. One is that the period of use seems to have been shorter in the controls.

DR. ABENHAIM: Obviously, yes. I think in the population there are very few people, probably around one percent of French and Belgium, cases and controls that would use the drug for more than a year. Very few people would use it for more than a year.

At this stage we estimated in the study that in France and Belgium altogether no more than 200,000 people had used the drug for more than a year consecutively. So all the reports and cases have to be reported to this effort and not to millions of individuals.

CHAIRMAN BONE: Thank you very much.

Other questions or comments from the Committee members?

(No response.)

CHAIRMAN BONE: If not, we'll go ahead with Professor Rich's presentation. This is on clinical issues of the IPPH study. Professor Rich is the Chief of Cardiology at the University of Illinois, Chicago.

DR. RICH: Thank you very much.

What I would like to accomplish this morning very briefly is give you a quick clinical overview of PPH. It's an extraordinarily rare disease. It is possible that there are less than a handful of physicians in this room who have ever seen a case, let alone treated it.

It is the subject of a lot of mythology of medicine in terms of who gets it, how sick they are, how you can treat it. And I think that's very relevant to the issue at hand.

And then I'll finish by trying to at least tell you what the current wisdom is about how it's related to drug use or risk exposure.

PPH is a very rare disease. In 1981 the NIH funded a national registry through 32 centers in the United States, which enrolled 194 cases. And the estimated incidence from the recent study in Europe is approximately one or two per million.

In terms of the mechanisms of PPH, there

are three mechanisms that are probably playing relative degrees in any individual, one being that there is obliteration of the pulmonary vascular bed due to several intimal proliferations. There is pulmonary arterio or vasoconstriction due to smooth muscle cell hypertrophy. And there is thrombosis in situ of the pulmonary arterioles.

Way back 20-some years ago one of the ideologies was thought to be recurrent micro embolism. There is no human disease of recurrent micro embolism to the lung.

This is a postmortem histology slide of a patient who died with PPH. The lumen really begins here. This is the inner-elastic lamina. What you see is severe concentric lamina in normal fibrosis, virtual obliteration of the lumen.

So it's easy to understand how pulmonary resistance would go up with the lumen now this small and how the marked medial hypertrophy could also be contributing to vasoconstriction.

Similarly, this is another arteriole of a patient with PPH where we see what's referred to as a colander lesion. This again is the inner-elastic lamina. And what you see is recanalization of thrombosis at the arteriolar level. Again, easy to

understand how obliteration of the pulmonary vascular bed can lead to pulmonary hypertension.

The link between this now is felt to be understood that the common bond is injury to the pulmonary vascular endothelium. This cartoon shows in the normal state the endothelium makes the pulmonary arteriole to be in a relatively relaxed state of increased tone and is anti-coagulant in properties.

When the endothelium is injured by any number of mechanisms, you develop contraction or vasoconstriction locally. And you develop a local pro-coagulant state. Hence, this would be the explanation for the medial hypertrophy, vasoconstriction, intimal proliferation, and thrombosis that has now been confirmed to be part of the etiology of primary pulmonary hypertension.

There are some clinical data also to support these hypotheses as well. This is a study from Vanderbilt, where they looked at urinary metabolite ratios of thromboxane to prostacyclin, prostacyclin being the locally produced vasodilator in the pulmonary vascular bed, thromboxane release a vasoconstrictor.

Patients with primary pulmonary hypertension had elevator ratios compared to normal

controls and patients with obstructive lung disease, suggesting either over-production of thromboxane or, what we feel is more likely, under-production of prostacyclin is present in patients with PPH.

Similarly, in a study that we did measuring FPA level, which stands for fibrinial peptide A, which is a peptide that is released when fibrinogens convert to fibrin, an in vivo marker, if you will, of thrombosis, patients with PPH had extremely elevated levels, normal being less than five nanograms. Some were of the highest ever reported in man.

Ever given 5,000 units of intravenous heparin and remeasured at 15 and 16 minutes later, we were able to block the thrombotic process, which not only supports the notion that thrombosis is actively occurring but that anticoagulants have the potential to be protective.

Well, in terms of clinical characteristics of PPH, it has been pretty well-defined now. The data I'm showing you is from the NIH registry. Mean age is 34.4 years. There is a female to male predominance. And the registry was approximately two to one depending on smaller series. Sometimes the female predominance is higher.

An important feature is that the patients are very, very sick at the time that they're diagnosed in the PPH registry. Seventy percent were New York Heart Association Functional Classes III or IV when they presented to the reporting centers.

One of the major frustrations is that the initial presentation of PPH is typically the symptom of dyspnea, of which eventually every patient has. The reason I say that it's frustrating is because dyspnea is a symptom of normal life.

If you've ever tried to run in a marathon, you have been dyspneic, even though you don't have any cardiopulmonary disease. And so, as you can imagine, an otherwise healthy appearing young individual who comes to a physician complaining of the symptom of dyspnea might not be pursued for the underlying cause of PPH, an extraordinarily rare disease.

Consequently, at least in the NIH registry, the typical time interval from the onset of the first symptom until diagnosis was over three years.

There are a lot of causes of pulmonary hypertension: heart disease, lung disease. I'm not going to go into all of the individual subsets here. But, by and large, the notion has been that primary

pulmonary hypertension is a diagnosis of exclusion.

The strategy has been to look for any possible secondary cause because the most successful treatment may, in fact, be attacking the secondary cause. If there is no secondary cause, we are left with PPH. And then we will try to do the best we can in dealing with that disease.

The workup that was established in the NIH registry that has been very successful is kind of outlined briefly here. Maybe I can have that focused a little better.

The point I want to make is that, first of all, in the NIH registry when patients were included because they had a thorough workup, we did not have any patient who on postmortem or open lung biopsy had any disease other than PPH, suggesting that you can make an accurate clinical diagnosis with clinical testing. It requires you to be fairly rigorous and to go through a thorough exam in any patient with suspected disease.

PPH is a devastating illness, if you don't already know that. Again, this is NIH registry data. Mean survival of the patient in the registry was 2.8 years, which makes it a worse disease than AIDS and a worse disease than most cancers.

The survival was related to severity of illness. If we look at Heart Association functional class, those who were Class II or III had a mean survival of a little over three years. Those who were Class IV had a mean survival of less than six months.

Similarly, if we look at hemodynamic correlates of severity, pulmonary vascular resistance, those whose pulmonary vascular resistance was greater than 15 units had a dismal prognosis compared to those whose resistance was less than 15 units.

Although it's not really known for sure, the case fatality ratio in PPH, at least as occurred in the area of the NIH registry, approached 100 percent.

The commonly used treatments for PPH are summarized very briefly here: digitalis because they present with right heart failure. Digitalis is a time-honored treatment of left heart failure. The extrapolation is that the right ventricle may respond as well. There are no data control trials suggesting that it is helpful or harmful.

The same logic applies to diuretics. They have severe venous congestion. They feel better on diuretics. There are no control trials telling that these patients are better off.

I'm going to very briefly focus on vasodilators, which has come under a lot of attention. I'm not going to focus on anticoagulants other than to tell you that in one retrospective study and one uncontrolled prospective study use of anticoagulants has been associated with improved survival, suggesting that the etiologic mechanism of thrombosis in situ is lessened somewhat to the benefit of the patient.

This is data from the University of Illinois. It's fairly old, but it relates to the point. There is a notion that the treatment of PPH is vasodilators, namely the calcium channel blockers. This came from our experience, which started in 1985, of using calcium blockers in patients with PPH with some success.

This is a plot of pulmonary vascular resistance in units. For those unfamiliar, normal is less than two units: the PVR value at baseline after 24 hours of drug initiation and then at years one, 3 and 5. And, as you can see, the calcium blockers seem to have a fairly dramatic effect in lowering pulmonary vascular resistance that was fairly well-sustained over five years.

I want to point out that this patient was the patient who did not take the calcium blockers at

the prescribed dose. Using nifedipine as an example, the recommended dose ranges in clinical medicine are between 30 and 90 milligrams a day. The doses that were required to achieve this hemodynamic benefit in these patients was 240 to 480 milligrams a day, a dramatically high dose.

This woman, who was reduced by her referring physician back to a lower dose, was alive at year three but did not have the sustained benefit of the high dose of calcium blocker.

The other point to tell you is that in 1985 only about one in five patients referred to us were able to demonstrate this magnitude of response, which we really felt was related to the fact that we were seeing them relatively early in the course of the disease.

In 1994 our success rate in high-dose calcium blockers went from 20 percent down to one percent. We are looking into this, but it suggests what's happening is that in the community physicians heard that calcium blockers are helpful, are prescribing low-dose calcium blockers, probably somewhat slowing the progression of the disease, but not causing the marked type of reversal that we had seen. And now we are seeing patients sicker later on

in the course of the disease.

This is a non-randomized prospective look at survival influence of high-dose calcium blockers in patients with PPH. R stands for responders. We had 95 percent survival after 5 years, compared to non-responders, the NIH registry data, and University of Illinois patients within the registry who had a 36 percent survival after 5 years. Although it was a non-randomized study, the difference I think was striking enough to allow us to publish that this probably had a beneficial effect on survival.

So the good thing about calcium blockers is that they may cause substantial reductions in pulmonary pressure and pulmonary vascular resistance associated with regression of right ventricular hypertrophy. They improve lifestyle and survival when administered appropriately. This caution is that we are finding out they are rarely used inappropriately outside of select centers in the United States.

The bad thing about the calcium blockers is that they have a marked ability to reduce right ventricular failure and death. They may worsen systemic oxygenation and in suboptimal doses did not appear to improve survival. Consequently, treatment requires great familiarity and expertise.

Seven days ago the FDA finally gave formal approval to the release of epoprostenol sodium, or prostacyclin, as a treatment of primary pulmonary hypertension in the United States. I want to, therefore, review very briefly the data about epoprostenol, or prostacyclin as I will refer to it.

It is a naturally occurring vasodilator. It has direct effects on pulmonary and systemic arteriole beds. It also has anti-thrombotic properties through its inhibition of complete aggregation and has been used in Europe and Australia as a heparin substitute for patients on dialysis. Intuitively vasodilator, anti-thrombotic properties seem that they may be beneficial in patients with PPH.

This is prospective, randomized, controlled hemodynamic data after approximately 12 weeks of use of prostacyclin showing that what the drug did hemodynamically was increase cardiac output, reduce mean pulmonary pressure, reduce pulmonary vasc resistance, and reduce right arteriolar pressure in the treated patients. And this was significant.

One of the major endpoints of the study was improvement in exercise tolerance using a six-minute walk time. In the patients who were receiving prostacyclin, there was a 15 percent

increase in walk time after 12 weeks compared to a 23 percent reduction in those kept on conventional therapy.

Survival was not expected to be a major endpoint, but the results were somewhat striking. In the patients who received conventional therapy, in a 12-week period of time, there was a 20 percent mortality associated with it. Two patients were transplanted. Of the people randomized prostacyclin, we saw no mortality. And we had one patient refer to transplantation.

Consequently, the FDA has recommended approval for prostacyclin and felt that the data is warranted to state that it improves quality of life, it provides hemodynamic stability and protects against right ventricular failure, that it improves survival.

The down side of prostacyclin is, first, it is very expensive. Although we do not know the current pricing of the drug in the U.S., the best estimates are that it will probably cost initially about $5,000 per month per patient.

Secondly, tolerance develops for the drug so that over time you have to titrate the dose of the drug upward, which is going to increase the cost. More problematic, it requires great diligence from the

physician in order to manage the patient correctly.

It is a complex delivery system. It is not an oral drug. It can only be given intravenously. And so we have to put in a permanent intravenous catheter, have an ambitory infusion pump system where the patient is trained. The patient has to mix the drug every day in sterile technique.

Consequently, it requires a chronic risk of infection and sepsis from catheter site and a risk of thrombosis or stroke if they have right to left shunting through a frainment or valley.

The court of last resort has always been felt to be transplantation. The current wisdom is that you need heart-lung transplantation, obviously the lung because of the pulmonary vascular involvement and the heart because there is heart failure.

This is really not true. State of the art today is to do bilateral lung transplantation. You can induce right ventricular hypertrophy regression in these patients.

This is one quick survival slide of the success of pulmonary transplant at the present time. I will tell you that patients with pulmonary hypertension have somewhat of an intermediate survival and that at five years a typical survival for these

patients is about 40 to 45 percent.

The good thing about transplant is that it returns them to a normal activity. And it improves survival in the patients with advanced pulmonary hypertension, particularly Functional Class IV, whose projected survival would be six months or less. However, it also is expensive.

There is a high incidence of chronic rejection, which is a major reason why these people die at four to five years. And it also requires constant medical treatment in serial cardiopulmonary testing.

I want to shift now very quickly a little bit to see if I can tie in this concept about some risk factor causing PPH and how these things may be linked.

Again, you've seen this data over and over again about Aminorex. The point I want to make here is that there seems to be some predisposition required because only one in 1,000 or less patients who receive the drug develop the disease. Histologically it was identical to what we call PPH.

Interestingly enough, although there were no prospective studies done, survival appeared to be better than in PPH, mainly that if the drug was

withdrawn perhaps you would do fine. But when these patients were looked at, although some patients recovered, some patients continued to deteriorate.

Now, from the IPPHS study, we have now seen that anorexigens, systemic hypertension, and obesity all appear to be risk factors for the development of PPH. And all they all probably appear to require some genetic predisposition because obviously the majority of the people with these risk factors do not develop PPH. There is a genetic basis for PPH. In the NIH registry, six percent of the cases reported had a documented positive family history.

It's an autosomal dominant gene. There's vertical transmission. There's incomplete penetrance, which means it does not express itself in every generation.

It has an unusual feature, which is referred to as genetic anticipation, which means that offspring get it at a younger age, so grandma at age 60, mom at age 40, the child at age 20. That, however, suggests a certain type of defect, which is referred to as trinucleotide repeat expansion. The current thinking is that PPH is probably polygenic in nature.

So that with respect to predisposition in PPH, some patients have complex genetic abnormalities resulting in spontaneous pulmonary hypertension, which we call familial PPH.

Some patients have genetic abnormalities that in the presence of a risk factor results in the expression of pulmonary hypertension, which we call the usual PPH. And it is possible that even some patients are genetically protected against developing pulmonary hypertension, even when exposed to a multitude of risk factors.

Now, one of the things that we looked at a result of the IPPHS study, namely that there are a multitude of risk factors that you can link to PPH, is I have summarized a list of things that appeared in the literature to be associated with the development of PPH: systemic hypertension. Anything that elevates wedge pressure or elevated left heart pressure can produce systemic pulmonary hypertension; obesity itself; anorexigens; thorosis or portal hypertension; congenital systemic pulmonary shunts; anything that increases pulmonary blood flow by other mechanisms; HIV infection; collagen vascular disease; hemoglobinopathies such that it now appears that, rather than PPH really being a disease of exclusion,

it actually may be a disease that is triggered by some risk factor to the expression of pulmonary hypertension.

So, in summary, then, to tie all of this together, we think that PPH represents a disease manifest by a hypertensive pulmonary arteriopathy. In most cases of PPH, there is a risk factor or trigger that can be identified. And the development of PPH is related to the degree of susceptibility and the exposure to the risk factor.

Thank you very much.

CHAIRMAN BONE:

Thank you very much, Dr. Rich. I'm sure there are some questions from the panelists. Dr. Borhani has a question.

DR. BORHANI: Thank you very much.

In view of what you just said and also in view of the fact that newly approved drug prostacyclin is so effective and in view of the fact that you have identified so eloquently the pathogenesis for this disease as being injury to the surface of endothelium, first I would like to ask you: Would you agree to add cigarette smoking among your risk factors?

And, secondly, in that the PPH study was any attempt to separate smokers from nonsmokers and

also in terms of the drug labeling, whether one of the recommendations of the company that recommends this drug will be that patients who are going to be put on this drug, they must stop smoking?

DR. RICH: Well, all I can say is that in the NIH registry, the frequency of cigarette smoking was no different than the population at large. In IPPHS we looked at cigarette smoking and could not identify it also as a risk factor for the development of PPH.

So, in all honesty, we cannot make the recommendation based on any scientific data that cigarette smoking is causative, contributory for, or aggravating PPH.

DR. BORHANI: So that means that brings into question, then, the validity of the hypothesis of the injury to the surface of endothelium because, as far as I know, cigarette smoking is just as powerful as LDL cholesterol to injure endothelium of the artery.

DR. RICH: Well, I don't know of any data showing that cigarette smoke injures the pulmonary vascular endothelium. And there may be a lot of differences in circulatory beds. Clearly we know there are a lot of physiologic differences. So it may

be more selective for systemic arteriole beds. And maybe the pulmonary vasc bed is relatively immune to it.

CHAIRMAN BONE: Dr. Rich, do you think there is a lot body of subclinical cases; in other words, patients who have insufficiently severed disease to have reached a diagnosis?

DR. RICH: Well, as I say, the registry documented a three-year delay from the onset of symptoms until the patient referred to the university center. And it is almost the rule, rather than the exception, that the patient typically is misdiagnosed for a long period of time.

The typical scenario, in fact, is an overweight young woman, who is told, "You've overweight. Lose weight, and come back and see me in six months," comes back in six months and says, "Well, you're six months older. And people get older, and they get tired."

We've often got referrals from psychiatrists because the patient is depressed because they're so limited in their activity. And their doctor tells them, "It's in your head." They see a psychiatrist, who says, "There's nothing wrong with this person other than pulmonary vascular disease."

So it's an experience in frustration. I think it's because it's such a rare disease and physicians rarely think of it in their differential diagnosis that they'll do a casual test, like a chest X-ray or an EKG, which are relatively insensitive screening tests, and then eliminate that there is a real pathologic component here.

CHAIRMAN BONE: Dr. Sherwin?

DR. SHERWIN: Knowing the pharmacology of this drug, could you speculate as to how this might be linked? And, you know, is serotonin theoretically involved in --

DR. RICH: Well, the only thing I can say comfortably is I do not believe that either Aminorex or specifically more fenfluramine or dexfenfluramine are pulmonary vasoconstrictors. So I would eliminate the notion --

DR. SHERWIN: Yes, I know.

DR. RICH: -- that that's the mechanism that is happening. Nor does it appear that they are pro-coagulant drugs and it causes thrombosis.

It is more likely that either the drug or a metabolite or serotonin will cause chronic injury to the pulmonary vascular bed in susceptible individuals.

CHAIRMAN BONE: Are there any further

comments or questions from the Committee on this? Dr. Illingworth?

DR. ILLINGWORTH: Just one question out of interest. Is there a risk increase to patients with carcinoid syndrome?

DR. RICH: With carcinoid?

DR. ILLINGWORTH: Yes.

DR. RICH: No, there has not been an association. But, again, published cases of carcinoid are few. The susceptibility we believe in terms of genetic susceptibility is uncommon. And so I can't discount that that could ever be related.

CHAIRMAN BONE: Was there a specific comment regarding this mechanism question? No?

DR. COOPER: No. I think there may be some other hypotheses we could still generate, but I'm not going to go into it.

CHAIRMAN BONE: Okay. Thank you.

All right. Thank you very much, Dr. Rich, appreciate your and Dr. Abenhaim's presentations.

We're turning now to the discussion on the neuropharmacology and neurotoxicity issues. The next presentation will be on neurotoxicity and efficacy of fenfluramine. Professor Lewis Seiden from the University of Chicago will be our next speaker.

DR. SEIDEN: Well, let me see if I can disagree without being too disagreeable. The purpose of this presentation is to review the neurotoxicity of fenfluramine in animals, its potential neurotoxicity in humans, and the efficacy of the drug for weight reduction in humans.

On the basis of the data that I will review, I have reached the conclusions that the risks of fenfluramine are high, its potentials as a beneficial appetite suppression are low, and fenfluramine should be used and presented with the greatest caution, if at all.

Furthermore, in light of the fact that fenfluramine is known to damage brain serotonin neurons in animals and thereby reduce brain serotonin levels for prolonged periods of time, even after the drug is discontinued, I have reached the conclusion that controlled studies are indicated in patients treated with anorectic doses of fenfluramine. That will be discussed further below.

These studies include comprehensive evaluations of physiological, psychological, and neurological functions known to involve brain serotonin systems.

Since the early observations of Harvey,

McMaster, and Klineschmidt and his colleagues, numerous investigators have presented data consistent with the conclusion that fenfluramine is toxic to 5-HT terminal in the brian.

Collectively these studies demonstrate that fenfluramine has the potential to produce long-lasting reductions in the number of 5-HT axonal markers, including 5-HT sub; 5-HIAA; long-lasting loss of uptake sites; long-lasting loss of tryptophan hydroxylase; changes in morphological data, which will be addressed by Dr. Molliver; and resistant tolerance.

As Dr. Molliver will discuss in his presentation, he and his colleagues have collected compelling evidence that long-lasting losses of 5-HT axon markers by the administration of fenfluramine are due to destruction of 5-HT axon terminals. That's the terminals there.

These conclusions have derived further supports from research by Wesphalen and Dodd. These investigators evaluated two possible reasons for the decrease in serotonin uptake besides what you see under Vmax. Either the serotonin terminals themselves are destroyed or uptake sites are lost from otherwise intact terminals. They evaluated these possibilities by using EDEQ, which is an ethylating agent which

temporarily blocks the serotonin uptake sites while leaving the serotonin terminals intact.

They noted that the effects of EDEQ and serotonin uptake differed from those of fenfluramine. In particular, following treatment with fenfluramine, there was a direct linear long-lasting relationship between percent of uptake site lost and the ability of the neuron to take up serotonin.

In contrast, following EDEQ, as the uptake sites became blocked, the neurons there were able to take up serotonin, in spite of the fact that only 66 percent of the serotonin uptake sites were there. This indicates to them and to me that with regard to the disappearance of the entire nerve ending in red is caused by fenfluramine.

Notably, evidence of fenfluramine-induced 5-HT neurotoxicity has been obtained in numerous species, including rats; guinea pigs; rhesus monkeys; mice; squirrel monkeys; and, as I will review below, in baboons.

Since the neurotoxic response occurs in so many mammalian species, to my knowledge, none seems to be protected. The logical inference of concern is that humans will be similarly affected.

As of note is the fact that in both

rodents and non-human primates, the dose of fenfluramine required to engender 5-HT neurotoxicity is close to the dose of fenfluramine required to suppress food intake by 50 percent.

For instance, the ED_{50} for the suppression of food intake in rats is five milligrams per kilogram. And one sees neurotoxicity at 6.25 and at 12.5 milligrams per kilogram. Thus, as noted by Schuster and Johanson, fenfluramine also produced a long-lasting completion of serotonin in the striatum, the hippocampus, and the rest of the brain, the dose of 6.25 milligrams per kilogram, only 1.25 times the ED_{50} for anorexia.

In the case of other anorexics, the minimal dose necessary to produce prolonged neurochemical effects varied from 10 to 40 times the ED_{50}. In other words, it does appear that fenfluramine is a significantly more toxic drug than the other anoregs tested.

Further, Brinly has found in rats doses of 2.5 for 5 milligrams per kilogram of fenfluramine were necessary to change various factors, such as food intake, glucose metabolism, triglycerides, and blood cholesterol.

Again, the dose that was efficacious for

their study is the neurotoxic dose in rats. A narrow margin between the efficacious toxic dose of fenfluramine is also evident in nonhuman primates.

The ED_{50} for suppression of food intake in baboons is two milligrams per kilogram. In the same species, five milligrams of fenfluramine caused a decreased and marked completion of regional 5-HT markers, showing the state.

Next slide. These slides were -- you can see the controls above, which have a bright fluorescence for this 5-HT again. And these baboons treated with fenfluramine showed a markedly reduced histofluorescence. These samples were done two to eight weeks after the cessation of fenfluramine.

It has also been observed that with methamphetamine, a structurally related amphetamine analog, when animals are treated for longer durations, toxicity can occur with even lower doses of the drug. And if this proves to be the case with fenfluramines, then the duration of administrations becomes an important variable since overweight humans using fenfluramine often continue taking the medications for periods of one year.

Of note, fenfluramine produces 5-HT neurotoxic changes which in some brain regions seem

irreversible. In this study, by Latig and his colleagues, you could see that in the levels of the uptake sites, they're still markedly reduced, even 32 weeks after the drug, although some of them appear to be coming back.

This is the hippocampus, where the 5-HT levels go up and then come back down after 32 weeks. And the metabolized levels are way down, and the uptake sites are way down. So there is a prolonged effect, even 32 weeks after the drug is discontinued.

Maghian and colleagues used the d-isomer of fenfluramine, d-fenfluramine, have found the loss of 5-HT axon markers induced by fenfluramine in the monkey brain lasted for at least 14 to 17 months beyond a short 4-day period of drug administration.

This has been shown both neurochemically and, as shown in the next slide, immunohistochemically. It's the same with the frontal cortex, the control. This is two weeks for the neuron state, where serotonins were wiped out. And this is 14 months later.

Thus the notion that 5-HT neurotoxicity induced with fenfluramine is always reversible is not substantiated by the available data.

It's important to note that Lovett and his

colleagues demonstrated that d-fenfluramine is just as, if not more, potent than the dL-fenfluramine in causing 5-HT neurotoxicity in rats.

This is a study that was done giving the dosing patterns for four days and waiting a period of at least two weeks before checking the animals. And one can see if one just focuses on why that the -- oh, boy -- d-isomer, as indicated by the circles, the dose-response curve, you gain more potency from the d-isomers than you do from either the dL mixture or the L-isomer.

Indeed Ricaurte and his colleagues have shown that a dose of 1.25 milligrams per kilogram of d-fenfluramine given twice daily for 4 days can produce 50 to 60 percent completion of monkey brain 5-HT axonal markers after 2 weeks. This I would consider to be a rather low dose.

Can I have the slide off for a minute? The portion of toxicity is going to has to get considered in the advent of efficacy. We can tell from animals studies that the margin between the toxic and efficacious dose of fenfluramine is low. Unless there are overriding differences between humans and animals, one can logically expect the same situation to be obtained in humans.

The human data submitted is a summary with the applications. It shows very small reductions of weight, 2 to 5 percent, even with the high dose of 60 milligrams bid. I refer you to Table 7 in the handout that I received. And I assume most people received the same handout. This was given to humans for a period of 12 weeks.

Furthermore, the weight loss is gained when they stop the drugs. Even with the 60-milligram bid dose and assuming that the data reached statistical significance, which under some analysis it does not, the weight reduction over a long period of time was only 2 to 5 percent above placebo controls, or approximately 2 to 4 kilograms, after 3 months on 60 milligrams twice a day of d-fenfluramine

Table 14 in that same handout summarizes results from 16 clinical trials. Although all reported a significant weight reduction over controls, the range of fenfluramine-induced weight loss was from 1.9 to 5.8 kilograms, while the placebo weight changes ranged from 1.6, a loss of 6.1 kilograms.

In many cases use of placebo and a weight-reducing diet seemed very efficacious, with fenfluramine adding only a small additional weight loss. Taken together, it seems clear that when one

considers the risk of fenfluramine-induced brain 5-HT damage, along with the efficacy, the application for use of d-fenfluramine should not be approved.

The summary is already up there. Of all the species examined, fenfluramine's neurotoxic and average dose are not far apart. The toxic dose effects of fenfluramine and 5-HT neurons are long-lasting, possibly permanent, up to 17 months in monkeys. In humans fenfluramine's effects on weight reduction are significant but small.

In view of the minimal efficacy of fenfluramine as a weight-reducing drug and risks of 5-HT neuronal damage in humans, particularly those whose use of fenfluramine may extend for prolonged periods of time, the application to market this should not be approved at this time. To do otherwise, one has to ignore toxicity data and the efficacy data.

This view is based on the evidence available to me at this time, but the record may otherwise reply. In the face of logic, it seems that we may make logical and scientific different judgments in the face of the data.

It could be argued that this application should not be reconsidered under any circumstances. If it were to be reconsidered, additional research

would be essential. In particular, preclinical and clinical studies should include toxicology studies in baboons identifying a non-neurotoxic but anorexic dose, a long-term double-blind study in humans, in which d-fenfluramine is tested for toxic physiological and neuropsychological effects.

Neuropsychological tests should include those directed at behavioral spheres in which serotonin has been implicated: depression, anxiety, impulsivity, cognitive functions, changes in aggression, depression, sexual function, neuroendocrine function, and sleep.

Biological measures in the study should include cerebral spinal measures, bioamine metabolites in PET studies as a 5-HT transporter, use the radioligand that has previously been validated in nonhuman primates.

The study should be multi-centered, designed by a team of investigators. Absence of more systematically obtained toxicological data in humans makes an informed decision of the safety of d-fenfluramine in humans very, very difficult.

CHAIRMAN BONE: Thank you, Professor Seiden.

I think what we'll do is perhaps we'll

proceed with Dr. Molliver's presentation and then have a combined question and discussion period. The next speaker is Professor Mark Molliver from Johns Hopkins University to discuss neurotoxicity with fenfluramine.

DR. MOLLIVER: Thank you very much. I'm very pleased to speak to this distinguished group today.

My laboratory has been involved for a number of years studying the mechanisms of drug-induced neurotoxic effects in the brain, particularly those associated with amphetamine derivatives. We are not involved in clinical trials, preclinical trials, or production or sale of any particular drug.

Most of our studies have focused on other amphetamine derivatives, but we have done a few studies on dexfenfluramine sufficient to lead us to conclude that it has identical neurotoxic effects to the other amphetamine derivatives. And I would like to show you some of the data to suggest that.

This first slide shows, as Dr. Moore eloquently showed you earlier, the serotonin nuclei in the brain stem which give rise to the majority of serotonin projections in the forebrain.

Here at higher magnification in the rat,

there were two such nuclei: the dorsal RAPHE -- this is stained with an antibody to serotonin -- and a second nucleus, the median RAPHE nucleus. These together give rise to almost all of the ascending projections to the cerebral cortex, striatum, and hypothalamus.

They form an extremely dense projection in the cerebral cortex. As you can see in this first slide, stained with an anti-serotonin antibody, if we can get this to focus and stay there for us, these golden brown fibers are serotonergic axons in the frontal cerebral cortex of the rat, indicating a high density of these neural fibers throughout the cerebral cortex.

These axons are a mixture of those arising from the dorsal RAPHE and the median RAPHE, but they're predominantly of dorsal RAPHE origin.

What we found several years ago was that there are two types of serotonergic axons in the forebrain: those that have minute varicosities, or beads, along them which go over the sites of serotonin release; and those with somewhat larger varicosities. It's these larger ones that arise from the median RAPHE and the small ones from the dorsal RAPHE.

I trouble you with this seeming detail

because we have subsequently showed that there is selective vulnerability of the upper group. The dorsal RAPHE axons, to most amphetamine derivatives that have an affinity for serotonin uptake carriers; whereas, the smaller number of axons from the median RAPHE are essentially absolutely resistant and invulnerable to any of these compounds.

Summarized in this slide here, it's differential vulnerability. You'll recall the fine dorsal RAPHE axons are the ones that are highly vulnerable. A photograph of these shows a fine axon. And these are some of the beaded axons of the dorsal RAPHE.

We now go back as part of the background and look at the effects of other amphetamine derivatives which constituted most of our studies. This is a controlled section from a rat. In the next slide we will see the section from a rat brain, the same region, that had received a dose of methylene dioxy-amphetamine, MDA, the neurotoxin.

I think you could see by going back and forth between these two slides the difference in the density of axons in those two sections. That is, this following treatment with methylene dioxy-amphetamine an extensive marked loss for serotonin axon terminals

in the cortex.

In addition, in the hippocampus, this is a control animal. And the next one was an animal that had treated with methylene dioxy-amphetamine. It shows a marked decrease in axons, but here you see in the dentate gyrus sparing of these invulnerable, these drug-resistant, serotonin axons from the median RAPHE nucleus.

So there were two sets of serotonin projections: one sensitive to these drugs and the other highly resistant. And they're intermixed and overlapping throughout the brain.

Now we come back to the effects of fenfluramine. And what we have found is while we haven't done exhaustive studies in our laboratory on fenfluramine neurotoxicity, as we have with the other amphetamines, everything that we have seen suggests that the effects of fenfluramine are essentially identical to those of parachloramphetamine and methylene dioxy-amphetamine, the known neurotoxins. And, in fact, the toxicity of fenfluramine is about halfway in terms of potency between those two compounds. It's somewhat less than PCA and somewhat greater than MDA.

This is a control animal. And this is an

animal that had been treated with four doses over two doses with five milligrams per kilogram of d-fenfluramine in the somatosensory cortex. The stain here is an antibody to serotonin, showing that search of axons are markedly diminished in either detectability or in number.

This shows a similar preparation, but this is from the cerebral cortex of a squirrel monkey, a normal and after treatment with 5 milligrams per kilogram 4 times of d-fenfluramine, a loss of serotonin axons at 10 days following treatment.

In a further study in rats, we looked at short survival times, of 48 hours, and found, in the lower panels, enormous swellings of serotonin axons that remained present at 48 hours following the treatment.

What we think is happening is that initially exposure to the drug, to fenfluramine, -- this was a fenfluramine-treated animal, d-fenfluramine-treated animal, five milligrams per kilogram four times -- exposure releases much of the serotonin and serotonergic axon terminals.

Over the next 24 to 36 hours, most of the serotonin axons are completely depleted of the transmitter. Over the following one day; that is,

about 48 hours after treatment, there is some aborted recovery of serotonin synthesis. So that one can pick up signs of some of the axons present of using antibody to serotonin. At that time these axons are enormously dilated, swollen, and appear to be degenerating.

Similarly, we have looked -- this is also serotonin axon terminals showing here swollen axon in this location and another one deep in the cerebral cortex, swollen axon in the rat following d-fenfluramine treatment using serotonin.

Several other examples I'll quickly run through. These are all obtained using a marker for antibody for serotonin. You can see these that are fragmented, swollen axons with classical features as described by the classic neuroanatomist Cajal as characteristic of degenerating terminals.

Another example here. As you can see, they can become quite repetitive because they all look the same and they look rather sick as they're dying and about to disappear.

One more. Okay. Similar findings have been seen in the rhesus monkey, in the squirrel monkey -- in the cynamolagous monkey, not in the rhesus monkey. This is from a rhesus monkey deep in the

cerebral cortex, showing these abnormal swellings of serotonin-positive axons.

This is from the hypothalamus of the same monkey, showing these dilated fragmenting axon terminals or axons with passage, another example from the rhesus monkey after treatment with fenfluramine, suggesting that these axons are in the stage of degenerating.

Another example from another monkey treated with fenfluramine at a dose of 5 milligrams per kilogram twice a day for 2 days, survival time 48 hours.

And the final example of the same; in fact, another one. I've thrown too many in there.

Now, one of the questions or criticisms that has been raised is that serotonin itself as a marker is not valuable because, for example, it is released and disappears. So it may not show you what is actually going on since it is such a labile substance. Well, in fact, in this case we have looked with an antibody against the synthetic enzyme for serotonin tryptophan hydroxylase. And that shows the same pattern of alteration and swelling and fragmentation of these.

Another example, with an antibody to

tryptophan hydroxylase. This is a large enzyme of protein present in the nerve terminals and associated with the synaptic vesicles, showing these somewhat odd-looking axons. And this is after 4 doses of dexfenfluramine, 5 milligrams per kilogram survival for 48 hours.

Well, I think that data is highly suggestive of some structural damage to these axons, certain pathological changes, but now let's look at another marker. I'm going to contrast this with some material upcoming. This is also using antibody to serotonin. This is a control animal, and this is following treatment with dexfenfluramine with a 48-hour survival, the same doses that I have been describing. Everything I'm showing is with the same dose today.

This is 48 hours after the treatment. This is from a series of rats, the next one one week after the treatment, showing that there is an acute loss which you see, but it persists. And, in fact, we'll see later that it actually persists for an even longer time because this is six weeks after. And we haven't looked at animals with fenfluramine much longer than six weeks after treatment.

Now, this slide uses a new marker that we

have recently worked on in collaboration with Dr. Randy Blakely from Emory University, now at Vanderbilt, who has cloned the serotonin uptake carrier and made an antibody to it. So this uses an antibody against the 5-HT uptake carrier, the target of these compounds.

This is again a stable, membrane-bound, large protein which is a component of the plasma membrane of the serotonin axon terminals. So using this antibody against the uptake carrier, you see here the search on axons looks very similar to how they do using antibody to serotonin.

Following 5 milligrams per kilogram of fenfluramine 4 times 48 hours later, there is a marked loss of axons which contain this protein, this large protein. So this is highly indicative of a loss of these axons. One can't go back to the argument that serotonin itself is depleted and, therefore, one isn't seeing ghastly axons that are empty but present. This is a protein.

This is at one week later. And then we come six weeks later. So you see that there is a persistent loss of axons that contain the serotonin uptake carrier.

Just to show you an example with another

form of illumination, this shows axons, normal axons, stained with an antibody to the serotonin uptake carrier. And now I'll show you several photographs of axons stained with the serotonin uptake carrier antibody showing damaged, structurally damaged, axons, such as these with large enlargements of the axons, which one doesn't ever see in the normal circumstance.

Now, that's probably all the bad news. That is, we feel we conclude from this that dexfenfluramine leads to by a mechanism not yet established degeneration for the serotonin axon terminals.

However, one of the novel interesting things about this compound is that it selectively affects the axon terminals without having any substantial toxic effect upon the cell bodies. The cell bodies in the RAPHE nuclei are spared.

And so the good news, then, is that following loss or pruning of these axon terminals, the cell bodies have the capacity to regenerate; that is, not to divide, but to sprout new axons which grow back into the cerebral cortex and re-innervate, even though the original axons were lost.

So the good news: There's sprouting after this drug-induced degeneration. And it has certain

characteristics. It's very much like the development pattern of serotonin axons.

There's a gradient. Serotonin axons enter the cortex in the frontal pole and then head back towards the occipital pole. And that same gradient occurs during the regeneration. It starts in the frontal cortex, and it proceeds caudally towards the most posterior cortex. They form two layers.

The first thing one sees in a long series of these studies is that the free terminal axons deep in the cortex grow in and then subsequently there is abundant sprouting of axon terminals up into the cortex to re-innervate the cerebral cortex, apparently some attempt to restore the lost and ablated serotonergic projection.

Now, further studies of this -- and I'll show you some of our data and results -- have not been done with fenfluramine because this was a recent finding. These studies take a long time. The studies that I'll show you now show the same phenomenon but with MDA, methylene dioxy-amphetamine, and PCA.

And, again, we feel that all of the other data that we have shows that fenfluramine effects are identical. So we should be able to expect with fenfluramine a similar pattern for free innervation as