FOOD AND DRUG ADMINISTRATION

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ENDOCRINOLOGIC AND METABOLIC
DRUGS ADVISORY COMMITTEE

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OPEN SESSION

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Thursday, September 28, 1995

The Committee convened in Conference Rooms G, H, I and J of the Parklawn Conference Center, 5600 Fishers Lane, Rockville, Maryland, at 8:00 a.m., Henry G. Bone, III, M.D., Chairman, presiding.

PRESENT:

HENRY G. BONE, III, M.D., Chair

KATHLEEN REEDY, Executive Secretary

NEMAT BORHANI, M.D., MPH

COLLEEN A. COLLEY, Pharm. D.

ROBERT S. SHERWIN, M.D.

CATHY W. CRITCHLOW, Ph.D.

MARIA I. NEW, M.D.

D. ROGER ILLINGWORTH, M.D., Ph.D.

ROBERT A. KREISBERG, M.D.

LEWIS SEIDEN, Ph.D.

MARK E. MOLLIVER, M.D.

STUART RICH, M.D.

LUCIEN ABENHAIM, M.D.

SOLOMON SOBEL, M.D.

GLORIA TROENDLE, M.D.

LEO LUTWAK, M.D., Ph.D.

BRUCE V. STADEL, M.D., MPH

ALSO PRESENT:

BARBARA C. HANSEN, Ph.D.

JUDITH S. STERN, Sc.D.

GLENN L. COOPER, M.D.

THEODORE VAN ITALLIE, M.D.

JOANN MANSON, M.D., Dr.P.H.

GEORGE BRAY, M.D.

RICHARD J. WURTMAN, M.D.

ROBERT Y. MOORE, M.D., Ph.D.

BOBBY Y. SANDAGE, JR., Ph.D.

GERALD A. FAICH, M.D., MPH

THEODORE J. CICERO, Ph.D.

LOUIS LASAGNA, M.D.

TAYLOR THOMPSON, Ph.D.

JOHN LEE, Ph.D.

BRUCE CAMPBELL, Ph.D.

JOSEPH F. CONTRERA, Ph.D.

S. EDWARD NEVIS, Ph.D.

ALSO PRESENT (contd.):

RUDOLPH NOBLE, M.D.

LISA STOCKBRIDGE, Ph.D.

NATHAN M. APPEL, Ph.D.

BALDEO K. TANEJA, Ph.D.

LEE-PING DIAN, Ph.D.

JAMES M. BILSTAD, M.D.

RICHARD GAMMANS, M.D.

MARK DEITCHER, M.D.

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(8:17 a.m.)

CHAIRMAN BONE: Good morning. I apologize for the slight delay in getting started and hope that we will not be experiencing any more delays during today.

I'd like to call this meeting of the Endocrinologic and Metabolic Drugs Advisory Committee 60th meeting to order.

Today, we will be discussing Dexfenfluamine for obesity. The first thing I'd like to do is ask the people at the table to introduce themselves starting with the FDA representative at the far end, and just working around, and giving a name and affiliation.

DR. LUTWAK: Leo Lutwak, Medical Officer, FDA.

DR. KREISBERG: Bob Kreisberg, Birmingham, Alabama.

DR. CRITCHLOW: Cathy Critchlow, University of Washington, Seattle.

DR. SHERWIN: Bob Sherwin, Yale.

EXECUTIVE SECRETARY REEDY: Kathleen Reedy, the FDA.

CHAIRMAN BONE: Henry Bone, the Henry Ford

Hospital in Detroit.

DR. BORHANI: Nemat Borhani, University of California, Davis.

DR. COLLEY: Colleen Colley, VA Medical Center in Portland.

DR. ILLINGWORTH: Roger Illingworth, Oregon Health Sciences University, Portland, Oregon.

DR. NEW: Maria New, Cornell, New York.

DR. ABENHAIM: Lucien Abenhaim, McGill University, Montreal.

DR. RICH: Stuart Rich, the University of Illinois at Chicago.

CHAIRMAN BONE: Thank you. Today, we're going to be discussing longer term of indication for obesity than has been previously approved by the Agency.

There have been a number of meetings and discussions about criteria for such indications, and we'll be interested to see what the data are like for this particular application.

Now Dr. Reedy will read the conflict of interest data.

EXECUTIVE SECRETARY REEDY: I also would like to apologize for the security checks, but you all know the reason for that: the Oklahoma City. And we

haven't had to deal -- this committee hasn't had to deal with that before. We've met outside the building.

So this is what it's like in the Federal Government.

The conflict of interest statement for the Endocrinologic and Metabolic Drugs Advisory Committee on September 28, 1995, the following announcement addresses the issue of conflict of interest with regard to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting.

Based on this submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions: in accordance with 18 United States Code 208(B)(3), full waivers have been granted to Dr. Joanna Zawadzki and Dr. Cathy Critchlow.

A copy of these waiver statements may be obtained from the Agency's Freedom of Information Office, Room 12-A-30 of the Parklawn Building.

With respect to FDA's invited guest speakers, Dr. Stuart Rich and Dr. Lucien Abenhaim have reported interests which we believe shall be made public to allow the participants to objectively evaluate their comments.

Dr. Rich would like to disclose that he has been a paid consultant to Servier. He has also participated as a member of the Scientific Advisory Committee of International Primary Pulmonary Hypertension Study which evaluated anorexigens in primary pulmonary hypertension, which incidentally is why we invited him.

Dr. Abenhaim would like to disclose that he participated in the International Primary Pulmonary Hypertension Study and has received consulting fees from Servier for an interpretation of the study and the same.

In the event of the discussions involved, any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement. And their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any

current or previous financial involvement with any firm whose products they may which to comment upon.

CHAIRMAN BONE: I'd also like to welcome Dr. Sobel and Dr. Troendle from the Agency.

The next item on the agenda is the open public hearing, or open public comment, portion of the proceeding. I would ask each of the speakers who make comments during this segment to disclose other interests as Dr. Reedy has mentioned specifically.

The first on our list is Dr. Barbara Hansen from the University of Maryland School of Medicine.

DR. HANSEN: I'm Barbara Hansen, and I'm currently President of the American Society of Clinical Nutrition. I met with some of you last January.

For those who might have a memory lapse, I was the one that showed you pictures of non-insulin dependent diabetic monkeys and obese monkeys and talked about the incredible data available now to show the importance of prevention of obesity.

Today I'd like to speak more broadly to some of the issues of obesity. I have prepared a written statement, and I will rather just highlight some of the comments and the Committee has the full

details.

I think we should all recognize here today that the largest nutrition problem in America is, without any question, obesity.

I accidentally wandered into the wrong conference room today, and ended up down the hall talking with C. Everett Koop. And he was talking with me about his Shape Up America Program.

And I said, "Well, you're doing a great job." And I said, "On the smoking remission," which is certainly true.

And his comment to me was, "It's much harder, much harder, to tackle the obesity problem than it is to tackle the smoking problem."

So it's very clear that we're dealing with an important disease, a disease that affects millions of Americans, and a disease that cannot be satisfactorily be addressed by behavioral means.

Now I know of what I speak because my original training was in the laboratory and the clinics of one of the most prominent psychiatrists in the field of obesity.

And so I began with behavioral modification as the Holy Grail. And I can tell you that in the 20 years I've been in the field, although

behavioral modification remains an important tool, it has not yet successfully changed obesity in any substantial number of patients, and certainly not on a long-term basis.

So we are dealing not with a psychosocial problem, but with one which we clearly know has a major physiological and genetic component.

I'm sure everyone in this room is aware of the recent discoveries of some of the obesity genes. But are you aware that there are now four that have been identified in rodents?

It means to us that the genetic basis, the physiological basis of this disorder, is extremely clear. It's not just in the rodents. It's clear in humans as well.

It's therefore very important that we develop and continue to improve our methods for dealing with obesity in a physiological and pharmacologic manner.

We have to accept that obesity is not a disease with a quick fix. There will be no quick fix for obesity in my lifetime. I guarantee that.

So we're going to have to work on mitigating factors, possibilities of reducing obesity in small proportions, hopefully incrementally.

We always must be concerned with safety. But I urge that we contemplate the risks of obesity. There is no question that obesity carries a tremendous risk of morbidity and of early mortality.

And therefore, that as we look at safety, we must compare it to the extraordinary increase in health risk and morbidity that obesity carries.

For those that aren't sure obesity is a disease, look at the incidents of heart disease, of diabetes and cancer, and especially of diabetes, and exam the degree to which obesity is the contributing factor to Type II diabetes.

Perhaps 80 percent of Type II diabetics would not be diabetic if we could successfully mitigate or prevent their obesity. That is a huge number and a tremendous cost to our country.

So toward the end of your deliberations today, on behalf of the American Society of Clinical Nutrition, I urge that every action taken by this group keep in mind its future implications and help us help the United States and help the world to develop better means, continuously better means, for addressing the problem of obesity, and accept the idea that obesity is a disease.

That despite the potential for abuse of

any anti-obesity agents, the risk of continuing obesity far exceeds the risks that might be occurred by abuse.

We have ways to deal with abuse. Let us deal with it. Thank you.

CHAIRMAN BONE: Thank you very much, Dr. Hansen. Sorry, did you make a statement about any interests?

DR. HANSEN: I have no conflict of interest with the company that is on the agenda today. I consult for, have consulted for, give lectures to and do research for virtually every company in this room.

CHAIRMAN BONE: Thank you. The next speaker also for five minutes is Dr. Judith Stern from the University of California of Davis.

DR. STERN: Thank you very much. I'm Judith Stern. In addition to being Professor of Nutrition and Internal Medicine at UC Davis, I'm also Vice President and Co-chair of the newly founded lead advocacy group, the American Obesity Association. And I'm speaking on behalf of AOA this morning.

And in terms of conflict of interest with respect to this meeting, I am on the Advisory Board of a major weight loss company, and we have received

money from multiple drug companies.

CHAIRMAN BONE: What company is that?

DR. STERN: Pardon me?

CHAIRMAN BONE: Which company is that?

DR. STERN: From Boots, now Knoll, in terms of consulting fees and from Roche in the last year. And AOA has received money also from Servier and Interneuron and Roche and Best Foods, as well as non-company.

A comment: I have to echo Dr. Hansen's concerns and comments. I was asked to testify in January because I chaired an Institute of Medicine committee that came out with a report in February of 1995 called "Weighing the Options" where we talked about new strategies for weight maintenance and we emphasized the importance of small weight losses that are maintained.

But again, to echo some of my testimony in January and again this summer, we are literally in the midst of an obesity epidemic.

I'm sure you all know that one out of three American adults are obese. But you may not know that one out of five children are obese and the data have been published for ages 11 through 19. But within the next week, the data will be published for

children ages seven through 11.

And that's very alarming to me as a health care professional.

And obesity kills. It's the second leading cause of preventable deaths, approximately 300,000 yearly. And it costs the country $100 billion.

Now the American Obesity Association is a lay organization. We're formed to promote the understanding of obesity as hopefully a treatable, identifiable disease. It is an identifiable disease.

And Dr. Bone, for the Committee's record, I would like to submit this 1985 consensus statement, conference statement, where NIDDK and NHLLBI did label obesity to be a disease. It is a consensus statement and it is a serious disease.

CHAIRMAN BONE: Thank you.

DR. STERN: And although the word "obesity" has negative connotations in the minds of many Americans, including some physicians and health care professionals, the ultimate goal of AOA is to change public perceptions so that this disease is given equal status to such diseases as diabetes and heart disease and cancer.

Now despite the tremendous cost in death

and disability that obesity exacts, it has not received the recognition that it deserves as a major public health problem and as the main nutrition and metabolic disease in this country.

And the lack of attention is widespread. For example, there have been no new drug therapies approved by FDA for treating obesity since 1973.

Novel drugs that are very different than from the old amphetamine-like drugs have gained acceptance in Europe and other countries.

So AOA hopes that the Endocrinologic and Metabolic Drugs Advisory Committee will take the important steps necessary to address the epidemic of obesity in America.

Although it remains extremely important to increase physical activity and dietary and behavioral changes, drug therapy is a valuable tool, especially for the large numbers of individuals who have failed repeatedly to lose weight and to maintain that lost weight.

And I echo Dr. Hansen's comments that as the research and to the nature and causes of obesity provides new information on the disease, it is clear that there is a large genetic component to human obesity.

And most physicians need to provide more for their patients than just the encouragement of healthy lifestyle practices so that the availability of new anti-obesity drugs that can be taken for long periods of time will compliment healthy lifestyle practices and will be a major addition to the options now available to obese people and their physicians.

So for this reason, AOA is hopeful that FDA's actions in the future will lead to additional research and the continued development of new obesity drugs for the future.

And I didn't know that Dr. Koop was next door. We could bring him in to read this quote that he read in front of the Committee in January, and this is quoting from Dr. Koop: "To our shame, we have done almost nothing about this major health threat. The Government, the medical community, the health insurance companies, no one has done much to encourage Americans to prevent the obesity that is costing us and killing us. All too often we fail to regard obesity as the disease it really is."

And to paraphrase Dr. Koop, obesity kills. And I trust this Committee will understand the seriousness of this health problem and the insufficiency of currently available and approved

treatment methods.

I urge the Committee, in their deliberations, to take into account the risk of being obese, the increased morbidity and mortality and the decrease in risks associated with small, but significant, weight losses that are maintained.

So that on behalf of the American Obesity Association and millions of obese patients who stand to benefit from your action, I thank the Committee for the opportunity to speak to you today.

CHAIRMAN BONE: Thank you, Dr. Stern. Thank you, Dr. Hansen. I think we're fortunate in being a little able to, in fact, not only catch up but get a little ahead on the program.

So at this time, I'd like to introduce Dr. Glenn Cooper, who will be, as he said, the master of ceremonies for the sponsor.

Would it be agreeable to the Committee members if we have questions after the ethicacy and safety summary and go through the presentations up to that point and then have another -- is that agreeable? That's what we'll do then.

DR. COOPER: Thank you. Good morning, Mr. Chairman, members of the Committee, Dr. Sobel and members of his staff at FDA. My name is Dr. Glenn

Cooper, President of Interneuron Pharmaceuticals.

This morning, we are pleased to have the opportunity to present data on the safety and ethicacy of Dexfenfluamine for the treatment of obesity.

Over the past several years, there has been a growing consensus in the academic medical community that obesity is a multi-factorial chronic disease with a strong genetic component, not merely a disorder of will power or lifestyle.

As with other chronic diseases such as diabetes or hypertension, there is a strong rationale in obesity management from use of appropriately safe and effective long-term pharmacotherapy to prevent morbidity and mortality.

As you will hear, the prevalence of obesity in America has been steadily rising. Obesity is not only a highly prevalent disease, it's also a serious disease.

Morbidities up to 300,000 deaths per year are attributable to overweight conditions, making obesity the second leading cause of preventable death after smoking.

Against this background, Dexfenfluamine is the first prescription drug for the therapy of obesity to come before the FDA for approval in over 20 years.

There has been a extensive international experience on the use of Dexfenfluamine in obesity. The drug is approved and marketed in 65 countries, including the member states of the European Community by the French pharmaceutical company, Servier.

Servier is the third largest pharmaceutical company in France, 25th largest worldwide, and is the leading company in the world in the field of obesity therapeutics.

Three of Servier's drugs have previously been approved in the United States.

Servier received its first Dexfenfluamine approval in European in 1985. And to date, over 10 million patients have been treated with the drug.

Dexfenfluamine is the d-isomer of the approved glycemic drug, fenfluamine, which has been on the market in the U.S. since 1973 for the treatment of obesity.

Over 30 million patients have been treated worldwide with fenfluamine, including several million in the United States.

Since fenfluamine is equal parts of Dexfenfluamine and Levofenfluamine, all of these patients have, in fact, received the full pharmaceutical of Dexfenfluamine.

The Dexfenfluamine NDA includes over 4,500 patients and subjects in U.S. and European clinical trials.

Interneuron licensed the drug from Servier, opened an IND for Dexfenfluamine on October 1991, and began U.S. clinical trials to augment and compliment the international clinical trial database.

We designed the clinical program in conjunction with the FDA's neuropharmacological division, the group that originally reviewed the IND prior to transfer of all obesity compounds in the Endocrinologic and Metabolism Division.

Although the clinical program was completed prior to recent Committee discussions on guidances for anti-obesity compounds, we believe the design and outcome of these studies are compatible with the criteria for approvability discussed by the Committee earlier this year.

The studies demonstrate, first of all, that Dexfenfluamine is an effective anti-obesity agent producing clinically important weight loss in a large proportion of patients.

As you will hear, in our largest 12-month placebo-controlled study, 40 percent of patients on Dexfenfluamine achieved greater than ten percent

reduction in their initial body weight, twice the placebo response rate.

The studies also demonstrate that Dexfenfluamine has a highly favorable safety profile.

I would like to point out to the Committee that the FDA has passed out this morning a revised statistical report on the analysis of the ethicacy database. You may have noticed a discrepancy in the analyses presented by the company and the FDA in your background packages.

But I believe with this revised FDA report, the analyses are now in agreement.

This is the agenda for our presentation this morning: brief CVs of the speakers have been included in the background books you have received. We have three speakers to discuss the medial and epidemiological evidence for the need for treatment in obesity.

These individuals, Dr. Theodore Van Itallie, Dr. JoAnn Manson and Dr. George Bray, are internationally recognized experts in epidemiology and clinical treatment of obesity.

Dr. Van Itallie is Professor Meritus of Medicine at Columbia University's College of Physicians and Surgeons. And for many years, Dr. Van

Itallie has been one of the country's leading scientists engaged in obesity research, has contributed over 200 research papers during the course of his distinguished career.

Following Dr. Van Itallie will be Dr. JoAnn Manson, Co-Director of Women's Health and Director of Endocrinology in the Division of Preventative Medicine at Brigham Young Women's Hospital and Associate Professor of Medicine at Harvard Medical School.

Dr. Manson's research includes epidemiologic obesity and other chronic diseases. This morning, she will share with the Committee recent data about the association between obesity and mortality published this month in the New England Journal of Medicine.

Dr. George Bray is Executive Director of the Pennington Biomedical Research Center in Baton Rouge and Professor of Medicine at LSU's Medical Center in New Orleans.

Dr. Bray is another leading academic figure in the area of nutrition and obesity research, is the founding editor of International Journal of Obesity, and the current editor-in-chief of Obesity Research.

Dr. Rich Wurtman will discuss the drug's mechanism of action and clinical pharmacology. Dr. Wurtman is the Cecil H. Green Distinguished Professor of Nerve Science at MIT, Director of MIT's Clinical Research Center, and co-founder of Interneuron.

He is one of the world's leading experts on neurotransmitters and serotonergic drugs and has done extensive primary research on the pharmacology of Dexfenfluamine.

Dr. Robert Moore will talk about the nerve chemical effects in animals of large doses of Dexfenfluamine. Dr. Moore is Professor of Psychiatry and Neurology and Neuroscience at the University of Pittsburgh. He is an expert in neuropathology and neurotoxicity and has studied the neurochemical effects of fenfluamine for many years.

The NDA ethicacy and safety database will be presented by Dr. Bobby Sandage, who is Senior Vice President for Research and Development and Chief Scientific Officer at Interneuron.

Dr. Sandage has 17 years of experience in drug development within the pharmaceutical industry and has been involved with the Dexfenfluamine IND and NDA from the outset.

Special safety considerations with a focus

on the issue of primary pulmonary hypertension as well as the overall risk benefit ratio will be presented by Dr. Gerald Faich.

Dr. Faich is an expert in pharmaco-epidemiology from 1983 to 1990, who is in charge of statistics and post-marketing surveillance at the FDA.

Dr. Faich is currently Professor at the University of Pennsylvania and a consultant in drug safety and epidemiology.

In 1973, fenfluamine and its isomers were provisionally classified as Class IV scheduled compounds due to a lack of understanding at that time of their pharmacological mechanism of action.

Dr. Theodore Cicero will discuss the lack of abuse potential of Dexfenfluamine. Dr. Cicero is Professor of Neurobiology and Neuropharmacology at the Washington University School of Medicine.

He's an expert in the field of drug addiction and abuse and was the Chairman of FDA's Drug Abuse Advisory Committee from 1986 to 1992.

And Dr. Louis Lasagna will finish with concluding remarks. Dr. Lasagna is the Dean of Sackler School of Graduate Biomedical Sciences at Tufts University School of Medicine.

He is also Director and Chairman of the

Board for the Study of Drug Development at Tufts. As an preeminent expert in clinical pharmacology and drug development, Dr. Lasagna has been a consultant to several of the National Institutes of Health and the FDA.

We also have with us today several other noted consultants and experts as well as scientific representatives from Servier and from Wyeth Ayerst, our commercialization partner.

These individuals may be called upon to address questions from the Committee.

I'd now like to introduce our first speaker, Dr. Van Itallie.

DR. VAN ITALLIE: Thank you, Dr. Cooper and members of the Advisory Committee and guests.

In the United States, the toll of preventable illness and death taken by obesity is second only to that inflicted by cigarette smoking. An estimated 20 million cases of illness and almost 300,000 deaths per year are attributable to overweight.

An appreciable number of these illnesses and deaths could be prevented by some degree of sustained weight reduction. Conventional weight control programs that rely on lifestyle changes are

plagued by high drop-out rates.

Moreover, a high proportion of participants who stay in such programs and reduce their weight by five to ten percent or more tend to regain most or all of the lost weight within a few years.

Hence, it's not surprising that physicians increasingly feel frustrated with this unsatisfactory state of affairs and are now looking to the potential for longer-term success in weight control afforded by pharmaco-therapy.

In the first part of this discussion, I shall mention the prevalence of obesity, the number of Americans who are severely overweight, and at especially high risk of developing obesity-associated illnesses, and the estimated numbers of excess illnesses and deaths in the United States that are attributable to over weight.

For the purposes of this discussion, we shall be using the terms "overweight" and "obesity" interchangeably. However, we do understand that these two expressions also have specialized meanings.

There are generally accepted criteria for what is considered overweight or obese. In the first line, you will notice the criteria established by the

National Center for Health Statistics, namely a BMI of 27.8 for men and 27.3 for women.

These values are slightly more than 20 percent above desirable weight levels for the Metropolitan Life's 1983 weight for height tables.

All of the BMIs shown here simplified 27 for both sexes represent, I think, a reasonable cut-off to make the point at which the health and mortality risks of being obese become substantial.

Rationale for this benchmark will be demonstrated shortly by data presented by Dr. JoAnn Manson.

It's apparent that in terms of NCHS's BMI criteria, the prevalence of overweight or obesity has increased strikingly among both U.S. men and women during the last decade, between NHANES II and NHANES III.

At this point, about one-third of U.S. residents over the age of 20 are clinically obese, and this is a most alarming set of statistics given our growing knowledge about the adverse health consequences of obesity.

In this slide, we see that of the more 60 million adult Americans who are currently overweight, 37.4 million have BMIs equal to or greater than 30, 36

percent or more are overweight.

As Dr. Manson will soon tell us, people whose BMIs are 30 and above are in a very high risk BMI range. And we're now talking about 21 percent of the entire U.S. adult population, 20 to 75 years of age.

The enormous impact of the U.S. pandemic of obesity is best brought home by considering the total excess illnesses and the numbers of deaths per year that are attributable to this condition.

This slide presents our best estimates, which we believe to be conservative, of the numbers per year of the cause-specific deaths seen over here from at best all causes, on the other side, that can be attributed to obesity.

And this table shows the approximate contributions of deaths from various illnesses shown on the left to the separately estimated total of 292,000 deaths from all causes attributable to overweight.

These deaths arise from a very large reservoir of extant illnesses such as NIDDM, hypertension, pulmonary heart disease, stroke and cancer that are attributable to obesity.

Here are the extant cases of hypertension

from NHANES III, NIDDM, coronary heart disease and cerebral vascular disease. We don't have good data on cancer. There are just too many unknown factors in getting that information.

Now the other side is the overweight-attributable column which adds up here to 20.7 million.

I believe these numbers, which begin to describe the magnitude of this public health concern, provide a useful background for the presentations of my colleagues, Dr. Manson and Dr. Bray.

Dr. Manson will describe new information about coronary heart disease risk and all cause and cause-specific mortality attributable to overweight generated by recent follow-ups of the Nurse's Health Study cohort.

She will also discuss recently published epidemiologic observations indicating that intentional weight loss, even modest amounts, can materially reduce these health and mortality risks.

At this point, I yield the floor to Dr. Manson.

DR. MANSON: Good morning. In terms of epidemiologic studies, the evidence is consistent and compelling that a body mass index of 27 and higher,

and especially a body mass index of 29 or higher, is associated with a substantial increase in risk of premature.

This slide shows our findings from the Nurse's Health Study, which is a prospective cohort study of more than 115,000 U.S. women aged 30 to 55 at entry. And these findings were recently published in New England Journal.

In this study, after we accounted for bias from cigarette smoking and underlying disease, we found that the women who had a body mass index 27 to 28.9 had a 60 percent excess risk of premature mortality compared to lean women.

Those women with a body mass index 29 to 31.9 had a 110 percent increase in risk. Those with a BMI greater than or equal to 32, 120 percent increase in risk.

Thus, those women who had a body mass index of 29 and higher had double the excess mortality of women with a body mass index of 27 to 28.9.

Overall, we found a strong positive association between body mass index and risk of mortality in this cohort of women. And the excess was substantial beginning with the body mass index of 27 to 28.9.

We estimate in this study population that about 23.3 percent of the deaths were directly attributable to overweight.

In terms of specific causes of death, we found strong associations between body mass index and risk of dying from cardiovascular disease and risk of dying from cancer.

For women with a body mass index of 29 and higher, the risk of dying from cardiovascular disease was three to four times the risk of lean women. And for cancer, the risk was twice as high as in lean women.

For cancer, the causes of death were primarily post-menopausal breast cancer, endometrial cancer and colorectal cancers.

Now similar findings have been observed in studies among men, and especially those larger scale prospective cohort studies that have accounted for the bias from cigarette smoking and underlying disease, have found very comparable results in men; specifically, the Harvard University Alumni Study, a very large scale American Cancer Society Study, Seventh Adventist Study and the Framingham 30-year Follow-Up Study.

Now mortality is not the whole story,

however, and there is very important increase in morbidity and non-fatal illness related to overweight.

In the Nurse's Health Study, we also looked at total coronary heart disease, recently updated our findings in JAMA and the total coronary heart disease was comprised primarily of non-fatal MI, as well as fatal CHD constituting a smaller proportion of events.

We found a very strong positive direct association in women between body mass index and total coronary heart disease.

The women who had a body mass index 25 to 28.9 had about double the risk of coronary heart disease events as lean women. Those with a body mass index 29 and higher had 3.6 times the risk of coronary heart disease as lean women

Similar results have been observed in men in the Health Professional's Follow-Up Study, Framingham Heart Study and other prospective studies in men.

Now in the Nurse's Health Study, we found that regardless of starting point of the body mass index in early adulthood, substantial weight gain conferred an increased risk of coronary heart disease, especially a weight gain of 11 or more kilograms.

This is between age at 18, BMI at age 18, and risk of coronary heart disease during middle adulthood at the time of entry to the study.

We found for the women gaining 11 or more kilograms, there was three to six, even seven, times the risk of coronary heart disease.

The strongest association has been with non-insulin dependent diabetes. We found a very striking increase in risk of NIDDM among women according to their body mass index. And those women who had a BMI 27 to 28.9 had nearly 20 times the risk of developing NIDDM as lean women.

And once the BMI was 31 or higher, the relative risk was as high as 40.

Now we've looked at the association between weight loss in early adulthood and the risk of subsequent NIDDM, and found that after taking into account the BMI in early adulthood at age 18, a weight loss, even a modest weight loss of only five to 10.9 kilograms, was associated with about a 50 percent reduction in subsequent development of NIDDM.

The women who had lost 11 to 19.9 kilograms had about a 75 percent lower risk of NIDDM. And those women losing at least 20 kilograms had an 87 percent lower risk of developing NIDDM in middle

adulthood.

Thus, even a very modest weight loss, five to 10.9 kilograms, nearly halved the risk of subsequent NIDDM.

Now previous studies of weight loss have been limited by not having information about whether the weight loss was intentional or unintentional. And one very important study that was recently published by David Williamson and colleagues at the Center for Disease Control had the ability to look at intentional weight loss specifically.

And in an American Cancer Society cohort, they looked at over 28,000 obese women who had -- age 40 to 64, who had no pre-existing illness. And they found that an intentional weight loss of 20 or more pounds, 9.1 kilograms or more, within the previous year was associated with a statistically significant 25 percent reduction in all cause, cardiovascular and cancer mortality.

They also looked at a sub-group of women, over 15,000 women, who had a body mass index of 27 and higher who had co-morbid conditions including coronary heart disease, hypertension, stroke, diabetes, et cetera.

And they found that an intentional weight

loss of any amount, even a very modest weight loss, was associated with a 20 percent reduction is all cause mortality, 30 to 40 percent reduction in diabetes-associated mortality, and a 40 to 50 percent reduction in mortality from obesity-related cancer.

So in conclusion, the epidemiologic research is strong and persuasive that even moderate overweight confers an increased risk, a marked increased risk of morbidity and mortality, and that intentional weight loss of even a modest amount can substantially reduce morbidity and mortality.

With that, I'm going to turn the podium over now to Dr. George Bray.

DR. BRAY: Thank you, Dr. Manson. Good morning, ladies and gentlemen, members of the panel and guests.

Not only is obesity a hazard to health, it increases costs of health care. And I've taken for this point data of Colditz from the Harvard School of Public Health where he has taken the costs attributable to obesity for a variety of diseases and summarized them, the leading one being cardiovascular disease with 22.2 billion estimated as attributable to obesity, 17 billion from musculoskeletal disease, and primarily osteoarthritis, and 11.3 million

attributable to the obesity that is related to diabetes.

The total for this group of six illnesses in his paper is 56.2 billion or 7.8 percent of total U.S. health care costs.

So not only is obesity a serious health risk, it is a major economic one as well.

That reduction in weight is beneficial has been suggested from the data Manson has reviewed a moment ago.

I have taken some additional data from a paper that Scott Grundy presented at a symposium earlier this year in which he estimated the effects of changing weight by 20 pounds on cholesterol, HDL cholesterol and blood pressure and the changes in cardiovascular risk, coronary heart disease risk, which would be attributable to these reductions in cholesterol and blood pressure and increase in HDL.

And the total attributable risk reduction by this 20 pound weight loss would be 31 percent. So it is a significant benefit with weight loss and a significant reduction in health care costs.

Obesity has many causes, and I've listed here some of these. In most cases, we cannot specify which one it is.

But in a condition which has a variety of different causes in a complex mechanism, one would anticipate a variety of treatments. And in this slide, you can see that many treatments have been used.

My analogy in treatment is with hypertension where a stepped approach using individualized drugs from a variety of different mechanisms for treatment are beneficial to a larger number of patients than any single drug by itself.

And I would suspect that precisely the same will be true for obesity as the armamentarium of available drugs increases. And this is the first new one to come before the panel in a long time.

When treatments are not used, weight regain is the expected. Where it's behavior or pharmacologic, drugs only work when used. You don't lower blood pressure permanently with a short-term treatment with an anti-hypertensive drug, nor do you lower cholesterol permanently with short-term treatment with an anti-cholesterol agent.

And similarly, you don't get and you should expect long-term effects on weight for people who have major problems if long-term treatment is not used.

These data on recidivism on weight regain are summarized from the Consensus Conference held at the NIH where drop-outs in most trials range from 20 percent or slightly less to up to 80 percent where weight regain at one year is of the order of 30 percent of more.

And by three years, most patients who are no longer in treatment will have regained weight as you would expect.

But in summarizing this first section, we have tried to make several points. And I will briefly review them and then turn the podium over to Dr. Wurtman to review the pharmacology of Dexfenfluamine.

First, obesity is a chronic disease which is increasing and prevalent. Second, obesity increases the risk for mortality and morbidity as shown so nicely in the work of Dr. Manson

Third, obesity increases health care costs to a major degree accounting for nearly eight percent of total health care costs.

Intentional weight loss of five to ten percent can significantly reduce the risks associated with obesity.

Obesity has many causes and many treatments, and it is the availability of multiple

localities for treatment, which I think will greatly improve our ability to effectively deal with this major health problem.

Finally, treatments don't work when not used. And recidivism is not only thus common, it is to be expected.

Dr. Wurtman, would you please review for the panel the mechanisms for action of Dexfenfluamine?

DR. WURTMAN: Thank you, Dr. Bray. Let's see, I'd like to introduce the pharmacology of Dexfenfluamine by showing you the compound. This is Dexfenfluamine. And you'll notice that it's a substituted phenyl ethyl amine.

The substitutions are alpha carbon. The most important one is probably this trifluorocarbon here, which I think is what makes it a serotonin drug and not a dopamine drug. And then this ethyl comes off the amine.

And if you look at the compound, it strikes you that it looks a lot like amphetamine. That's the only resemblance it has to amphetamine.

Amphetamine works by releasing catacholamines and blocking their re-uptake. So when the brain -- it works via dopamine principally.

This compound has no effect on

catacholamines. This compound works solely by increasing serotonin-mediated neurotransmission. And as you'll see, it does so by three mechanisms involving inhibition of re-uptake, direct release and via metabolite direct stimulation of post-synoptic serotonin receptors.

Now you'll notice that there's an asymmetric carbon here in Dexfenfluamine. That's why there can be a Dexfenfluamine and a Levofenfluamine.

All of the therapeutic activity of fenfluamine derives from the dextro isomer, from this isomer here.

The L-fenfluamine, which comes along in racemic fenfluamine is a dopamine drug, but it's a dopamine receptor antagonist, and it has no contribution to the therapeutic utility of Dexfenfluamine.

The principal metabolite of Dexfenfluamine is the de-ethylated compound. That is Dexnorfenfluamine. And his metabolite, which accounts for about half of the total present in brain at steady state has very important biological activities.

As we'll see, Dexfenfluamine, by itself, is principally a serotonin re-uptake blocker. But Dexnorfenfluamine directly releases serotonin into

synapses and Dexnorfenfluamine also activates the post-synaptic 5HD2 receptors.

And all three of these effects participate in the physiologic action of the drug.

Now a brief description of what happens within serotonin nerve terminals, the actions of the drug. This is a serotoninergic nerve terminal. And as you can see serotonin -- is that in focus? It's complicated enough.

The serotonin nerve terminal was synthesized from tryptophan, and then serotonin in then released into the synaptic cleft.

The serotonin interacts with post-synaptic receptors, principally 5HD2 receptors, but also interacts with pre-synaptic receptors which tend to inhibit the subsequent synthesis and release of serotonin.

And it's activated by being taken back up by a re-uptake pump.

Now when Dexfenfluamine is administered and when the brain contains Dexfen and Dexnorfen, there are three actions again. The Dexnorfen enhances directly the release of serotonin into the synapse. The Dexfen suppresses the re-uptake of serotonin, and the Dexnorfen act directly on post-synaptic on

serotonin receptors.

If one gives mega-doses of Dexfenfluamine to animals, that is doses that raise brain levels to at least ten times higher than they are in people taking the drug, then this enormous in serotonin in the synapse, feeding back via pre-synaptic and also post-synaptic receptors, slows the firing of the serotonin neuron and slows the synthesis of serotonin and produces prolonged, but entirely reversible, decreases in brain serotonin levels.

Dr. Moore will discuss this in more detail in a few minutes.

So comparing the pharmacology of Dexfenfluamine with previous drugs given for obesity, Dexfenfluamine is not a sympathomimetic agent.

Dexfenfluamine has no effect on norepinephrine release. It doesn't raise blood pressure. It doesn't increase dopamine in the brain.

What it does do, as I've said, is to inhibit the re-uptake of serotonin, release serotonin and act as a serotonin antagonist these last two via its metabolites.

In contrast, the amphetamine-like drugs release norepinephrine in the periphery, raise blood pressure, release dopamine in the brain, and can act

directly as adrenergic agonists.

So I think the key to this compound is its chemistry. The key to the compound is that it's different from the other anorexic drugs in that it's a serotonin drug, not a catacholoaminergic drug.

Now what -- a little bit about the pharmaco-kinetics and the metabolism of the compound: firstly, the bio-availability of the compound is good, about 68 percent. It crosses membranes well and distributes well and is absorbed well.

Only a little bit of it binds to protein, and so this decreases the likelihood of significant drug interactions.

The volume of distribution is quite large. And the half-life of the compound is about 18 to 19 hours, which is compatible with twice-daily administration of the drug. And that's how it's been given in all of the studies reported in the new drug application.

Something that's not shown in this slide is the fact that, as you'll see later, the drug does not accumulate in the brain. It reaches a steady state in the blood in three or four days, and in the brain a little bit thereafter.

And so as you'll see, brain levels of the

compound at ten days, 30 days, 90 days of treatment are the same.

Now how does it work? Well, serotonin, by itself, has at least three effects that tend to reduce body weight.

Firstly, drugs that release serotonin or the direct placement of serotonin in the brain tends to increase satiety. So the animal or the human starts as many meals, but the meals tend to be smaller.

Secondly, serotonin suppresses the inappropriate craving for carbohydrates, which drives a lot of people to overeat snacks, snacks which unfortunately are also full of fat which can contribute many calories.

And thirdly, serotoninergic drugs have a small effect on basal energy utilization, about 100 calories per day.

The involvement of serotonin in appetites was shown by -- a few months ago. Maybe you saw the study showing that knock-out mice that lacked 5HD2 receptors had a big increase in weight because they ate too much.

So Dexfenfluamine will reduce daily calorie intake by these mechanisms by about 400 to 600

calories per day, and will increase basal energy utilization by another 100 calories per day.

So the net of therapeutic doses is about 500 to 700 calories per date, either reduced intake or increased use.

Dexfenfluamine tends to work in virtually all of the animal models of obesity in which it's been studied, including, by the way, the Ob/Ob mouse. It's very effective, the Ob/Ob mouse.

So whether the animal becomes fat because you squeeze its tail or it has a bad gene or you gave it sweet foods or what you, the drug tends to work in all the animal models that have been studied.

In studies on people, it's been shown the drug also decreases food intake. Every study in which food intake has been measured, whether it be meal intake or snack intake or both, it's been shown to suppress food intake.

This is just a summary of those studies. Let me show you an example of one such study we've done in which we took subjects, we treated them for eight days with therapeutic doses and then measured, in our clinical center, how much they ate and broke it down into protein and carbohydrates and fat.

What you see here are data on total

calories, proteins and carbohydrates. And the point is it reduces mealtime calorie intake about 300, reduced snack intake by about 300 here.

The entire significant reduction here was in carbohydrate, and of course in fat intake. It tends to be selective. It does not significantly reduce protein intake.

So in summary, Dexfenfluamine works by increasing serotonin mediated neurotransmissions by at least three different mechanisms. And it is not a sympathomimetic.

It enhances satiety and reduces daily calorie intake. It also slightly increases energy utilization and results in a net decrease of about 500 to 700 calories per day.

I would now like to introduce Dr. Robert Moore, who will describe in more detail the neurochemical effects of very large doses of Dexfenfluamine in animals.

DR. MOORE: Thank you, Dr. Wurtman, members of the Committee. It is my task to discuss the interpretation of the neurochemical effects of large doses of Dexfenfluamine given to animals.

This has a long history that I will not recount. The issue is, and has been, whether the

neurochemical effects from Dexfenfluamine in animals indicated potential risk to humans.

Acute decreases in brain serotonin content have been observed following high dose Dexfenfluamine administration in animals, and prolonged decreases have also been reported, as Dr. Wurtman indicated.

All of the currently available evidence indicates that the reduction in serotonin content is observed with high dose Dexfenfluamine administration represents a pharmacologic and not a neurotoxic effect.

There is no study to date that has reported any finding that could be interpreted as histologic lesion.

We can look at the alternatives in terms of the explanation of the reductions by looking at these cartoons of a serotonin neuron.

The serotonin neuron is an unusual neuron. It has a cell body in the brain stem and a long axon that extends into the forebrain and produces a widespread terminal plexis in the forebrain.

This shows an intact neuron with the intact terminal plexis.

One interpretation of the effects of high dose of Dexfenfluamine is that it is, indeed,

neurotoxic and that it prunes back the terminal plexis so that one would reduce the total number of terminal varicosities in the axons.

The alternative explanation is that Dexfenfluamine depletes the serotonin out of the axon terminal plexis. That is, the yellow part is gone, and what one sees is an intact plexis but with decreased serotonin content.

To put this into somewhat of a real context, this shows you the serotonin neuron cell bodies in the mid-brain RAPHE nuclei and the dorsal RAPHE here. Each of these brown dots is a cell body of a single neuron.

These neurons have axons that go out to here. This lazy network of fibers that you see is in the frontal cortex.

The bulk of the evidence available now supports the depletion explanation that I offered you a few moments ago. The basis for this is that the depletion of serotonin is not associated with indices of neuron damage.

These indices are such things as abnormal accumulation of silver with certain silver stains and argyrolfiliam. One does not see this with Dexfenfluamine in doses that deplete serotonin

content.

Similarly, the damage of axons will produce a response of other elements in the nervous system. And lastly, retrograde transport is normal in the face of serotonin depletion.

If we again look at the cartoon of the serotonin neuron, that if this were to degenerate, as it degenerates, one would expect it to show silver staining. And this is not seen.

And similarly, one would expect to see silver staining in the cell bodies. And this is also not seen.

Further, if this were to degenerate, one would expect to see a response in non-neuronal elements surrounded in glial cells, a gliosis, an stral gliosis. And this is not seen.

And finally, a measure of integrity of the terminal plexis is achieved by placing a ligand in the vicinity of the terminals which is taken up by the terminals, and then retrogradely transported to the cell body where it can be shown by appropriate methods.

This retrograde transport is a function of the number of terminals that are present in the terminal plexis.

And so if this is reduced, one would expect to see retrograde transport reduced. And if there was a problem with the rest of the neuron, one would expect to see it not transported. And this is not effected.

If we compare Dexfenfluamine with a series of known neurotoxins that affect serotonin neurons, peraclonal amphetamine 5.7 dihydroxitriptamine and another methamphetamine derivative, MDMA, each of these produces argyrofiliam. Each of them produces gliosis.

And each of them that has been tested produces a reduction in retrograde transport. In contract, Dexfenfluamine does none of these.

We can look at this further by examining the effects of Dexfenfluamine given in 21-day oral dosing regimen to rats and then looking at long-term effects if this is done with doses of two milligrams, four milligrams, eight milligrams and 16 milligrams per kilogram.

And the results are shown as percent of control for everything except the four, eight and 16 milligram per kilogram which are shown as percent of pair-fed control.

With this, you can see that there -- at

one week, there is an acute decrease in serotonin content with the high dose administration of Dexfenfluamine, that this begins to recover as time goes on at 13 weeks, and that it is effectively totally recovered by six months.

There is no difference between the pair-fed control and the high dose Dexfenfluamine treated animals.

In another study, which I think is extremely important with respect to looking at the long-term effects of Dexfenfluamine, this study was one in which mice were administered 27 milligrams per kilogram per day of Dexfenfluamine in feed for 106 weeks.

Again, the results are expressed as a percent of the control values. And in this, at the end of two years of treatment, there was no change in serotonin content in the brain. In addition, there is no change in paroxetine binding.

Paroxetine binding is another independent measure of the integrity of the plexis that shows the serotonin transporter in the axon terminals.

And so with both of these, there is no change at the end of two years. And two months later, there is still no change in either of these measures.

And at the end of treatment, the brain level is 51 micromolar. And you will see subsequently that this can compared to the brain level that one obtains in humans with a therapeutic dose, which is the range of about four micromolar.

There have been some concerns about extrapolating from animal studies to human studies. Can one use the animal studies?

And in extensive analyses done by the Servier Company, they have shown that the acute effects of Dexfenfluamine on brain 5HT levels are related to combined brain Dexfen and Dexnorfen concentrations, and that this is quite stable across rats, mice and a series of primates.

Thus, it appears that the species' differences that are seen are pharma-kinetic rather than wild species' differences.

With this background, we can look at the issue of human brain levels obtained with therapeutic treatment. The therapeutic dose of Dexfenfluamine is 15 milligrams BID.

In this study, a series of obese patients was administered Dexfenfluamine over as period of 90 days. And at ten days, 60 days and 90 days, brain concentrations of Dexfenfluamine and Dexnorfenfluamine

were measured by magnetic resin and spectroscopy, a new method that allows one to obtain accurate measurements of fluoridated compounds in the brain.

And at the beginning of the study, you can see that the concentrations were zero. At ten days, as Dr. Wurtman indicated, the concentrations are slightly above four. And these remain stable throughout the remainder of the period of treatment.

Thus, there is no accumulation of Dexfenfluamine and its metabolite in the brain with prolonged therapeutic treatment.

Thus, I think we can say that acute high dose Dexfenfluamine administration produces reversible changes in brain serotonin content in animals without evidence of neural damage.

High dose Dexfenfluamine administration to mice for up to two years produces no alteration of brain serotonin or brain trans-serotonin transporter content.

Human brain Dexfenfluamine and Dexnorfenfluamine concentrations are stable and do not accumulate with extended treatment. The brain concentrations achieved in the two year mouse study with high dose administration a no-effect level with respect to serotonin content predict at least at least

a ten-fold margin of safety.

And let me now introduce Dr. Bobby Sandage who will speak about issues of ethicacy and safety.

DR. SANDAGE: Thank you, Dr. Moore, members of the Advisory Committee and guests. We're here today to seek the Committee's recommendation on the approvability of Dexfenfluamine for the management of obesity for patients on a reduced calorie diet.

The first part of my presentation sill concentrate on the ethicacy of Dexfenfluamine, primarily focusing on the placebo-controlled trials and open label long-term trial.

I will also discuss several studies in obese patients with co-morbid conditions and discuss what we believe is a medically prudent way of using Dexfenfluamine for those patients most likely to benefit from treatment.

The second half of my presentation will concentrate on the safety database.

There were 18 double-blind, placebo-controlled weight loss trials and one dose ranging study that together enrolled over 2,300 patients.

Twenty-two other trials are included in the database, bringing the grand total of patients and subjects in the NDA to almost 4,600.

Placebo-controlled trials included approximately 800 patients from the United States plus approximately 1,500 patients from Europe with an additional 2,000 patients coming from uncontrolled studies, primarily from Europe.

The NDA database included 85 percent women whose average age was 40 years old. The BMI of approximately 27 was used as the entrance criteria for the clinical trials.

In actuality, they had body mass indices that averaged 33, 34 milligrams per square meter across all studies.

In addition, they approximately 50 percent over their idea body weight.

I'd like to concentrate my presentation on these four placebo-controlled weight loss studies. First, a three-month dose ranging study was conducted in the United States in two six-month studies in which patients who had some success with a diet prior to randomization.

And then finally, I'll discuss the one-year multi-center trial conducted in Europe.

I'd like to point out that though I'll present only the four placebo-controlled studies that I showed you on the last slide, the remaining 15

trials showed Dexfenfluamine produced more weight loss than placebo.

Weight change in kilograms is listed on the Y axis and the individual studies run along the X axis.

Dexfenfluamine is shown in green and the placebo in red. The difference reached statistic significance in 14 of 15 of these other controlled trials.

The first study I'll present is the dose-response study. These patients were to be at least 20 percent above their ideal body weight at entry, which was approximately a BMI of 27.

In actuality, they were an average of 50 percent over their ideal body weight at entry, and had an average BMI of 34.

They are well-matched at baseline for all other key demographic parameters.

Following a two-week run-in period when the patients were placed on a diet, which was a Weight Watchers like, or also described as a balance deficit diet, of 1,200 to 1,400 calories for women and 1,600 to 2,000 calories for men, 339 patients were randomized to either placebo twice a day, Dexfenfluamine five milligrams twice a day,

Dexfenfluamine 15 milligrams twice a day or Dexfenfluamine 30 milligrams twice a day while remaining on this diet.

Patients were then treated for 12 weeks, and the study included a four week post-treatment period.

The results are shown on this slide: time in weeks plotted on the X axis and weight change expressed as a percent of initial weight plotted on the Y axis.

There was a statistically significant linear dose response observed.

The Dexfenfluamine 15 milligrams, shown in green here, and the 30 milligram BID group shown in blue here, produced a statistically significant more weight loss than did the placebo shown in red and the five milligram BID dose group shown in yellow.

No statistical difference was observed between the 15 milligram BID dose group and the 30 milligram BID dose group.

The 15 milligram BID dose appears to be an effective dose producing significant weight loss. And as I will describe later, it was used in all the other clinical trials.

In addition, the 15 milligram BID dose was

well tolerated in comparison with the 30 milligram BID dose. The higher dose showed a doubling of discontinuations due to adverse events compared to the other doses.

The placebo discontinue rate was 7.1 percent. The five milligram at the low dose was 4.7. The 15 milligram BID was 8.5 and the high dose group had a discontinue ration rate at 16.1.

We have not extensively studied doses higher than 15 milligrams BID, so there are no recommendations for the physician to increase the dose.

The next study was conducted by Dr. Rudolph Noble in the United States. He recruited patients who had been on a diet of their choice and had lost four and a half kilos in the previous year.

In actuality, each group had lost on average about 7.5 kilograms during the past year.

Following a four-week run in period where the patients were to have a stable weight, they were then randomized to placebo or Dexfenfluamine 15 milligrams twice a day with a diet of 1,200 calories for women and 1,500 calories for men.

Patients were treated and followed for six months.

As you can see from this slide, the patients were well matched from gender, age, height, weight and BMI, and were approximately 50 percent over their ideal body weight as determined by the Metropolitan Life Insurance Company tables.

Dexfenfluamine, shown in green here, was shown to produce significantly more weight loss when compared to placebos, shown in red, using the last observation period for analysis.

The difference was seen within the first month of treatment and continued for the duration of this six-month study.

The treatment differences approached five percent when analyzed for observed cases. Approximately 65 percent of the patients completed the study.

Now the FDA and this Committee have been evaluating other ways of analyzing weight loss data. One of these methods involves using what has being called a responder analysis, specifically, determining the percentage of patients that have achieved either a five or ten percent weight loss by the end of the study.

As you can see in this analysis, when this analysis was applied to this study, more than twice as

many patients treated with Dexfenfluamine achieved five percent weight loss, and almost three times as many reached a ten percent weight loss.

The results were even stronger when you look at the complete observed cases.

Another analysis that has been suggested by the FDA and this committee is to compare the distribution of percent of patients achieving a certain amount of weight loss by weight loss category.

And when this categorical analysis is applied, you can see that more patients in the placebo group, in the red, did not lose or gain weight rather than lost weight which actually shows the amount of recidivism that you might expect with diet alone.

In contract, there was a higher percentage of patients that lost five to ten percent or greater than ten percent of their initial weight when compared to the placebo.

Now this trend using the last observation carried forward failed to reach a statistical significance, although the analysis of the observed cases or completers did reach significance.

The next study I would like to present was conducted by Dr. Nicolas Minor in the United Kingdom. The study is known as UK-18.

Now this study enrolled patients that were 50 percent over their ideal body weight, and might be considered by some experts as being morbidly obese.

Patients entered an eight-week, very low calorie phase run in diet that restricted the patients to only 330 calories a day.

The investigators, by no coincidence, chose the Cambridge diet to use in this study.

The patients were randomized to either placebo or Dexfenfluamine 15 milligrams twice a day with a diet that included adding 200 calories in snacks and 400 calories in meals, bringing the total daily calorie intake for these people at randomization just over 900 calories.

Patients were then treated and followed for 26 weeks. Again, the patients were well matched with respect to demographics except placebo patients were, on average, several years younger than the Dexfenfluamine treated patients.

Now prior to reanimization, the very low calorie diet here produces significant drop in body weight over the eight-week run in period of approximately 11 percent.

At times zero here, the patients were then randomized to one of the two treatment groups.

As you can see from this figure, Dexfenfluamine-treated patients continued to lose an additional 40 percent of their body weight and maintain it over the 26 week period.

This was compared to the placebo group who gained 2.3 percent by the end of the study.

Now 26 weeks, this difference here, reached 6.3 percent between the two groups. Approximately 70 percent of the patients completed this study. And the observed cases analysis was very similar.

When the responder analysis was applied to this dataset, significantly more Dexfenfluamine-treated patients achieved a five or ten percent weight loss from the point of randomization when compared to the placebo group.

Almost a seven-fold increase was observed in the placebo -- in the five percept respondent group, and no patients treated with placebo achieved a ten percent weight loss over the six-month treatment period using either the last observation period forward or completers.

Again, when the categorical data was applied to this dataset, statistically significant difference was observed between the treatment groups

K almost 65 percent of the patients not losing any weight or gaining weight on placebo versus approximately 75 percent of the patients treated with Dexfenfluamine losing weight and remaining stable after this very low calorie diet run in.

The last of the four studies is known as the INDEX trial. "INDEX" stands for the International Dexfenfluamine Study. This study was conducted in 24 centers in nine countries in Europe.

Patients who were at least 20 percent over their ideal body weight were first enrolled into a 15 day run in period with a diet that was administered according to that clinic's usual practice.

These diets averaged approximately 1,400 calories a day across the centers during the treatment period.

They were then randomized to either placebo or Dexfenfluamine twice a day.

Patients were stratified at randomization into two groups: those between 20 and 35 percent of their ideal body weight, or those greater than or equal to 35 percent of their ideal body weight.

Patients were then continuously treated for 12 months and followed for two months of post-treatment.

There were no differences between the two strata and the absolute weight change. Therefore, I'll only show you the pooled data.

As you can see from this slide, the treatment groups were again well matched. The average BMI was 35 and the patients were approximately 57 percent over their ideal body weight.

Now the protocol defined end points included a change in baseline in body weight, percentage change from initial body weight, percent change in the amount of overweight, and the percent of patients losing either five, ten or 15 percent of their initial body weight.

Now that conforming produced statistically significant differences in all analyses. But I'll only present the percent change in the body weight in the responder analysis.

The Dexfenfluamine, shown in green here, produced significantly more weight loss when compared with placebo in red beginning at month one and continuing for the full 12 months of the study.

Patients on average reached their nadir at approximately six months, and then the weight stabilized after that point.

Dexfenfluamine and placebo differences

were statistically significant in both strata. It's worth noting that greater than five percent difference was observed with the treatment groups when percent change per baseline was analyzed by intra-strata for those between 25 and 30 percent of their ideal body weight.

Now by the end of the study, approximately 50 percent of the placebo patients and 40 percent of the Dexfenfluamine-treated patients had dropped out.

And with this drop-out, it is important to assess the magnitude of treatment effect in the early drop-out groups.

Therefore, we conducted an analysis of drop-out cohorts. Specific placebo cohorts are represented in red here, and are delineated by different symbols.

Dexfenfluamine cohorts are in green and also have matching symbols to their placebo cohorts.

For example, at month two, 50 patients treated with placebo dropped out and 39 Dexfenfluamine-treated patients. The purpose of this analysis would see if any of the early drop-outs responded differently than the patients that continued.

And as you can see, the difference noticed

between the cohorts were similar. So there are no apparent reasons for differences in early drop-out groups in response to the drug.

Moving on to the responder analysis, we found significantly more Dexfenfluamine patients achieved a five, ten or 15 percent weight loss when compared to placebo.

Sixty-four percent of the Dexfenfluamine patients lost at least five percent of their initial body weight compared to only 43 percent of the placebo group.

For observed cases, this difference was 22 percent or 72 versus 50, which is actually a 44 percent, additional 44 percent of the patients, achieved a clinically significant amount of weight loss.

Forty percent versus 21 percent achieved a ten percent weight loss and 21 versus ten percent achieved a 15 percent weight loss.

When the categorical analysis was applied to this data, there were more patients that had no weight loss or gained weight with the placebo, whereas more patients not only lost weight when treated with Dexfenfluamine, but lost more weight when treated with Dexfenfluamine.

And when you perform the same analysis on change in BMI units, 65 percent of the Dexfenfluamine-treated patients lost greater than two BMI units compared to 38 percent of the placebo- treated patients.

Additionally, 34 percent of the Dexfenfluamine patients lost greater than four BMI units compared to only 17 percent of placebo-treated patients.

Although no a placebo-controlled trial, I'd like to present one other trial, a one-year treatment study trial.

Now this study is known as the EFIM Trial and was conduced in France and involved 293 centers. One thousand, eight hundred and thirty five patients were enrolled into this study.

And as you can see, we're very similar to those patients in the controlled trials.

In this setting of actual clinical use, Dexfenfluamine produced weight loss similar to that seen in the INDEX trial of approximately ten percent of their initial weight over the one year period.

Although for this categorical analysis I don't have a placebo comparative group, it is worth noting that this study showed that 75 percent of the

patients lost more than five percent of their baseline body weight, and a majority of patients lost greater than a ten percent from their baseline weight.

Now as you've heard from Drs. Bray, Manson and Van Itallie, weight loss, in and of itself, is an extremely more important medical intervention for the improvement of morbidity and mortality of all obese patients.

Additionally, the weight management of patients that have co-morbid conditions related to their obesity is extremely important.

Although it was not the focus of our NDA, there had been a great deal of data generated in obese patients with some typical co-morbid diseases, such as hypertension, diabetes and dyslipidemia. And we thought it would be important to show this to the Committee.

Now many of these studies involving obese hypertensive patients are short-term, clinical pharmacology-type experiments.

We knew the Agency and this Committee would be interested in the long-term effects of Dexfenfluamine with blood pressure. Therefore, we conducted a post-hoc analysis of the INDEX database.

Now what this graph shows is a cohort of

patients who were identified at baseline as having a diastolic blood pressure of greater than or equal to 90 millimeters of mercury.

Two hundred and 13 patients randomized Dexfenfluamine and 208 randomized the placebo, fit this criteria. Baseline diastolic pressures were not different and were on the average of between 99 and 98 millimeters of mercury.

And as you can see, Dexfenfluamine produced a beneficial effect beyond that scene with placebo and reached statistical significance in month one, two, four, eight, ten and 12.

If you do the same analysis for patients who, from medical history, were identified as having hypertension, the significant differences were observed at month two, six, eight and ten.

Now on this slide, I plotted the change in hemoglobin A1C in four placebo-controlled studies in which Dexfenfluamine was given to obese diabetic patients ranging from three to 12 months.

The Dexfenfluamine is shown in green and produces statistically significant beneficial drop in hemoglobin A1C in all four studies.

In the interest of time, I'll not discuss the details of these studies. However, Dr.

Rubinstein, a renown expert in the field of diabetes from the University of Chicago, has reviewed this data, is here with us today, and would be glad to field questions at the end.

Dexfenfluamine has also been given to a group of obese dyslipidemic patients for three months on a baseline total cholesterol average 282 milligrams per deciliter.

In this placebo-controlled study, Dexfenfluamine was found to significantly lower cholesterol by 13 percent, the LDL cholesterol by 32 percent, the LDL triglycerides by 15 percent.

Favorable trends were seen with triglycerides LDL and HDL, although these last three variables did not reach statistical significance.

As with blood pressure, we also conducted a post-hoc analysis of the INDEX database evaluating the effect of Dexfenfluamine on total cholesterol levels.

Like hypertension, it shows a cohort of patients who were identified at baseline as having elevated total cholesterol levels of greater than 250 milligrams per deciliter.

Sixty-one patients in both treatment groups fit this criteria. Baseline cholesterol levels

were not different and were, on average, about 285 milligrams per deciliter.

Percent change from baseline is shown on the Y axis here. And the two time points where cholesterol was measured were shown on the X axis.

As you can see, Dexfenfluamine produced a significant beneficial effect beyond that seen with -- at both six and 12 months.

We found that Dexfenfluamine produced significantly more weight loss than placebo in 18 of 19 control trials including the dose response study.

The actual difference in percent of weight loss from placebo ranks from two to eight percent, depending on the duration of treatment in the placebo response.

Regardless of how weight was assessed, whether by percent change from baseline, the responder analysis or categorical analysis, Dexfenfluamine was shown to be superior to the placebo.

Significantly more patients lost a clinically meaningful amount of weight than did the placebo-treated group.

Subset analysis and special studies indicate that Dexfenfluamine favorable affects blood pressure, glucose and lipids.

And although I didn't show the data, reduction in the amount of overweight, which is the emerging data suggesting that that is the real culprit in determining risk, was reduced anywhere from 15 to 50 percent in the Dexfenfluamine-treated group.

Now as I mentioned when I started my presentation, I wanted to show you what we believe is a unique approach for identifying those patients most likely to benefit from the therapy of Dexfenfluamine.

In other words, a simple way to limit drug exposure to those patients who are most likely to benefit.

A benefit was mutually agreed upon in discussions with the FDA as a ten percent weight losses from baseline.

Now this slide shows all the factors that we analyzed in an effort to find variables that would predict a potential responder.

Along with the treatment group, we included the following variables in this statistical model: gender, age by several categories, activity level, alcohol use, smoking status, duration of obesity, family history of obesity, and whether a four pound weight loss was observed in the first month of treatment.

Now the inclusion of a one pound per week weight loss for the first four weeks of treatment in this statistical model was a suggestion made by the FDA and is the rate of weight loss consistent with the preservation of the lean body mass.

This analysis was applied to the INDEX study and the one-year open-labelled FM trial.

And as expected, Dexfenfluamine treatment was predicted of a ten percent weight loss. In addition, the observation of a four pound weight loss in the first month of treatment was predicted of a ten percent weight loss by the end of the study.

In practical terms, we found that 22 percent of the patients that randomized to Dexfenfluamine did not lose four pounds in the first month of therapy.

And 91 percent of those patients did not go on and lose ten percent of their body weight. This was compared to 78 percent that did lose four pounds as the first month -- but which 60 percent went on to lose ten percent of their body weight by month as well.

Therefore, we believe that a four week trial of Dexfenfluamine therapy is predictive of which patients are most likely to achieve a ten percent

weight loss with continued treatment.

And equally important, those patients unlikely to achieve a ten percent weight loss, we have proposed -- we have included language in the proposed package inserts suggesting to the physician that therapy should be discontinued. The patient has not lost four pounds in the first month of treatment.

I'd like to move on now to the safety database which was included in the NDA. The order of topics are listed here. I'll present the scope of the database, extent of disclosure, adverse events, discontinuations and conclude with a brief discussion of the proposed marketing experience.

First, I'd like to remind you that we collected safety information in over 3,000 obese patients exposed to Dexfenfluamine and compare those findings to the over 1,100 placebo-treated patients.

As you can see from this exposure chart, because our largest trials were also our longest, the majority of patients were treated for greater than six months with over 35 percent of the patients being treated for one year.

Within the body systems listed here, statistically significant treatment emergent events from the placebo-control trials that occurred in

greater than or equal to two percent include asthenia, which was described mostly by patients as a general weakness and chills as a body whole system; within the digestive system, diarrhea was noted.

Thirst was noted within the metabolic nutritional system. The nervous system included dry mount, somnolence and vertigo. Bronchitis was reported within the respiratory system, and urinary frequency and polyuria were reported within the uro-genital system.

Now we followed the patients with the most common adverse events: asthenia, dry mouth, diarrhea and somnolence.

And we found that these adverse events were self-limiting and subside over the first few weeks of therapy.

Now because Dexfenfluamine's action is primarily in the brain, I have listed all the CNS adverse events that occurred at a rate greater than or equal to one percent.

I have listed them in decreasing incidents and have highlighted those CNS adverse events that were found to be significantly different from placebo. They are dry mouth, somnolence and vertigo, as I listed on the previous slide.

So this slide shows the discontinuations for all the placebo-controlled trials. Sixty-seven percent of the Dexfenfluamine patients completed versus 63 percent placebo-treated patents.

Six point nine percent discontinued due to an adverse event in the Dexfenfluamine-treated group versus 5.2 in the placebo group.

Ineffective medication was five percent. The discontinue rate for Dexfenfluamine versus 9.4 percent discontinuation rate for the placebo group. All other groups were comparable.

There were no clinically significant differences in laboratory variables. Five patients discontinued due to abnormal laboratory findings, one Dexfenfluamine-treated patient and four placebo patients.

No adverse trends were observed in vital signs for electrocardiograms.

Post marking surveillance and experience has been accumulated since Dexfenfluamine was introduced in 1985. The reports have come from spontaneous prescriber reports, national adverse reaction centers in Europe, from clinical investigations and from the scientific literature.

As might be expected when treating 10

million patients, a number of sporadic, serious and adverse events in association with Dexfenfluamine treatment have been reported and are delineated in your background package that you received.

During the course of this post-marking experience surveillance, a single serious adverse event, primary pulmonary hypertension, has emerged as a possible epidemiological signal.

Although no cases of primary pulmonary hypertension were observed in the controlled clinical trials, a cluster of several cases were observed in -- after Dexfenfluamine was marketed in Europe.

A prospective case control study was conducted to evaluate this observation.

Now Dr. Jerry Faich, the next speaker on the program, and Dr. Abenhaim later in the day will discuss the findings of this case control study as it relates to Dexfenfluamine.

In conclusion, this NDA has documented numerous well controlled studies that Dexfenfluamine 15 milligrams twice a day, administered with a reduced calorie diet for three to 12 months is associated with a statistically significant and clinically meaningful weight loss in obese patients compared to patients treated only with a diet.

Dexfenfluamine 15 milligrams BID has also been shown in European and U.S. clinical trials to have good patient susceptibility.

We believe Dexfenfluamine represents a new effective therapy for the management of obesity with a highly favorable safety profile given the morbidity and mortality of obesity.

Thank you very much. I'll be glad to entertain questions from the Committee at this point.

CHAIRMAN BONE: Thank you very much. We would also have questions for any of the other speakers from the presentations. Dr. Kreisberg?

DR. KREISBERG: That was a very comprehensive -- I have -- I'm pressing.

CHAIRMAN BONE: No, you're not supposed to press. It says "push to mute."

(Laughter)

DR. KREISBERG: I knew I should have worn my glasses.

(Laughter)

DR. KREISBERG: It occurs to me in the presentation that perhaps Dr. Wurtman would address the issue of similarity and mechanism of action between the sponsor's drug and common drugs available

for psychiatric illness such as fluoxitene and paroxitene, and whether or not you would expect or predict any type of adverse interaction if a patient were on both types of drugs.

And then for Dr. Sandage, I just wonder if there were any male/female differences in ethicacy. I don't think that was addressed in any of the data that was presented.

DR. WURTMAN: I'm just trying to think if I'm really the right person to answer that first question. I can say one thing about it.

I guess the most commonly used psychiatric drugs now would be the serotonin uptake blockers. And Dexfenfluamine, of course, shares with Prozac, for instance, in that capacity.

It has these two additional capacities, I think, which explain why it maintains its long-term ethicacy without any change in dosage; namely, it releases serotonin and whether the neuron is firing or not, and its metabolite which does that also, interacts directly with post-synaptic receptors.

As far as interactions, I wonder if I could ask one of my colleagues to deal with that.

DR. COOPER: We haven't formally interactions between Dexfenfluamine and other

serotonergic drugs. But because of the similar mechanism of action to fluoxitene or paroxitene, we are recommending that the drugs not be combined in clinical usage.

We don't think that would be prudent. Your other question?

DR. KREISBERG: Had to do with male and female differences in ethicacy.

DR. SANDAGE: As I explained to you, the database is primarily females, 85 percent. But in those studies, we're -- in the key studies especially, we did look at gender effects, and there was no difference between male and female in response to Dexfenfluamine, although those samples were small.

DR. KREISBERG: Thank you.

CHAIRMAN BONE: Are there any questions immediately from the Committee members? I have a couple of questions that have to do with pharmacology. I'm not sure who the best person to answer this is, so --

DR. SANDAGE: Ask the question and we'll find out.

CHAIRMAN BONE: You have a twice daily dosing for a drug that achieves steady state in the brain and maintains that after several days. It's a

little surprising that you're using a BID dosing schedule, at least to me. Will you discuss that?

DR. SANDAGE: We did do early on a small study looking at giving it once a day, 30 milligrams once a day, of what we believe the total daily dose, effective dose, is and paired that to 15 milligrams PID.

And there were twice as many side effects with the single dose compared to the BID dosing. So it seems to be better tolerated when you split it up and you don't get accumulation with the drug.

CHAIRMAN BONE: I see. Okay, other questions? Dr. Critchlow?

DR. CRITCHLOW: Again, that was a very clear presentation. I just have two questions just for clarification.

In the UK-18 study, was the baseline considered the pre-very low calorie diet?

DR. SANDAGE: No, at the point of randomization, it was open label up to the time the patient was --

DR. CRITCHLOW: So in the responder analysis, those figures were pre --

DR. SANDAGE: The responder analysis starts at the --

DR. CRITCHLOW: -- at the point "O?"

DR. SANDAGE: -- time count of zero, at the time of randomization.

DR. CRITCHLOW: At the time of randomization, which is after the --

DR. SANDAGE: Right.

DR. CRITCHLOW: -- after the diet? And on the -- among those with co-morbid conditions, did you see similar increases or improvements in measures if you looked at people with borderline diastolic blood pressure of say 80 to 89 or similarly in the borderline elevated cholesterol?

DR. SANDAGE: Yes, we didn't do that specific subgroup. I can tell you that in general, the patient population, obese patient populations, are borderline to start with.

And although it wasn't consistent in patients that were not classically hypertensive, there was a beneficial effect, although it didn't reach statistical significance all the time. But in those, clearly it would be categorized as hypertension if there was an effect.

CHAIRMAN BONE: Dr. Sherwin?

DR. SHERWIN: Just two questions. One relates to the differences between this drug and

Pondimin, which has been available for a while. Has the company looked or compared the two drugs in terms of ethicacy, and what is the data on that?

DR. SANDAGE: No, there have not been any long-term comparative trials with the two drugs that have been conducted.

DR. SHERWIN: The other question relates to the duration effect. Clearly you get an initial response and the response slows down the time. And this seems to be related, at least in animal studies perhaps, to re-accumulation of their transmitters in the brain or at least restoration.

And the question is, what would you predict long-term -- I mean, do you think that there would be a waning effect of the drug over time given those two phenomenons in a shorter-term study?

DR. SANDAGE: Well, I'll try to answer part of that, and then I think Dr. Wurtman has a couple of comments.

As he stated in his first comment, this has a dual action, not only a block re-update, but it will also release it. So even if you get the feedback, you continue to get an effect.

I think the one year data strongly suggests that the effect does not wane. It can reach

a plateau.

And as Dr. Bray said, there are many causes of obesity and we're affecting maybe just one piece of that in bringing the patients down to a certain point. And that's all the drug is probably going to do.

DR. WURTMAN: When you give therapeutic doses of Dexfenfluamine, there are no changes in brain serotonin. There is no depletion of serotonin.

This only occurs when you given the mega-doses that raise brain levels to at least ten-fold higher than they are in people. So I don't think the obtaining of a plateau in many people is related to the fact that the serotonin neuron is now functioning at a different state.

CHAIRMAN BONE: Dr. New and then Dr. Illingworth?

DR. NEW: Was any attempt made to estimate what the caloric intake was during this period of weight loss on Dexfenfluamine?

DR. SANDAGE: Well as Dr. Wurtman said, there are a number of studies that have been done to look at that. And in our long -- yes, in the controlled clinical trials, the only two studies he conducted, he brought the patients in, kept them in-

house and counted in a very systematic, well done way caloric intake.

The other studies, we tried using diaries, and it was not very consistent results.

DR. NEW: I just found it remarkable that patients with a BMI of 32 to 35 could stay on a 900 calorie diet for 12 months.

DR. SANDAGE: The 900 calorie diet was in the UK study, but they -- as you remember, they were supposed to be on a 900 calorie diet, but they regained 2.3 percent of the weight they lost. So people were cheating obviously.

DR. NEW: Okay, thank you.

CHAIRMAN BONE: Dr. Illingworth?

DR. ILLINGWORTH: You commented that the weight loss was due to reduction of caloric intake, but also an increase in metabolic rate.

Does this persist with long-term therapy?

DR. SANDAGE: Dr. Wurtman?

DR. WURTMAN: I don't think it's been examined over the long term. I think these are short-term studies.

DR. ILLINGWORTH: It would seem to be an important thing to look at under carefully controlled metabolic conditions.

DR. WURTMAN: Yes, I think it's something -- I agree, but I think it's something that one sees with serotonin drugs in general. Roboxamine will do it. Nicotine will even do it, and I think it's done by releasing serotonin.

CHAIRMAN BONE: I think Dr. Sherwin had a comment.

DR. SHERWIN: No, that's okay.

CHAIRMAN BONE: I had a -- oh, and Dr. Borhani, did you have a question?

DR. BORHANI: This was a very comprehensive presentation. I thank you. It was beautiful. I have two questions. First, I just don't understand this last observation carried forward. Can you tell me statistically what that means?

And the second question I have is, have you observed at all in any of these studies whether those people who did not continue taking the drug, how did their weight react? Did you have any observation on that?

DR. SANDAGE: I'll take the second one first and then I'll turn it over to the statistician to talk about the other one.

Three of the trials had a very brief follow up period, one month or two months duration.

There was some trend to start regaining the weight after the patients came off.

Although within one month and two months post-treatment, they were still significantly different from the placebo at the end of the post-treatment period.

So two months is not enough time for the patient to start regaining. There is a great deal of evidence, as you know, that once you come off agents like this, that patients will eventually regain the weight, or most patients.

Dr. Lee, can you make a comment? Oh, I'm sorry.

DR. BORHANI: No, I would like to know if you have any scientific data that tested those scientific observations in terms of the possible effect that -- will have on serotonin, which I accept as a -- does that make any sense -- or action in this case?

Now when the patients don't take the bills, how long will this continue? In other words, what is the residue of this effect that might be still on serotonin?

DR. WURTMAN: Only so long as the drug itself is present in the brain. Again, in therapeutic

doses, there are no long-term effects on the synthesis, release, update, anything of serotonin. It's simply an acute effect.

It's only when you give, as I said, these doses that cause brain levels to be in an order of magnitude higher than those that you see in humans did you begin to have long-term effects.

The mechanism of the long-term effects is sort of interesting, and it's sort of a theoretical thing. It reminds one of the fact that anti-depressants have to be given for three or four weeks, as you know, before they begin to have a reaction.

There are a number of tardive systems in the brain that will accommodate to the sledgehammer-type treatment. And this, I guess, is one of them. But it has no therapeutic relevance.

DR. SANDAGE: Doctor Lee, would you answer the question about --

DR. LEE: Hello, I'm John Lee, vital statistician. To answer your question really is mass observation carried forward, and there's a method to mending the drop-outs. That's one steady -- matter.

However, to supplement that, we did analyze the patients that completed the whole trial.

We look at the outcome of those photo

analyses, they are in agreement.

DR. BORHANI: In other words, like censoring.

DR. LEE: In the sense it is, yes.

DR. BORHANI: I have no questions.

CHAIRMAN BONE: One or two additional questions that I have, perhaps either Dr. Sandage or Dr. Cooper would deal with the first one.

And that is, if I understand correctly, the drug and its active metabolite are large secreted by the kidney or excreted by the kidney?

DR. SANDAGE: Dr. Campbell?

DR. CAMPBELL: Bruce Campbell, Director of International Scientific Affairs for Servier. I've been working on this job for 25 years, so perhaps I can answer a few of the questions.

It is metabolized in the liver to the extent of about 90 percent. The metabolized other than norfenfluamine, which we've seen before are active, are polar, non-active compounds. And these are all eliminated with the urine.

So 95 percent of the administered drug is eliminated with the urine. So the majorities unchanged and not-active.

CHAIRMAN BONE: And of the renally

excreted material that metabolized, what proportion is active?

DR. CAMPBELL: Ninety percent is inactive.

CHAIRMAN BONE: So about ten percent of that would be active?

DR. CAMPBELL: Yes, a combination of the fenfluamine and the norfenfluamine as we heard.

CHAIRMAN BONE: I wonder if you have looked at levels for effects in patients with renal insufficiency?

DR. CAMPBELL: This has not been done, but there is nothing to suppose that there would be a change in the levels because of the fact that these metabolites are inactive.

CHAIRMAN BONE: Okay, because I have --

DR. CAMPBELL: It hasn't been formally looked at.

CHAIRMAN BONE: There wasn't anything in the --

DR. CAMPBELL: That's correct.

CHAIRMAN BONE: -- warnings or precautions concerning use in patients with a renal insufficiency. And in the absence of data, that might be something to keep in mind.

DR. CAMPBELL: I think this is something

which could be considered later on.

CHAIRMAN BONE: Okay, thanks. The other question I had was for Dr. Manson. And we are very impressed with the results of the information we are getting from the nurse's health study. But obviously, this has a different character from a randomized intervention study.

One of the things which occurs to us in looking at that is that the difference in fat may be not the only difference between the nurses who are overweight and those who are not.

In fact, there might be an important difference in fitness. And differences in fitness, differences in muscle mass and so on would affect all of the co-morbidities that you've described.

Do you have any idea how to attribute those advantages between fitness and body fat?

DR. MANSON: Well, we did make an effort to control for some of those potential confounding variables. In that first slide, we did -- we looked at never smokers and control for smoking.

We had information on physical activity level and looked at quantities of physical activity and dietary saturated fat intake, alcohol intake, post-menopausal hormone use, tried to control for some

behavioral variables.

But you're completely correct that it is impossible in an observational study to take full account of potential confounding, by other lifestyle, variables.

That's why it's so important to have the randomized trial data. But the results are very much consistent with the metabolic studies and the clinical, very controlled studies in terms of weight loss resulting in randomized trials, reductions in blood pressure, improvements in lipid profile, reductions in blood sugar.

That would be expected to translate into these reduced risks of diabetes, coronary hear disease and total mortality.

So I think the results are very much consistent with the clinical trial results, but in an of themselves could not be considered confirmatory.

CHAIRMAN BONE: Would you say this same problem is probably a concern with virtually every epidemiologic study that would be looking at patients as they are or subjects as they are?

DR. MANSON: I think it is a limitation of all observational research. But the strength of the association I think suggests that there is not a great

deal of confounding going on, that there is still some independent effect of overweight.

If the effect were more on the order of only 20, 30 percent, then I think you could very much attribute it to confounding.

But seeing statistically significant 60 percent, 120 percent increases in risk, it's less likely. The consistency across studies and the dose response in terms of increasing mortality with the increasing level of weight I think suggests that there is some cause or relation there.

CHAIRMAN BONE: For example, did you attempt to relate lean body mass to glucose metabolism?

MR. MANSON: Well, these women are spread out across the country in 11 of the larger U.S. states, so we don't have that specific information.

But we did -- the women did measure their waist to hip ratio. We looked at that. We reported that in the study. Actually, a total adiposity or body mass index proved to be a stronger predictor of all cause mortality. But we don't have that specific data here.

CHAIRMAN BONE: Okay. Dr. Illingworth and then Dr. Critchlow.

DR. ILLINGWORTH: Just one more question, Dr. Campbell. Any more information about potential drug interactions that might compete with metabolism in the liver of Dexfenfluamine?

DR. CAMPBELL: Over the 20 years of use of the DL and the recent ten years of use, we haven't actually found any interaction, but we haven't formally looked at them.

We've looked at the database from the INDEX study and there's no suggestion that there's any interaction there.

We've also looked at the metabolism. And it seems to be, certainly from rat data, that we showed 3A4, 2A1 and 1A1.

There isn't likely with that combination to be a serious interaction.

DR. ILLINGWORTH: Would you expect the drug to be potentially accumulated in patients with coesstatis?

DR. CAMPBELL: Not necessarily. I mean, we don't know enough about it to be able to say that one for all. But when we look at the -- we have monitored the drug levels, for example, in the INDEX study, and looked at some reasons why some people are higher or lower. And there is nothing that clearly

comes from it, elderly, renal reasons.

So it doesn't look as if there is any interaction, and particularly with this low -- as well.

CHAIRMAN BONE: Have you carried out animal drug interaction studies at all?

DR. CAMPBELL: In terms of kinetics or in terms of --

CHAIRMAN BONE: Drug interaction.

DR. CAMPBELL: No, we haven't. To be quite honest, I'm not sure of the relevance.

CHAIRMAN BONE: Oh okay, I just wanted to know. Dr. Critchlow had a question.

DR. CRITCHLOW: I was just going to ask Dr. Manson, in looking at the association between mortality and weight loss, was the comparison group those that maintained a stable weight or did it include women who had gained weight?

DR. MANSON: In the Nurse's Health Study, that was the women who had a stable weight. That was the reference for the change in weight and then development of IDDM.

CHAIRMAN BONE: Dr. Borhani had a question?

DR. BORHANI: I think it's important, at

least for the record, in defense of observation studies, especially one so elegantly performed by Dr. Manson and her colleagues, it's commonly accepted among epidemiologist, and I remember very well the Dr. Lillanfeld, my teacher, who used to say that with regard to the cigarette smoking and lung cancer.

If the observation studies are properly conducted and analyzed, they can explain at least 60 percent of the variability by the differences observed. One is pretty much certain that the clinical trials "prove" the causality will follow suit.

And this has been proven not only in the case of lung cancer and cigarette smoking, but a few other diseases as well.

So I think this particular observation study, even though it is still observational and Dr. Manson is right that you are not going to draw a causality from this data, but they are pretty much convincing in terms of their relationship between mortality and obesity.

CHAIRMAN BONE: Dr. Sherwin?

DR. SHERWIN: I just wanted to clarify something for myself. And that is, how much of an effort did you make to define the outcome and drop-

outs? I assume that all of the 50 percent drop-outs all ultimately failed at the end of the 12 month period.

And if that was the case and that was put into the equation, how would that affect statistics. It's my understanding is that intention to treat is the way you assess statistical outcome.

DR. SANDAGE: Right. I may have Dr. Lee say something about that. But part of the reason for doing the last observation period forward is to take that into consideration when you do that.

In addition, a longitudinal analysis has been performed to take into consideration drop-outs and was performed by the FDA, an expert in that technique and statistics in the data is similar. And you may hear about that this afternoon when the FDA makes their presentation.

CHAIRMAN BONE: Further to that question and going back to something that was discussed at a prior meeting of this committee, did you ascertain the follow-up weight through -- to the end point in the drop-out?

DR. SANDAGE: No. All of our studies completed for your committee met and discussed that in July. In fact, some of them finished in the late