

Transcript: A War on Obesity, Not the Obese
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Casparly Auditorium

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Ira Flatow: There's not going to be an overture so we're going to just start without the music. Welcome. I'm Ira Flatow. I'd like to welcome you all this evening to Rockefeller University. For those of you who are new to university, here is a thumbnail, a quick introduction to the magnificent surroundings around you. Rockefeller is a world-renowned center for research and education in the biomedical sciences. It's made up of more than 70 laboratories. Now I know you walk around New York and you say, "where are all the laboratories?" right? (laughter) I do, so... Because you never think you know you can walk down 2nd Avenue, 1st Avenue and never even know that there's this building here or this complex here. Seventy laboratories -- each of them is headed by a world-class scientist. And believe it or not it's not like a normal university; there are no academic departments here. This is really, as I say, a unique laboratory based structure that encourages highly creative, highly interdisciplinary investigation. And it's been very successful here because this approach has fostered a lot of success over the past hundred years. You have 23 scientists associated with Rockefeller who have won Nobel Prizes in medicine or chemistry. So tonight's event is part of a series of public lectures that go on here at the university. It's a great place to have them; it's a great auditorium and they're held here each year.

Before we get started though, I'd like to tell you about upcoming events that are happening that, boy I'm going to try to get in on some of these. Next week, on February 9th, there's going to be a concert and panel discussion featuring several winners of the Van Cliburn Foundation. You know the Van Cliburn Awards? They're going to be here -- The International Competition for Outstanding Amateur Pianists. So if you like piano playing, February 9th is your date. And then on March 29th the renowned French neuroscientist Jean Pierre Changeux will be awarded Rockefeller's Lewis Thomas Prize. You remember Lewis Thomas; there's a prize named after him for writing about science and this gentleman is the author of many books on connections between the human brain and the mind and these books strive to bridge that gap between science and the humanities. And he's going to give a public lecture that evening entitled "The Physiology of Truth: Toward a Neuroscience of Human Knowledge." And if you know anything about neuroscience these days this is really where things are at about trying to understand how the brain works and that should be a very, very interesting talk. If you'd like to be on the mailing list for these and other events, they've been giving out cards in the lobby. They're not to get a haircut someplace; they're for these sorts of things to sign up for the future events.

And tonight you're very fortunate because you're here to hear one of the country's great speakers and great scientists about obesity. Jeffrey Friedman is a medical doctor and a researcher in the field of genetics. He's received many distinctions including, this is a tough one, being elected to the U.S. National Academy of Sciences; very few people are able to do that. And about ten years ago Jeff discovered

leptin. Now leptin is a hormone that plays a crucial role in how our bodies maintain a constant weight. We're going to be talking a lot about weight tonight. So everything you ever wanted to know about weight, obesity, we're going to talk about it up here for a while and then I'm going to open the floor up for discussion and your questions and you're more than welcome to ask your questions.

So we'll talk about that, how your body maintains weight, how it doesn't, how you try, when you can't lose weight, well why is that. And that discovery has contributed to a debate ever since, among scientists and in the media, about obesity, which everybody knows is a national public health problem. Should it be a public health problem? Why is it? What about our conventions that we think about why people are obese? What's wrong with what's going on with the mythology about it? So we're going to get started. I'm going to ask Jeff to have a seat here and while he's finding a seat, what am I going to ask you to do? Turn off your cell phones. That's right. So please do that and we'll get started.

IRA FLATOW: Now let's see if they can still hear me. Good. Hi there. Let's talk about an article you wrote in Science not too long ago that has gotten a lot of attention. Share with everybody what you said in this very inflammatory article and why it's gotten such attention.

JEFFREY FRIEDMAN: Well, I think in contrast to almost every other medical condition where the lay public would just leave it to the scientist to inform them about what causes it, what the nature of the problem is, and what we should do about it, obesity is a condition where absolutely everyone has an opinion. Everybody has a deeply held set of personal beliefs about what causes the problem. And I have to tell you that in most cases people are much more interested in what they have to say about it than what I might have to say about it. (laughter) And because of that I decided I had to write an article. So the article essentially espoused at least my view and the view of a lot of other scientists who study this problem about what causes it and how we might think about it. And embedded in that is the idea that it's useful to set aside, I think, people's preconceived notions about what the nature of the problem is and the article sort of tried to do that.

IRA FLATOW: Tell us basically, the article talked about how the public can be stigmatized about obesity and you're trying to de-stigmatize society about it because we have some preconceived notions -- everybody is trying to lose weight, everybody in this room at some time or another has been trying to lose weight. I'm surprised they asked me to talk about obesity tonight because I'm on my own little campaign. But you talked about how we are, as opposed to just deciding for yourself "hey I'm going to go on a diet and lose weight," it's just not that easy to do that because we're hard-wired for a certain weight, right?

JEFFREY FRIEDMAN: Yeah, so if you think about it in general terms, you can explain differences in weight in the population based on three possibilities. So one possibility would be that the obese lack will power; this is a point of view favored by lean people, I generally find. (laughter)

IRA FLATOW: 'Cause it's the first thing people say, "Why don't you just stop eating!"

JEFFREY FRIEDMAN: Right. The second possibility that people consider is that we live in a toxic environment and that it's the environment's fault. And then the third possibility is that there are biological drives that lead us to eat what we eat and ultimately weigh what we weigh in the same way as some of us are tall and some of us are short, others of us are destined to be heavy and others lean. And so I think most moderate scientists believe that of course that all three can be relevant but that biology has really an underappreciated role in accounting for difference in weight and we know a lot about the system now and so I think there's a powerful set of data that supports that point of view.

IRA FLATOW: Now you've shown that there's an appetite-regulating hormone called leptin. This is an important part of this idea that our brains are hard wired for losing weight, gaining weight, that actually answers the question why it's so hard. Talk about this discovery of yours about leptin and how it actually helps rewire our brains, which I thought was an amazing thing.

JEFFREY FRIEDMAN: So we found this hormone leptin because there was a genetically obese strain of mice. These mice were just found in the laboratory by chance and if you looked at these animals it's quite amazing; one animal can weigh three times as much as another sibling littermate animal. So it's the brother and a sister mouse, one weighs three times more than the other, and it was surmised in the 1950s that the reason that animal is fat is because it has a single genetic defect. And in 1994 we identified the gene that caused this obesity and found that it had coded for a hormone that regulates weight.

So hormones work in the following way: they're made by one tissue in the body; they circulate in the blood and act somewhere else. This hormone is made in fat tissue. It's secreted from fat in proportion to how much fat there is, circulates in the blood, and acts on basic brain centers that regulate appetite to, in a sense, inform the brain how much fat is available so that adjustments can be made in the amount of fat that maintain weight at a relatively constant range.

IRA FLATOW: And so do fat people have more of this hormone or thin people have less of it? How does it work?

JEFFREY FRIEDMAN: Well it actually depends. I think in the case of this fat mouse, the mutation leads them to make no leptin and that's why they're fat. There's no signal that there are adequate fat stores. That animal ironically thinks it's starving because it doesn't make the hormone, doesn't get the message that it has fat, and it keeps eating and eating and eating and getting fatter and fatter and fatter but never generating the signal that tells it to stop. In humans there are some cases, a couple of dozen probably, of leptin mutations, and these individuals are similarly massively obese and the one cohort that was described you had two children, a three year old and a seven year old. The three year old weighed 80 pounds; the seven year old weighed 200 pounds. All is a consequence of a single genetic difference.

Now so in some cases the failure to make leptin causes obesity. The majority of obese people, however, actually make too much leptin. Because if the brain doesn't sense properly the leptin that's made and

that more keeps on being made to try overcome that. And so an important question really is now to understand why doesn't the leptin that the body makes work well enough in the obese. Why is the sensitivity to the hormone dialed down in the way that it appears to be?

IRA FLATOW: So when people are fat and they're overweight, there is a major genetic factor here. It's not as simple as saying "I have no will power" or "I tried the diet, doesn't work." There could be real hard wiring that's the problem.

JEFFREY FRIEDMAN: So some of the most powerful evidence that this is a biological problem and not a "behavioral one" (in quotation marks) is genetics. And so there are a number of ways to assess the genetic contributions to a trait. It turns out if you look for obesity it is probably the second most heritable trait, second only to height, with which it is quite close. Based on estimates that can be done by analyzing twins, 80 percent of the variability in weight can be accounted for by genetic factors.

Now that's not to say there aren't environmental things that modulate it but, to a greater extent than many traits that all of you believe have a genetic component, obesity comes out on top.

IRA FLATOW: Yeah. We keep hearing over the last six months, the last year, we keep hearing about what an epidemic there is in people being overweight. I mean did something happen? If it is genetic, did we all get our genes changed somewhere along the line? You know, go through the airport machine once too many times and get X-rayed or something?

JEFFREY FRIEDMAN: That's an argument I get all the time because people say, "Well, there's a huge change in a short period of time in the amount of obesity and that therefore it can't be genetic." First of all, actually, that's wrong. Genes in a population can change very rapidly as environment changes. In fact that's the whole purpose of having variation in a population. As the environment changes in acute circumstances certain variants are selected and then predominate.

But setting that aside actually, I think people have a misconception about the role of environment in this because of misuse of statistics. Let me explain what I mean. Obesity is distributed in the population. Some people are thin; some people are heavy; most people are in the middle; and you have a curve, a bell-shaped curve. Now there's a known phenomenon in epidemiology that when you have a normally distributed trait, meaning a bell-shaped curve, and a fixed threshold that defines a disease, if that average value shifts even a small amount you get a disproportionate number of people who exceed the threshold.

So let me give you an analogy for IQ here and then I can tell you the actual data for weight. Imagine that 40 years ago the average IQ was 100 and there was a bell-shaped curve. Imagine now that our educational system improves and the bell-shaped curve shifts a little and the average IQ is now 105. With that you could imagine that the number of people who have an IQ greater than 140, so-called geniuses, might have doubled. Now is it more useful to think about how our education is doing by saying, "average IQ increased 5 points" or "number of geniuses is doubled." I think probably both are of interest but the former seems to me more informative.

Ok. So how does that analogize to weight? Over the time period that you've heard that the obesity rates have quote "doubled" or gone up by 70 percent, the average weight gain is 7 to 10 pounds. Now I'm not here to argue that that's not important; it is important from a public health point of view. But if we then say that's what environment contributes to differences in weight over that time frame, think about the fact that 7 to 10 pounds is almost nothing compared to the hundreds of pounds of difference in weight that you might see in any two people walking around the street today, both of whom essentially have unlimited access to calories.

IRA FLATOW: So why is the focus then so much on what we're eating? If genetics is such a big factor, why don't we hear about that -- we just hear the focus on McDonald's, stuff like that. Is that not a factor, too?

JEFFREY FRIEDMAN: The key factor it appears to many scientists about why weight increases or changes: access to calories. It is completely unknown whether it matters what foodstuff you get your calories from, with respect to weight at least. And that confusion actually is illustrated by the fact that at the same time as you might see one book arguing don't eat carbohydrates you'll see another book arguing don't eat fat and then a third book that says don't eat anything, which is probably the only book that makes any sense if you want to lose weight. (laughter)

IRA FLATOW: But yet our culture is focused on this. Is the focus wrong?

JEFFREY FRIEDMAN: I think the focus is wrong and there are many levels at which to answer the question.

The first is that the idea that you can change your weight voluntarily is one that the diet industry has a huge financial interest in. And so anybody can tune into infomercials telling you what you need to do to lose weight is fork over some money to their diet plan, eat it or not eat it and you'll lose weight. And I don't think that message and that marketing muscle can be easily counteracted by what scientists have to say about it. Part of the problem is that that notion fits in with people's intuition. And this gets very complicated. It's a control issue; people want to feel like they're in control of what they eat and what they weigh. But at a certain point you need to ask yourself, "How much am I really in control of it?" So to illustrate this point it's often useful to do an experiment and that is to make an offer to anyone here, including you, that I will give you \$10 million. All you have to do is stop breathing between now and the end of our session. (laughter)

Now think about it. All of you, I imagine, are highly motivated to stop breathing right now to claim your reward. At the same time you all know intuitively that there's a basic drive to breathe and no one -- did anyone actually try to stop breathing? (laughter). Because intuitively you know that the basic drive is going to win out. And you can recognize it when it comes to breathing.

Now all of our drives operate over a time frame. You might be consciously highly motivated to drink less or have sex less or eat less but over time the drive will get more intense and for almost all of

these things they overcome the conscious motivation in time. Now the problem for feeding is that the time frame with which this drive expresses itself is out weeks to months to actually years. And so by the time the drive exercises its power people don't recognize it as a drive, and they simply imagine that it's a loss of will power, not thinking of it as rather an expression of a basic biological drive.

IRA FLATOW: Well then are they -- if it is a basic biological drive -- are people then who have this drive, are they just doomed to gain weight and be obese?

JEFFREY FRIEDMAN: Well, you know, the available evidence would suggest that the vast majority of people who find themselves at a particular weight -- be it thin, medium, or heavy -- that's pretty much their weight. Now actually one of my neighbors heard me talking about this at one point and he said, "Oh, but that's so sad." Well, I don't know, I mean --

IRA FLATOW: -- that was my next question --

JEFFREY FRIEDMAN: Well, I guess it's sad. I mean it's also sad if you don't like your height and you don't like your eye color and you don't like lots of things about yourself. It's that somehow people think this is something they ought to be able to control. And they accept all these other things you can't control that are just who you are. But people are very loathe to believe that what they weigh is who they are.

IRA FLATOW: Yeah, but we're told that it's unhealthy to be these things also. Not just sad, but you go to your doctor and "Hey, you should lose 10 pounds. If you lose this... the Type II diabetes is running rampant. There are kids..." Aren't these valid concerns with being overweight?

JEFFREY FRIEDMAN: Well, it's sad when people get diseases. It's sad that people have hypertension and have strokes and lots of other things. I mean, there's no question that obesity confers a health risk and that for most people who are overweight, losing weight can improve their health. Now what's important to remember here is that you get a disproportionate health benefit for a relatively small amount of weight loss, an amount of weight loss that is probably achievable.

IRA FLATOW: Ok, give me an example.

JEFFREY FRIEDMAN: So, most people in my estimation operate within a range, 10 lbs., maybe 15 lbs. And weight loss in that amount can improve health, can improve the diabetes of obese people who are diabetic, can improve hypertension and so on. The problem is not that small amounts of weight that improve health can't be achievable; I think it can be. The problem is that's not what most obese people want or the public wants. The public wants to be normal weight. And so I would much prefer to see that the dialogue and the issue center on improved health and achievable goals rather than setting up some societal construct that says everybody has to be perfectly wonderfully thin, a wish that really runs counter to almost everything science has to tell us about this problem.

IRA FLATOW: But being thin, you know, it's everywhere in the culture. You look at size zero now on television. My wife and I were talking

about this the other day. You know in the 60s, Sophia Loren was the epitome...she's a healthy girl as they used to say. Today you have J. Lo, people like that are size 1, size zero, is what the teenagers are aiming for.

JEFFREY FRIEDMAN: That changes. Historically, being obese was the desirable body habit as so. If you go to museums... all the rich people in Egypt would pay extra money to have extra chins put onto their sculpture. Rubenesque figures were the vogue in the 1700s. Renoir's characters were all heavy. In aboriginal societies the chieftains were all quite obese. For reasons that -- you all have as good an idea about as I do I guess -- things changed here about what our views of what was attractive in the 60s and it set up an idealized view of what people should weigh and who they should be that just isn't matched by our genetic endowment.

IRA FLATOW: So are you saying then that it's a losing battle to try to get our kids who may be becoming obese at an early age and possibly headed towards Type II diabetes? First of all is it a false connection? Is there not really an epidemic in Type II diabetes?

JEFFREY FRIEDMAN: There is certainly an increase in Type II diabetes among children. It's something we need to understand. And I think people should make their best efforts but recognize, but not be prejudicial about the fact, that for many people most of the things you do aren't going to work. And so my argument is not "we shouldn't think about the problem, we shouldn't address it." The issue has to do with "what are we going to do about it." And so I would argue what we shouldn't do is fall back on simple nostrums like "eat less, exercise more." Just so you know -- do you know whom the first person to propose that was?

IRA FLATOW: Columbus? I don't know. (laughter)

JEFFREY FRIEDMAN: Actually it was Columbus' grandfather. (laughter). It was Hippocrates.

IRA FLATOW: I was getting close. (laughter)

JEFFREY FRIEDMAN: So -- who was Columbus' great-great-great-grandfather?

But the point here is that what the society has to say about this is no different in substance from what Hippocrates had to say. And so I would say this is an important health problem; we need to understand it. But that maybe we can do a little better than simply reiterate what some 2,000 year-old Greek guy had to say about the problem. And what that means is thinking about this problem the way we do any other medical condition -- understand the biological factors that underlie it, that provides a framework to think about how environmental factors modulate it, and finally, and this pertains to your initial remarks about neurobiology, understand how conscious factors interact with the basic drive to eat and that leads us all to sort of reflect some balance between the power of the drives that we're composed of and the conscious factors that we literally bring to the table.

IRA FLATOW: I'll get to the neurochemical things in a minute but I want to continue this line. So what do you say to parents or doctors or physicians who are seeing these overweight kids? What do you say to them? You're saying it's hard for them to change their lifestyles. It's hard wired into them to be overweight. They're doomed to find a higher weight level and you know, you're on your own, basically, I hear you say.

JEFFREY FRIEDMAN: Well, no, I think I wouldn't quite say that. First of all no one's asked me what I thought until tonight so...

IRA FLATOW: No one?

JEFFREY FRIEDMAN: So I can rehearse now what I'll tell the media. So when they ask now I'll have rehearsed my answer.

I think that to the extent that increased weight has health consequences, people should do their best. It certainly is a good thing to be fit. And it is a good thing to eat a heart healthy diet. And it's probably a good thing to make one's best efforts to keep one's weight under control. So that means not doing much different than what Hippocrates would have recommended. But I think at the same time we have to recognize that those measures are rather limited in their efficacy and that to make the leap therefore that people who are not successful at keeping their weight off are at fault is just wrong headed. And there are all kinds of attributes about each of us that might draw the next person to draw a conclusion about them. But to draw conclusions about obese people, I think, is unenlightened to say the least about what their personal characteristics are.

IRA FLATOW: So to stigmatize them is sort of making fun of the situation that they don't have much control over.

JEFFREY FRIEDMAN: I think that's right and the ironic thing is that I think the more of an outlier one is for weight, the more obese, the more difficult it would be to actually normalize weight. And so if anyone should be stigmatized it would be someone like me who could easily lose 10 lbs. and doesn't. I think for the people who are really significantly overweight, it's just who they are -- to a very, very large extent.

IRA FLATOW: Let's talk a little bit more about the brain chemistry here. What do you need? What other research? What other stuff do you need to understand about the brain? And talk to me a little bit, because that's just fascinating, about how the hormones actually rewire the brain; it's like plastic and it can be rewired this way.

JEFFREY FRIEDMAN: Right. So all of your basic drives are centered at a brain region, to a large extent, known as the hypothalamus. This is where the drive to eat is centered. This is where the drive to drink is centered. This is where sexual drive is centered. A lot of the basic body biology is centered in this region known as the hypothalamus. Actually, it's interesting, the hypothalamus hasn't changed very much from fish till humans, meaning that the wiring of our basic drives hasn't changed very much as organisms because of course every organism has to regulate these biological processes.

In fact, just as an aside, I often comment to people that if you want to argue that weight in humans is controlled by higher conscious factors and not the hypothalamus you would have to argue that food intake is controlled by the hypothalamus in every organism up to including monkeys, but that when we got to humans we jettisoned all that and left it to our higher brain centers, which is just ridiculous; there's an interaction.

Now a lot is being learned in recent years about how the hypothalamus regulates appetite. It turns out there are a number of signals, including leptin, but other metabolic signals in other hormones that convey nutritional information to the brain activating some neurons, turning other neurons off, all of which then lead to a drive to eat, or stop eating, or an impulse to eat more or less. We've also learned in recent years that the nature of that circuitry is very dynamic, with connections being formed and connections going away in a very rapid time frame. So it's a very complex dynamic system. But what's exciting is that the molecules that compose that system are being identified with increasing frequency, providing lots of opportunities for new ways of looking at the problem.

IRA FLATOW: Is it possible to rewire the brain so that you might change your appetite?

JEFFREY FRIEDMAN: It does not appear at the moment as though people can rewire their brain. The rewiring is actually part of the response that returns weight to the starting point. It is not something that now can change weight in one direction or the other later in life. It's part of the biological mechanism to keep things at a constant level.

IRA FLATOW: But if you can take away some of that desire to want to eat, then your weight would drop, right?

JEFFREY FRIEDMAN: So the way that's being approached -- and I think it's a very exciting time in this field -- is as follows. Leptin and other molecules act on neurons that in some cases increase appetite and in other cases decrease appetite. These molecules themselves convey signals and so new drugs are being developed that block the molecules that increase appetite and mimic the molecules that decrease appetite. And there's a whole new generation, I think, of therapies that are going to emerge that are based on an evolving understanding of this neural circuitry.

IRA FLATOW: And the realization that neurochemistry is so important, instead of the will power and the dieting. Is there any diet that works? (laughter)

JEFFREY FRIEDMAN: Well I don't know, you might have seen in the New York Times there was an article that said that none of the diets worked with the possible exception of Weight Watchers, where people achieved somewhere around 3 to 4 percent weight loss, which actually is a good thing from a health point of view. It doesn't meet the objectives of many people who are on it, but I'm not sure that's what people should be worried about. It'd be much better to forget about the stigma and assume people weigh what they weigh and then encourage people to do what they can to improve their health.

IRA FLATOW: Is it possible for people to be overweight and physically fit at the same time?

JEFFREY FRIEDMAN: Yes, it absolutely is. In fact there's a big debate about whether obese people are better off, as it's said, being "fat and fit" or thin and unfit. And we don't actually know the answer although there's certainly reason to believe that being fat and fit is a better thing than being fat and unfit.

IRA FLATOW: We're going to take questions from the audience. So if you have questions...already! Ok. Do we have a mic we can get to them or are we just going to...? Do you think we're ever going to have a genetic profile someday of what you can expect later in life?

JEFFREY FRIEDMAN: So I already mentioned that the twin studies and others say it's highly genetic but it actually goes deeper than that. Meaning, when we talk about something as being genetic it could mean that there are many different genes that interact and that's sort of a nebulous idea -- we don't know what a lot of the genes are -- but sometimes it's alterations in a single gene which is the case in these people who lack leptin. We now know that 5 percent of morbid human obesity is a consequence of these so called "single gene defects," like [in] Huntington's Disease or familial breast cancer. 5 percent. So when you see a very obese person walking down the street there's a very, very significant possibility that that individual just has a genetic alteration that makes them so. And there are tools now that can allow us to tell the difference. I think actually that 5 percent is a low number; it's going to grow in time. And what that means is there would be ways to predict likelihoods in advance.

IRA FLATOW: So all those years when you saw a very obese person and they said, "I have a glandular problem," they were telling the truth in a certain sense genetically speaking. (laughter)

JEFFREY FRIEDMAN: Well I think so. They just didn't know which gland. (laughter)

IRA FLATOW: OK, I like that. Yes.

AUDIENCE QUESTION No. 1: When someone has a surgical intervention such that a massively obese person of, let's say, 400 lbs. or 500 lbs. removes part of his colon and attains a weight more normal to his size, for his height. Does that rewire the person or does that then remold itself into the norm and the body strives to achieve the larger weight yet again?

JEFFREY FRIEDMAN: There's a two-part answer to that question. The first has to do with why does the procedure work. For people that don't know, these are procedures on the intestine where they rewire the intestine so that the length is reduced and so it reduces absorption. So the trivial explanation is that people just can't consume as many calories as they did before. Surgeons, however, argue that you also change the levels of a lot of metabolic signals that come from the intestine and you get an added benefit from that. And we don't actually know for sure what the relative importance of each of those two possibilities is. It's being actively studied. But there's another feature of this surgery that people, I think, ignore, and it's this: when you do this

procedure you limit the intake of a person to about 700 calories a day. Just so you know, none of you could consume 700 calories a day for very long; it is a very small number of calories. Despite that fact, these people still end up being clinically obese at the other end of the procedure. They lose a lot of weight but they would still on average be definable as significantly obese on average after the procedure. Now think about it, they're eating 700 calories a day and they're still obese. I mean if that doesn't say that there's something metabolically different about the obese than the lean, I don't know what does.

AUDIENCE QUESTION No. 2: That's the wrong thinking. If somebody starts out 400 lbs. and loses 100 or 150 that person is still perhaps overweight and it's not natural to think that after one month or two months or five months that 700 calories a day is going to impact materially on the major obesity when they stop...

JEFFREY FRIEDMAN: No, I think that's the point.

AUDIENCE QUESTION No. 2: Well, but if you start with a person of 150, 700 calories a day will impact materially on that person's weight, very quickly so.

JEFFREY FRIEDMAN: Well, no. If they're consuming 700 calories every day they're going to be expending more than that. And so what you would find, you would expect to see is as long as they're that imbalanced they're going to keep losing and losing and losing and losing. That's not what happens in these people; they plateau and they stop losing weight at what is definable as a significantly obese level. Now, if I had that procedure you probably wouldn't see me in profile anymore because I would just get so thin. That's not what happens to these people and it appears that in the face of reduced intake the body shuts down caloric expenditure and they can't lose any more weight.

IRA FLATOW: What has been the reaction to your thesis from the public and other nutritionists?

JEFFREY FRIEDMAN: Rejection. Uniform rejection. (laughter)

IRA FLATOW: No, I mean how do you react to that?

JEFFREY FRIEDMAN: As I said, everybody has an opinion and I don't think anyone, by and large, many people respect my opinion any more than their own. Everybody has a very personal set of experiences with food and weight and they know what works for them and if they don't know what works for them they know what works for their relatives. And so everyone thinks they understand the problem. I think that for some people what I'm saying is intuitive and they just accept it. For other people they just have an unshakeable belief that people can control their weight with conscious factors. It makes it like everything else.

AUDIENCE QUESTION No. 3: What is my ideal weight? What should be my ideal weight?

JEFFREY FRIEDMAN: There have been a lot of studies -- there was one in South Africa where they weighed a large number of people every week or every month for years and years and years. People's weight in general, if they're not actively trying to diet or don't develop an illness is

unbelievably stable, amazingly stable. So I think everybody knows what their range is; it's the range you've been at for the last number of years, not withstanding a general tendency of people to gain some weight as they age.

Let me put a slightly finer point on it. Everybody eats on average about 1 million calories a year. 1 million calories a year. That means if your weight doesn't change you have to balance the million calories you took in with one million calories burned or else your weight's going to change. You can calculate that the precision of this system runs at about 99.6 percent. Contrast that to the error rate on the caloric content of food you eat, which is 10 percent. So if you basically ate only based on the number of calories you thought you were eating you'd be doing two logs worse than nature does for you. And arguments like that, which I can go on at length about, really lead people who do what I do to believe that there's a very powerful biological system that counts calories with much greater precision than your cortex ever could.

IRA FLATOW: So if you're just 10 percent off in counting the calories you could be 25 lbs. off in...

JEFFREY FRIEDMAN: More than that.

IRA FLATOW: More than that. That's what he's saying basically.

AUDIENCE QUESTION No. 3: One more quickie. Do you eat multi-vitamins? Are they fraudulent or do they help?

JEFFREY FRIEDMAN: I think vitamins are good. I'm all for vitamins. (laughter)

IRA FLATOW: OK, this woman over here. And then we'll move around.

JEFFREY FRIEDMAN: I just want you to know, my daughters are here and they're fast asleep. (laughter)

IRA FLATOW: Ah, such a compelling moment when they're sleeping. OK.

AUDIENCE QUESTION No. 4: OK, I have a question. Have you ever studied with the rats or, I don't really know how to pose this question, but you're saying that the leptin levels can affect the appetite and not. When people smoke marijuana, and I'm not trying to be funny here, what does that do to those levels because when you do smoke, when I did smoke years ago, I would get really hungry and want to eat and eat and eat and eat and eat and eat and there was no governor on my appetite.

JEFFREY FRIEDMAN: I've heard about this. (laughter)

AUDIENCE QUESTION No. 4: Yeah, haven't we all?

JEFFREY FRIEDMAN: It's a very interesting phenomenon. (laughter)

AUDIENCE QUESTION No. 4: And also there's another part that I wanted to ask you about something called gerlane that I've heard about.

JEFFREY FRIEDMAN: Ghrelin.

AUDIENCE QUESTION No. 4: Ghrelin. OK.

JEFFREY FRIEDMAN: So there are two questions there.

So actually this munchie thing is an interesting one. So it turns out that the active ingredient of marijuana are called cannabinoids and they act on receptors in your brain, which is why you feel what you feel and, in that case, eat what you eat. Now it turns out that there are cannabinoid-like molecules that your own brain makes, your own body makes, that act on these receptors that the drug sort of co-opts for its nefarious purposes. So it turns out, as you might imagine, those neural pathways stimulate appetite. It also turns out that those pathways are downstream of leptin, and that is one of those molecules I was referring to as being part of the system that normally stimulates appetite and, moreover, there's a drug in development that these endogenous cannabinoids called Rimonabant, which is in clinical trials, some of which has been made public. And so that's a specific example about how a knowledge of these neural pathways is going to lead, I think, to new types of therapy, you know, in some cases based on personal observations like that. Now with respect to ghrelin, it turns out leptin isn't --

IRA FLATOW: What is ghrelin, just for people who don't know.

JEFFREY FRIEDMAN: So leptin is not the only signal; it's not the only hormone. Ghrelin is another hormone, that's made by your stomach, that also goes into the blood and sends a signal to the hypothalamus. In this case ghrelin fires when the stomach is empty and is thought to send a signal that says, "I'm hungry; it's time to eat." So leptin sends a signal "I have enough fat; it's time to stop eating." Ghrelin send a signal that says "my stomach is empty; it's time to start eating."

IRA FLATOW: When you exercise you feel less hungry; is there a stimulation of a hormone that says, "don't eat?"

JEFFREY FRIEDMAN: Yeah. There's a lot of anecdotal evidence that says that exercise plays an important role in modulating weight. But how it does it is completely unknown.

IRA FLATOW: It's not just pure calorie burning; it may be something else.

JEFFREY FRIEDMAN: Well, that's debatable. I mean, I think that exercise has some added benefit that can't be accounted for by calorie burning. Because I know if I go to the gym and then have two beers afterwards it's a net loss, and yet it seems to help a lot of people. (laughter)

IRA FLATOW: Yeah, but you're skinny to begin with. You're your own argument; you're skinny to begin with after those beers.

Ah, yes, this woman and then we'll go down here.

AUDIENCE QUESTION No. 5: My question is, there's lots of thermal supplements that you can take. What do they do? Are they worthwhile? I'm looking for a fix. (laughter)

JEFFREY FRIEDMAN: Well, yeah. So this is part of the problem that people have and why the intuition is that this is something that you can consciously control. Now it's an absolute fact that if you don't eat, you're going to lose weight. The issue though, is what happens when calories are freely available? And there you see a wide variability in what people weigh. So we all eat -- pretty much have free access to calories -- and some of us are heavy and some of us are thin and that's the question we'd like to answer. Now the answer probably is not going to be taking away people's food, because I think you'd hear a lot of complaints if you tried that.

Just to give you another example, if you watch the "Survivor" series, all these people go on the show and they're looking kind of, I don't know, healthy. They go on the island and they look terrible; they've lost a lot of weight 'cause there aren't enough calories. You put them back in modern times and they go back pretty much exactly where they started. I mean, that's the dilemma.

And there's actually a deeper issue here. I remember when I was a kid in the 1960s there were commercials that said, "no one in America should go hungry." There were people who weren't getting enough calories and that was viewed, correctly, as a big problem. Well, now everyone gets sufficient calories, starvation has been eliminated in the U.S. and is probably going, in a large extent, to be eliminated worldwide. That's a good thing but now we face the other side of the coin. When you give everybody free access to calories, some people are heavier, some people are thinner, we need to understand why and the question is: how are we going to understand why. And there are no quick fixes.

AUDIENCE QUESTION No. 5: What about the thermal supplements?

IRA FLATOW: What are thermal supplements?

JEFFREY FRIEDMAN: I'm not exactly sure. I think it has something to do with heat. (laughter)

IRA FLATOW: Let me write that down.

JEFFREY FRIEDMAN: Let me follow up on that a little bit. It turns out that how many calories you burn is important here. It's not just what you eat; it's what you burn. And there are agents that stimulate energy expenditure. In fact there was one introduced in the 1930s called dinitrophenol. This is a compound that poisons your mitochondria, increases energy expenditure, and it was a very effective weight loss measure in the 1930s or '40s or whenever it was introduced. It had the slightly problematic side effect of sudden death...

IRA FLATOW: Details, details, details (laughter)

JEFFREY FRIEDMAN: ...and so was abandoned but it actually -

IRA FLATOW: But you stopped eating. (laughter)

JEFFREY FRIEDMAN: Right. But it turns out that there's a whole other set of research now that seeks to understand how the number of calories we burn is regulated and seeks to develop methods of just increasing energy expenditure a little bit in ways that will be safer than dinitrophenol, which proved the point actually. And I think there's a whole other set of opportunities there. None of the supplements that I think you were referring to satisfy that criteria to my knowledge. But I think that's going to be a really powerful area of research and new drugs that you'll probably hear about in, I don't know, five to 10 years.

AUDIENCE QUESTION No. 5: But if you're not exercising more or expending more energy, how can they burn calories?

JEFFREY FRIEDMAN: So most of the energy you consume during the day is not accounted for by exercise. It's like the basic processes of life -- it's breathing, it's maintaining your temperature -- more than half the calories you burn come from that. Voluntary exercise is a relatively small percentage, I think it's 10 percent or so, of the number of calories you burn. And most of the differences in energy expenditure that are activated or deactivated when you lose or gain weight are not involuntary activity; they're in these basic metabolic processes. And we're learning a lot now about how that's controlled and that's going to provide new types of therapy that modulate that in one direction or the other.

IRA FLATOW: There was a study just out a week ago, I think, about people who fidget. Right? Is that what you're talking about? Just a little fidgeting and you burn up a lot of calories.

JEFFREY FRIEDMAN: So it turns out - and this was some lovely work done by Jules Hirsch here at Rockefeller [this study, published in the *New England Journal of Medicine* in 1996, measured the metabolism of people who lost weight through a precisely controlled diet] --] it turns out they burn many fewer calories than you would predict based on their newer weight.

So let me put a finer point on this. Imagine you're 250 pounds. and you lose 100 lbs. to 150 lbs. Now you ask how many calories does that person burn compared to someone who started out at 150 pounds. They burn like 300 or 400 calories fewer per day when they're at that reduced weight. Now think about it. That person is hungry and now can only eat fewer calories than the equal weight person to maintain that weight despite the fact that they weigh the same amount. Now that difference in calories, those reduced calories, appears to have something to do with the amount of fidgeting people do. It does not have to do with voluntary activity and it may have something to do with basic machinery, but it may also have to do with involuntary movements.

IRA FLATOW: So fidgeting, could that also be, you know, people who are running up and down stairs for little brief periods during the day? You know, if you're at home or you live in a split level and you're going up all the stairs all the time, you don't even think about all these little things that add up?

JEFFREY FRIEDMAN: I think that probably has a lot to do with it. Like some people probably to a large extent are determined to sit at their

desk and other people are getting up and down and moving around; that's just who they are. You know when we looked at these fat mice, they don't move around. They do not move; they just sit there. You give them one or two injections of leptin and they start to move around normally again. So we all assume that we're deciding when we move or don't move, it may be that --

IRA FLATOW: -- where leptin is doing it.

JEFFREY FRIEDMAN: Where leptin is doing it. Or something like it.

IRA FLATOW: What an age we live in. You had a question. Yes.

AUDIENCE QUESTION No. 6: It's interesting this lady commented about that because I'm speaking from a business point of view, not a scientific point of view. I got involved with, or should say, I tried it or whatever, these herbal supplements. ...The point is, what you said, the metabolic rate, it definitely is increasing your metabolism and curbing your appetite and boosting your energy; it definitely does have a factor there. And as far as your saying that if you don't eat, basically you're going to lose weight, I basically found I don't necessarily lose a lot of weight without doing anything else, with just not eating. What is your comment about that?

JEFFREY FRIEDMAN: So there are two points. Well the first thing is, as an accountant you would surely appreciate the importance of proper ledgers, and our body has a ledger for our number of calories and counts them very precisely. God, that was forced, but anyway (laughter) --

IRA FLATOW: You got there though.

JEFFREY FRIEDMAN: Yeah, sort of; it was really tough. I forgot what I was saying.

IRA FLATOW: You had a ledge there.

JEFFREY FRIEDMAN: People then often hear what I have to say and say, "Well, what about so-and-so? They lost 150 pounds. And how did that happen? So I don't believe anything you've said." Well, if you take it to the next level of complexity it goes something like this. You eat what you eat and you weigh what you weigh in part because of a basic drive -- the drive to eat -- the power of which might be different in each of us and also because in some people you might have a conscious desire to eat more or less. And what you eat ultimately is some balance between those two. I can't imagine too many people disagree with that. We might disagree on the relative potency of the two. But let's take it to the next step. The conscious desire to eat less is not metaphysical. That's compounds, that's neurochemistry, it's just a different part of your brain, And so, we could ask the question: is the chemistry of the cortex different -- or more importantly, are the connections between the cortex, where higher cognitive effects are, and the hypothalamus different in some people? Maybe some people who have a powerful basic drive to eat also have very strong cortical connections and they can modulate it better than others. So I think what we really have to do is take a step back and say this is all happening in our brains -- at least people like me believe -- this is all about brain chemicals and

that the challenge now is to understand how the basic drive to eat is wired and how it interacts with parts of the brain that control higher functions.

IRA FLATOW: What about the other parts that control metabolism? Is it true that some people burn food faster and so it's not the brain part and it's just their thyroid, or whatever it is?

JEFFREY FRIEDMAN: A very classic study was done about 15 years ago by a guy named Claude Bouchard. And Claude gathered up a set of identical twins and overfed them 1,000 calories a day for 84 days. And he asked what happened. So these people were in a room, they were given calories, they were forced to eat 1,000 extra calories a day; they should have put on a lot of weight. Some people put on a lot of weight, other people put on hardly any weight at all. And when they looked, the twins were highly similar to one another, suggesting that there was some genetic predisposition to either put on weight or not put on weight when you were given extra calories. The people who didn't put on weight activated metabolism because of metabolic circuitry and didn't put on the weight. And this observation that some people can eat whatever they want and never put on weight and other people put on weight just by looking at it has been more or less proven based on that study, which actually was observed as far back as the 1700s.

IRA FLATOW: This gentleman up here.

AUDIENCE QUESTION No. 7: I worked at McDonald's, Burger King, Dunkin Donuts, Haagen-Dazs, Chock-Full-of-Nuts, Pathmark, Juniors Cheesecake, I've worked around food relatively young. I'm wonder if I'm contributing to the obesity problem. (laughter)

JEFFREY FRIEDMAN: Well no, I think you're combating the starvation problem. (laughter)

AUDIENCE QUESTION No. 7: Another thing, about two summers ago I ingested some citronella by accident. And I lost 75 pounds that summer. Is there any way you can research that? (laughter)

JEFFREY FRIEDMAN: That's how the anticannabinoid antagonist was developed, sort of. So yeah, anything is possible.

IRA FLATOW: Is that true?

JEFFREY FRIEDMAN: No I don't know, but anything is possible.

IRA FLATOW: Maybe it's from all the throwing up he did. (laughter)

JEFFREY FRIEDMAN: Well, it's true. When you talk about weight loss remedies you have to be very careful sometimes because it's very hard often times to distinguish, at least in animals, something that really shuts off appetite from something that made the animal sick. But I think there's, underlying this, a debate and again people's intuition about whether there are particular types of food that are more likely to make you fat than other types of food. And so everyone's intuition is that McDonald's makes you fat and other types of food make you less fat. And I'm actually agnostic about it. There's actually no evidence

that where you get your calories from is particularly important. It may be true, but we don't have the data.

IRA FLATOW: So a calorie is a calorie is a calorie.

JEFFREY FRIEDMAN: I believe, based on what I know, a calorie is a calorie is a calorie, but I'd be prepared to be proven wrong if there was actually evidence. Now the reason it gets confused is this: it is clear that particular diets are heart unhealthy. And so the saturated fats and transfatty acids and other things in a McDonald's diet are not good for you but it has less to do with weight and more to do with cholesterol and that kind of metabolism. This is actually a really important question that we don't know the answer to. And I think for public policy it's an important thing to ultimately understand.

IRA FLATOW: Is there any connection between these hormones and other motivating factors. I mean, you've seen teenagers who are bulimic and things like that. Is there leptin...is anything involved there?

JEFFREY FRIEDMAN: Well, I think we assume, for now, and there's no reason to believe otherwise, that these other things are psychologically driven. But there are other possibilities here and I think there's even reason to believe, in some cases, that the circuitry is different in such cases. But that particular field is in its infancy and it's something that I think we need to monitor.

IRA FLATOW: Who's got the mic? Start over there with whoever's got the mic.

AUDIENCE QUESTION No. 8: Yeah, I just wanted to ask how you reconcile, if it's entirely genetic, the relative proportion of overweight people in America relative to a country like Japan, if you say that it's an entirely genetic factor.

JEFFREY FRIEDMAN: First of all, I don't actually say it's entirely genetic. For complex traits like obesity or blood pressure or height -- it's genes modulated by environment. And historically, such problems have been best approached by figuring out what the genes are and figuring out how environment acts on them.

Now let me come up to your specific observations, When I started to think about this IQ analogy and the way the curves might not have shifted so much and that we're overestimating things by defining obesity as a fixed threshold in the way it is, I actually contacted the epidemiologist named Katherine Flegal, who publishes all the reports that are highlighted in the press every time we hear, in five year intervals, the weight problem has increased dramatically. And I asked her exactly that question. "Well, what about obesity in other countries? Could it be, for example, that the curve in England or Europe has just shifted a little bit to the left?" Now I asked her the question and she said it might be but no one knows. The data have not been gathered in these other countries in a way that would allow you to compare. So the supposition that this problem is so much worse in the U.S. is not based on actual data.

And in addition, if you look at Europe, at least, obesity is an increasing problem there and I think we really need to understand what the distributions are there compared to the U.S.

Now Japan, well, gene pools in different populations are different. But remember, also, the Japanese who moved to the United States end up getting taller if they're raised here. So is height an environmental difference? No, it's genetic, but there are environmental modifiers.

And so the last point I would say is that genes play an important role. They determine where you are compared to your peers in the rank order of a given environment but between environments there can be shifts.

IRA FLATOW: Yes, another question.

AUDIENCE QUESTION No. 9: The question that I have is back to the point that you made about the person who loses a large amount of weight and then their calorie tolerance is less than the person who started out at that weight. Having had this experience myself over and over again, every time you lose some weight, you gain it back plus more. Does that explain that phenomenon, do you think, or is there something else operating there?

JEFFREY FRIEDMAN: You know, I don't know that literature as well perhaps as I should. There are some people who believe that you yo-yo down and then you go higher. I don't know. I'm pretty sure you go back to where you were. I don't know what the evidence frankly looks like in terms of how often you actually overshoot or not. It's hard to say because people who do this are always trying to modify their weight so they may not have been at their maximal or steady state weight when they started.

AUDIENCE QUESTION No. 9: That was my next question. You just didn't get there yet -- [overlap talking]

JEFFREY FRIEDMAN: Or you started out at a lower weight than would have been your set point because you were trying a little bit and then you try really hard and then when you give up the ghost you go back a little higher to where you would have been had you not been trying so hard in the first place.

IRA FLATOW: There was a news item that said New York's Dept. of Education is considering putting kids weight on their report cards. Talk about stigmatizing kids.

JEFFREY FRIEDMAN: Well, you know I would ask everybody, listen to what I have to say and then think about the things you'll read in the press about obese people and then substitute any other human characteristic in there in place of obesity. You'd never get away with it; you'd get arrested or something. I mean, the things that get said (people clapping). I'll give you a few examples. I was listening to Imus in the political campaign and they were talking about Bill Richardson as a possible vice-presidential candidate and a *Newsweek* reporter says Bill Richardson is being dismissed as a vice-presidential candidate because he's too obese. What else could you have said and gotten away with? William Sensenbrenner, a congressman, is quoted in the *New York Times* as saying to the obese, "Look in the mirror because you're the one to

blame." I could go on and on. You have an opera singer fired because they're too obese. And she correctly pointed out that this is the last bastion of stigmatization in the country. And so when you read these things, think about it. Should they be putting a kid's height on the report card? I don't know. Probably not.

IRA FLATOW: Or their IQ, or something.

AUDIENCE QUESTION No. 10: What specific avenue are you currently investigating?

JEFFREY FRIEDMAN: I'm really interested in a lot of things, but one of the main things is this neural circuitry. In particular, how the brain centers, at least in animals, that confer the basic drive are wired up and then how they communicate with higher centers. Now, it's actually more complicated than that. Feeding is what's known as a complex motivational behavior. That's in contrast to a reflex. A reflex you give a defined stimulus and you get an invariant response. A motivated behavior meets many factors that influence the likelihood of the behavior but no single factor guarantees it.

So let's think about feeding. Your leptin level makes a difference. Your emotional state makes a difference. Sensory factors, like smell, taste, vision, make a difference in the likelihood that you would eat. But no single factor guarantees that you will eat or not eat. So there are a lot of relative inputs that go into whether you eat or not that are ultimately converted into a binary decision. You either eat or don't eat at any moment in time and we'd like to understand how that happens. Now, not only do we not know how that information is processed, we don't even know where it's processed. And so we'd like to figure out where it's processed as a prelude to trying to understand how it's processed.

IRA FLATOW: So if you like to eat Haagen-Dazs and you know it's not good for you 'cause you're going to gain weight, don't put it in the house. Right? Give yourself that extra factor that you have to leave and go out and get it, then maybe you won't go.

JEFFREY FRIEDMAN: Right. Because of course another factor is the motivation. Do I want to walk out into the cold? But just to put a slightly finer point on it, imagine that you hadn't eaten for two days and the only food was rancid, smelled bad, you wouldn't eat it probably. But at five days, seven days, you might eat it. And you can play games like that all the time - complex information is processed.

IRA FLATOW: This woman here and then we'll move down to the front.

AUDIENCE QUESTION No. 11: Hi, Jeff. I came to a lecture here about one or two years ago and you spoke about your discovery of leptin and explained why it's not working in humans. So, I'm a nutritionist and I've told many people who come to me - and the first thing they say is "I hate myself," because they've been trying to lose weight all their lives -- and so I say what you said, there's this fellow named Jeff Friedman at Rockefeller University who says it's not your fault. So I think one of the most important things that you've done is really, if we could get the word out, to take the guilt off. And proof of that is -- I'm sure you've heard the stories of how many women have lost 100

lbs. for their daughters' weddings and gained the whole thing back plus more. But anyhow, given that, I don't want you to think that I haven't heard a word of what you've said but I still want to ask, there are some people who have literally been rails, so thin - Twiggy boned - until they're about 50 and suddenly they're hugely overweight, like 50 lbs. It seems as if it happens in a couple of years. How can you explain that?

JEFFREY FRIEDMAN: I'll come back to leptin in a second. But with respect to that, there are clear cases of people who are at a particular weight for most of their life and then it changes. And that's a really -- I can't explain that by an orthodox leptin system, I think there will be explanations in time but we really don't understand that at all. I'll just give you an example though about what could happen and this is a little bit abstract but, well, let me give it a try. Has everyone heard of narcolepsy? Anyone know what causes narcolepsy?

It turns out narcolepsy, which develops spontaneously, is a result in the majority of cases, of the loss of a specific neural population in the brain. Probably autoimmune, but it's not entirely clear. And then people develop narcolepsy because the neurons that control sleep just disappear. Well, we know in animals if you can make particular neurons in the hypothalamus disappear, weight can change, either increase or decrease. So it's possible. I'm arguing that maybe neuronal populations are shifting later in life and that accounts for it. We don't know that yet but what I want to point out is that it's at least conceivable that there be a biological explanation for these things in time.

Let me just make one comment about leptin. So leptin is in clinical development for a number of conditions. There's very good reason to believe that leptin can treat a subset of human obesity, probably not all, but a non-trivial subset. Just to give you an example, those leptin deficient kids are given leptin now and both of them are normal weight now; it's quite amazing if you look at the before and after there -- much better than anything you'll see on an infomercial.

AUDIENCE QUESTION No. 12: I just was curious, there's so much talk about genetic modified food. And we all seem to be involuntarily eating them. I was just curious, have there been any studies done maybe with leptin there, if there be a connection maybe, or a cause?

JEFFREY FRIEDMAN: So, there's no evidence I know of that genetically modified foods contribute to this problem and even if there was -- and if you're implying that you can ingest leptin, it's a hormone, it's like a protein and it would get digested in the stomach. So in order for leptin to have any effect at all it has to be injected. So I don't think oral leptin is probably likely to have too much...

AUDIENCE QUESTION No. 12: No, I was suggesting that maybe the foods we are eating nowadays are genetically modified and maybe it could influence the hormone.

JEFFREY FRIEDMAN: So, I don't know of any evidence that it's anything more complicated than the number of calories.

AUDIENCE QUESTION No. 13: I find it hard to believe that the gradual weight gain and the large weight gain in our population is not due to environmental factors like the increase in junk food and the more sedentary lifestyle. So my question is, if you believe that this weight gain is due to a genetic shift rather than environmental factors, why would it be selected for, like when, #1) it's not considered to be desirable and #2), it's not healthy and it even reduces fertility.

JEFFREY FRIEDMAN: I guess the first point is that I don't think there's been a genetic shift. I think there are environmental factors that exacerbate the problem. I think the debate is more about how powerful a factor is that. What does it have to contribute, versus genes, to difference in weight in the population?

So let me say it a little differently. There are two things we need to understand: why has average weight changed the amount it has over the last couple of decades, 7 to 10 pounds. We definitely need to understand that has important public health consequences. We also need to understand why today, in an environment where everyone has free access to calories, do some people weigh 400 lbs. and some people weigh 120 lbs. Those are both important questions. My view is that we'll best understand that by understanding the biological system that controls weight and then trying to deduce how environmental factors modulate it. I think that's probably more effective than just telling people to eat less and exercise more but time will tell.

IRA FLATOW: The whole idea about portion control would seem to fall into this idea of having more food available to you. If you ate a whole meal and you had half the size portions that you had you'd be eating half the calories, right?

JEFFREY FRIEDMAN: Well, yeah. But that makes the assumption that you couldn't get up and get another portion, which is what people will do.

IRA FLATOW: OK.

AUDIENCE QUESTION No. 14: Two questions. The first one is: what's your general opinion of appetite suppressants? It sounds like from some of the things that you're saying that appetite and weight being this equilibriate type of system, that unless you're willing to take them your entire life, you're eventually going to come back to where you were. And the second question is: the Atkins diet that has been very popular seems to have this view that you can eat as many fat and protein calories as you like and you'll, as long as you limit your carbohydrates, you'll either lose weight or be able to maintain your weight.

JEFFREY FRIEDMAN: OK, so the first question. It's almost certainly the case that you'll have to take any drug that modifies appetite for your whole life. That's probably a good thing. I don't know that I'd want to take a drug that permanently changed my neural chemistry. And these drugs are in development; they'll be tested.

But there's a deeper question, which is: given the prevalence of the problem, would you want to be giving a drug to everybody? I think you would if it could clearly confer a health benefit without a health risk. But on the other hand, you wouldn't want to take it lightly

either. So I think you'd want to look very critically about what the safety was and be willing to follow it long term. Because often times problems don't become evident with the relatively small number of patients who are in a clinical trial. OK, and the second question was Atkins. First of all --

IRA FLATOW: You've already said a calorie is a calorie is a calorie.

JEFFREY FRIEDMAN: People who believe Atkins works say you eat less carbohydrate, you make less insulin, and insulin is required to deposit fat and that's why it works well. At the same time, other people argue if you eat less carbohydrate, you store less glucose as glycogen and if there's less glycogen that's a stimulus to eat more and that's why a low-fat diet is better. So, there's a lot of different opinions about this, I think the thing that you can say with greatest confidence is that if you can convince people that that diet really works, you'll make a lot of money on your book. Whether or not one diet is better than another, independent of calories, is just an open question.

IRA FLATOW: You said that we don't have enough data to understand why there's been a 7 to 10 pound weight increase. Do you have a hypothesis of your own about why this might be?

JEFFREY FRIEDMAN: What I think is happening is this. It turns out that that weight increase isn't uniform across the population, and there's actually really good epidemiologic evidence to suggest that. I think that a lot of the weight gain is concentrated in specific ethnic groups. And I think that what we're seeing now is ethnic groups that are predisposed to obesity are now getting access to unlimited calories. And I think that has a lot to do with that weight increase. And there's some evidence to support that but it's not definitive. Actually a lot of the epidemiologic data that you would really want to understand things like this is lacking.

IRA FLATOW: Because it...

JEFFREY FRIEDMAN: Hasn't been collected properly.

AUDIENCE QUESTION No. 15: Can you genetically assay for a number of genes that are involved in obesity and tell that person you have one mutation, you have three, etc.?

JEFFREY FRIEDMAN: I think that's where things are headed. Right now we know enough to say that 5 percent of morbidly obese people have an alteration in a single gene that could be identifiable if you looked. Now most people don't bother to look if there's not a treatment for it, which in most cases there isn't now. But you could look and you could find it. That's probably a low number; it's probably higher than that. And I think as we learn more and new therapies develop, there'll be an increased impetus to try to figure out what the genetic basis for any given individual actually is.

IRA FLATOW: There's a new food pyramid that the government has put out. Any reason to pay attention to that?

JEFFREY FRIEDMAN: Well, I think that has two purposes. You should pay attention to the extent that to a large extent reflects what's a heart

healthy diet. And so I think it's a good thing. There's an implication that those same diets are beneficial or preventative for obesity, and I think the evidence for that is much less certain.

AUDIENCE QUESTION No. 16: People say that as you get older you gain weight. And I'm not sure if there's any studies done to actually measure the production of leptin or whatever among older population. The reason why I'm asking is because as you get older, supposedly, there's an onset for Type II diabetes and things like that, so that's one of the questions. And the second question is, I'm pretty sure you know, there's an obesity drug that's in clinical trial at this pharmaceutical company called Regeneron, and what your personal opinion is with that drug.

JEFFREY FRIEDMAN: There are a lot of anti-obesity agents in development. In the end, you have to get more data about what the efficacy and safety is, and time will tell for that drug and many others because there's a whole wave of these things coming. Now, it's a fact that people and animals get heavier as they age. We don't understand why that is. It appears that leptin levels go up and some people lose leptin sensitivity as they age. We have no idea why. I'll just digress to one other point that gets to your issue about the 7 to 10 lb. average weight gain. When you look at these data, they're not corrected for age, and so, if the population is aging, that could contribute also to the perception that weight is changing.

IRA FLATOW: We're also seeing a lot of fat little kids.

JEFFREY FRIEDMAN: Well, again. What you would have to do to really understand that is look at the curves and look at the distributions and that hasn't been done to the extent that it has -- it turns out actually that these really obese kids are concentrated in particular ethnic groups and the gene pools are different in different ethnic groups. I think there's a lot of complexity in how we look at the numbers here and the causes, but to simply to take the whole cross-section of the population, not thinking about what it's composed of and counting the number of people over a particular level of adiposity or BMI, which itself is flawed, is probably not the most nuanced way to think about the problem.

IRA FLATOW: What's the best way to judge for yourself if you're overweight or not? How do you know that?

JEFFREY FRIEDMAN: I'm thinking of a Potter Stewart quote.

IRA FLATOW: "I can't tell you what it is but I know it when I see it."

JEFFREY FRIEDMAN: Right. The most important thing is what your general health is. If you're overweight and not diabetic and not hypertensive and not hypercholesterolemic, then there's a lot less to think about than if you're diabetic and hypertensive and hypercholesterolemic.

My own opinion, and this is just an opinion, is if you're overweight and otherwise healthy, I would say try to be fit, try to eat a heart healthy diet and minimize your risk factors and try to enjoy yourself. (laughter and clapping). If you're diabetic and have these other

problems, then make your best effort to lose weight to the extent that it improves your health, do your best as you would for anything else.

IRA FLATOW: So you said, you can be fit and overweight at the same time.

JEFFREY FRIEDMAN: Right.

IRA FLATOW: Just a couple more questions.

AUDIENCE QUESTION No. 17: I just want to ask you about something you spoke about earlier when you were describing the difference -- I think you said the cortex in some people can be strong enough to overrule this leptin urge. Isn't that almost biological will power?

JEFFREY FRIEDMAN: Well yeah. This, I should tell you, is purely hypothetical but it at least represents a construct by which we can think about how do conscious factors interact with basic drives and so on. But that's the whole the point: what is will power? Well at the end of the day, you either believe we're metaphysical or we're not metaphysical, and I think at some point in the future we're going to say more about the chemistry of will power -- what part of the brain it's in, what kinds of neurons and what kinds of chemicals they might make. We don't know any of that stuff but that's really where science is heading.

IRA FLATOW: Is that different than addiction, chemically?

JEFFREY FRIEDMAN: Different parts of our brain confer different behavioral responses -- there are parts of your brain that are wired for reward and addiction taps into them.

IRA FLATOW: Could you be addicted to food? You could be overeating but it's just like an addiction to food and be treated or researched the same way you might be addicted to alcohol or drugs or anything else.

JEFFREY FRIEDMAN: This becomes a semantic argument but the truth is we're all addicted to food.

IRA FLATOW: It's a good thing to a certain extent.

JEFFREY FRIEDMAN: Well, yeah, you have to eat. And so we need to understand that wiring but clearly other compounds and chemicals can sort of intervene or co-opt that machinery.

IRA FLATOW: OK, one more question.

AUDIENCE QUESTION No. 18: Thank you. My question relates back to the controversy over the calorie quantity vs. quality, and I'd like to tie that into the context of the identical twin studies. I think the twin studies do a great job of showing that we don't have so much control over our biological urges for food consumption. However, the disappointing thing about those studies is you're looking at people who are brought up in a similar environment, raised on a similar diet. So I was just wondering if there were any studies examining... let's say you had two people with the same genotype -- identical twins - and the same genetic disposition for obesity. You had one that was raised with a

modern western diet, unlimited access to calories, highly addictive foods, high GI foods, bad fat ratios, in a sedentary lifestyle. And then you'd have the second person who was raised on a more traditional diet with no refined grains, no processed foods, no high fructose corn syrup added to beverages, no hydrogenated fats, not nearly as palatable a diet as the first person with the western diet, but also with regular physical activity and also unlimited access to calories. It's sort of a round about way of asking..

IRA FLATOW: I think you left out TV viewing in there. (laughter)

AUDIENCE QUESTION No. 18: But seriously, if you have these two scenarios where you're clearly taking somebody out of the mainstream western society where you really don't have much of an option whether or not you consume the high GI refined grain product or the burger with the loads of saturated fat, the burger buns ... are there any studies that really show a distinction between types of..

JEFFREY FRIEDMAN: Yes. There are two studies. First of all, these twin studies were criticized for exactly that reason, although phrased slightly differently. And they were then redone with identical twins reared apart compared to fraternal twins reared together. So you're actually biasing against the identical twins so now the heritability falls from 80 percent to 70 percent. Still 70 percent -- and the other 30 percent could not be accounted for by the environment for those kids. Another way to look at this, actually, is to take kids who are adopted and ask on average, do they resemble their adoptive parents or their biological parents, making the assumption that some go to one environment, others to the other. They, to a very large extent, resembled their biological parents independent of the environment that their adoptive parents provided.

IRA FLATOW: Thank you very much Jeffrey Friedman. Thank you all for coming.