The Science of Fat (2004)
Lecture One—Deconstructing Obesity
Jeffrey M. Friedman, M.D., Ph.D.

1. Start of Lecture One (00:15)

[ANNOUNCER:] *From the Howard Hughes Medical Institute... the 2004 Holiday Lectures on Science. This year's lectures, "The Science of Fat," will be given by Dr. Ronald Evans, Howard Hughes Medical Institute investigator at the Salk Institute for Biological Studies, and Dr. Jeffrey Friedman, Howard Hughes Medical Institute investigator at the Rockefeller University. The first lecture is titled "Deconstructing Obesity." And now, to introduce our program, the president of the Howard Hughes Medical Institute, Dr. Thomas Cech.*

2. Introduction by HHMI President Dr. Thomas Cech (01:04)

[DR. CECH:] Welcome to the Howard Hughes Medical Institute and the 2004 Holiday Lectures on Science. We're web casting this live, and our audience consists of high school students from throughout the greater Washington, D.C. area. This is the 12th lecture in our series. To learn more about these lectures and other HHMI activities, go to our web site... Now, the title of this series is "The Science of Fat," and we picked that title somewhat carefully, because we know that many people are uncomfortable thinking about or talking about their own weight. Now, rather than point fingers, we want to explore the science behind obesity and weight control. Ron Evans and Jeff Friedman will be our guides for understanding "The Science of Fat." Is obesity a disease? What does science tell us about the health impact of being overweight? How much does your heredity contribute to maintaining a healthy weight relative to your diet or exercise? And can science help us find treatments for the negative health consequences of obesity? Now, our first speaker is Jeff Friedman, who is a Howard Hughes Medical Institute investigator at the Rockefeller University in New York City. Jeff was long interested in how single genes can affect complex behaviors like appetite, and in 1994, he grasped what is a holy grail of obesity research. He identified a hormone that appeared to control whether mice were obese or thin, and it turns out that the same hormone has a very similar function in humans. He named the hormone leptin. Since his seminal discovery, Jeff has gone on to understand, in molecular detail, how leptin works and begin to understand how the brain plays a key role in controlling weight. The title of Jeff's lecture is "Deconstructing Obesity." And now, let's have a short video to introduce Jeff Friedman.

3. Introductory interview with Dr. Jeffrey Friedman (03:33)

[DR. FRIEDMAN:] Growing up as a kid, I always wanted to be a veterinarian because I loved dogs, but in the family I grew up in, being a doctor was sort of the highest level of achievement. My folks encouraged me to go into medicine. They didn't actually think it made much sense for me to go into science, but it turns out, that's what I wanted to do. And I remember being absolutely mesmerized by the fact that behavior and affective state could be controlled by molecules. And I was just interested in that general theme. There's a genetically obese mouse. The animal weighs 3 times that of a normal mouse and has 5 times as much fat because a single gene is defective, and so over the course of the next 8 years, efforts to refine the chromosomal location of the gene were advanced, ultimately leading to the identification of the defective gene. So the gene that we ended up finding or localizing in that fashion is now known as leptin, which is a hormone that plays an important role in regulating food intake and volume. Well, that was an unbelievable experience. I mean, to have worked for 8 years on something, never knowing for sure if you're gonna identify it or what it's gonna be when you do, and then to have that moment of discovery was just amazing. The problem that nature had to solve is quite extraordinary, really. We consume a million calories a year, tens of millions of calories over a decade, and for most of us, our weight doesn't change very much. And I think the identification of leptin really suggests or has

told us, to a large extent, how, in part, how nature counts calories. And so I think one of the challenges is gonna be to understand or identify as many of the components of the system as we possibly can so that we can also get entry points to develop new therapies. I would like to communicate to the students what a scientific view of obesity looks like. I think there's a lot of attention paid to this in the lay press, but I think what you often read about is driven not so much by the science, but rather market and economic forces. And the second thing I'd like to try to do is share with the students the sense of excitement that I feel about a career in science and at least know the type of research that we do and the sorts of questions that are now available for inquiry.

4. Understanding human diversity through science (06:04)

Welcome. It's really a great pleasure to be here and follow up on the remarks I made a moment ago. I'd actually like to begin, of course, by thanking Dr. Cech for the kind introduction and also thanking the Institute for-- I have deep roots with the Institute, and it occurs to me that they began supporting the research I'm gonna tell you about when I was closer in age to all of you than I am now, at a time when it was not at all clear where the research I'll tell you about was headed or what it was gonna show when it was concluded. So, I thought I'd begin by just asking you a couple of questions. Who in the audience is seriously interested in a career in science? Most of you, actually. Have you thought about why? I can't imagine you haven't. I thought I'd begin by telling you a few of the things that I think are important about doing science-- at least for me, and perhaps for the broader enterprise. I think the quest for knowledge and the excitement that accompanies discovery is a fundamental attribute of our species, and for many of us, it's a way to act on our innate sense of curiosity and experience the exhilaration of discovery. And I can tell you from personal experience, it's about as exhilarating an experience as there is. I think, in a cultural sense, advances in science improve the diagnosis and treatment of disease and improve people's lives as a consequence. I think part of what I want to communicate today, though, is that science, I think, can also help think us more deeply and critically about who we are and the basis for our differences. And I think in many instances, it can lead us, as people, to be more compassionate and perhaps celebrate and better understand our differences and our diversity rather than making judgments about them. I should tell you that evolution has a very deep interest in making sure that our species is diverse. By having a wider array of phenotypes, as it were, or differences, the species is able to better cope with the inevitable or frequent, and often catastrophic changes in environment that often allow only a subgroup of the population to survive. So diversity, from an evolutionary point of view, is absolutely critical. So, that diversity is expressed for almost every one of our features, including-- not surprisingly, based on the title of the lecture-- the amount of fat we carry. And as I mentioned in the preamble to this, nature has a problem. It has to manage our calories, which are stored as fat, in an intelligent way-- leaving us fat enough to survive the inevitable famines that took place over the course of our human history, but also not so fat that we develop some of the diseases that I'm gonna tell you about today. So, in the first lecture, I'm gonna talk in general terms about what are the factors that lead-- that regulate the amount of fat, and how nature achieves the sort of exquisite balance that it does. And then tomorrow I'm gonna share with you at least some of the scientific questions that we're grappling with at the moment. So, the title of the talk is "Deconstructing Obesity," and what I'd really like you to do for the next 40 minutes or so is set aside whatever preconceptions you have about this problem and join me in trying to think about it the way a scientist might.

5. People have opinions about what causes obesity (09:25)

Now, part of the problem here is that for almost every disease, save obesity, people don't generally have an opinion about what causes it and would leave it to the experts. So, if I were up here talking about heart disease, ulcer disease, mental illness, or cancer, or AIDS, I think if someone asked you what causes these problems and how would we treat it, you'd probably react that-- "Well, let's leave it to the experts." That's not the case, I think, to the same extent for obesity. So, let me ask for a show of hands. Who has an opinion about obesity? What causes it? I'm surprised that's all. Well, that's actually not as much in many

audiences, but certainly a lot of you have an opinion, and it shouldn't be surprising that you do. It's all over the newspapers, and as we'll mention in a moment, it's frequently the subject of television shows. To follow up on this a little bit more, let's go to the next-- to the first poll question. There's a wide array of weights, and some people--and we'll define this in a moment-- are morbidly obese. Let's ask the question: Is it fair to hold the obese-- the morbidly obese-- responsible for their condition? Is it their fault? Let's see what the poll says. Remember, this is anonymous. We will not know who voted for which, so you'll all get your bag of goodies no matter what you answer. 43% say yes; 57% no. Well, I would say, based on my experience, this is an exceedingly enlightened audience.

6. Obesity is associated with many diseases (10:56)

OK. Well, whatever you think about the causes and the level of responsibility of the people who are afflicted, this is an important health problem. Obesity, for reasons that we're only beginning to understand-- It's associated with a series of diseases: Type 2 diabetes, hypertension, heart disease, fatty liver-- a precursor of cirrhosis-- that in aggregate are the major causes of morbidity and mortality in the developed world. And for all of these conditions, weight loss, even moderate amounts of weight, have a disproportionate health benefit. So, if you suffer from these conditions and are obese, losing weight is going to improve the problem. Now, we'll talk in a moment about why it's actually a lot more difficult to lose weight than it seems it ought to be. So, let's think about this now, instead of as a cultural problem for the moment, a scientific problem, and let's think about how we would approach something that affects, perhaps, 40% of our population.

7. Definition of obesity and the body mass index (BMI) (11:56)

Well, the first thing we should do is define-- figure out how we're going to define and measure the problem. Then we'll think about what causes the problem, and then we're gonna talk about what we can do about it. OK, let's talk about the definition and the measurement. Obesity: an excessively high amount of body fat or adipose tissue in relation to lean mass-- which is basically muscle and bone mass. And as I just mentioned, the amount of fat, and also its distribution, have important health consequences. It turns out fat in your midriff is worse than fat elsewhere in your body-- again, for reasons that aren't well understood. Now, the definition here says that we need to know how much fat an individual carries, but it's actually quite cumbersome to measure fat directly, and so all of the lay press that discusses obesity refers to an easier measure of the percent fat that's sort of a surrogate measure, known as BMI. And this is weight in kilograms over height in meters squared. It's a sort of semiempiric measure that's designed to basically assess your weight without penalizing you for being big. So it's your weight corrected for your size, as it were. And this, as I'll show you in a moment, has some reasonably good correlation with fat content. And for those of you who want to know what your BMI is, I think in the materials that were passed out to you, there's a wheel, and so you can all calculate your BMI, but perhaps a little bit later. Now,

8. Animation: BMI and body shape (13:18)

what does BMI actually look like? And could we roll the video here? This videotape just scans across what the BMI would be for a 5' 10" individual, a male, at a different weight. So, this man has a BMI of 24. He's 5' 10", 167 pounds. He is not obese. And, of course, there are many people thinner than this fellow. If he weighed 126 pounds, he'd have a BMI of 18. Scan up. Above 25, people are said to be overweight, so this fellow looks not the thinnest person around, but he's overweight here, because his BMI is now 25 with a weight of 174 pounds. Let's scan up. If you have a BMI of 30, weight of 209 pounds, you're said to be obese-- clinically obese. A BMI of 35, your weight is 244 pounds, it's-- obviously this fellow is significantly obese now. And at a BMI of 40, which corresponds to 5' 10", 279 pounds, this is said to be morbidly obese. But there's a range. You just walk the streets, and you'll see a range such as this. Now, there are some problems with the BMI. I'll illustrate one here. It doesn't really

distinguish whether your fat-- your weight is coming from fat or muscle, and so it's a reasonable measure from a public health point of view, but it's not a perfect measure for the individual. In fact, actually it was derived exclusively—originally from actuarial tables setting life insurance rates.

9. Limitations of BMI (14:50)

Well, there are a number of other problems with BMI besides the issues having to do with muscularity. Another is that it's often not corrected for age, and I can tell you from personal experience that people get heavier as they get older, and so one really needs to take into account ages when using BMI. One can also ask, "Why is it height squared?" And that's a completely empiric designation. It seems BMI over height squared gives you a slightly better answer than other exponents. And, as I'll come to in a few moments, the fact that we define it as a fixed threshold is a little bit arbitrary and can create, I think, misconceptions about the actual changes in frequency of the problem. Let's just take a quick look at some real data that I think some of you-- Who participated in that Bod Pod experiment? So the Bod Pod is a way to measure fat directly, and so what's shown here is a data set that includes many of you comparing BMI to fat mass measured directly using a new method known as a Bod Pod. And what you can see here is that there's a reasonable correlation between BMI and percent fat, but it's not perfect, and if you look at, for example, BMI of 25, many of these people are lean based on definitions, and others are-- are quite obese with percent fat above 30, in some cases, versus below 20. So, BMI is, by no means, a perfect measure. So, we find it useful in certain instances, but I'll come back, as I mentioned, to explain why it has important limitations. But let's ask a different question. Forget about BMI for the moment. Look at percent fat-- really variable. Some of you had a quarter to a fifth as much fat as others of you. Wide variation. Why is there such variation?

10. What causes obesity? (16:39)

What causes this difference, or what causes the problem of obesity? In a very general sense, I can think of 3 possible explanations. There may be more, but I think, in general, they can be grouped into one of the 3 headings. Obese people, you might argue, suffer from a lack of willpower, and they don't exercise the same sort of restraint for food intake that lean people exercise. I find this point of view is generally favored by lean people. Other people argue this is a lifestyle problem. The problem is our environment-- this modern environment where a sedentary lifestyle combined with overeating or free access to calories, that's what causes the problem. And then a third possibility is that there's a biological explanation for differences in weight that has to do with our genes. Now, I want to emphasize at the start that these are not mutually exclusive explanations. And for many other human traits, what we have is a network of genes being modulated by environmental factors and willpower-- conscious factors-- that might affect behavior in a local environment for that individual. And we really, in the end, would like to understand how these all interact, and I think that's the challenge. Unfortunately, I think, much of what's public discussion on this centers on assumptions about the powerful contributions of willpower and environment to the exclusion of the powerful effects of biology. Let's take another poll now with respect to these 3 possibilities. Which of the following do you think is the most important factor causing obesity? Remember, I think we can all agree they probably all contribute, at least to some extent, but which do you think is the single most important problem? Vote "A" for lack of willpower, "B" for lifestyle, "C," biology and genes. OK. Do you have any poll results? This reminds me of Election Day a little bit. I'm nervous, waiting for the votes from Ohio. OK, most people think it's lifestyle: 57%. 18% think it's primarily willpower; 25% biology and genes. Now, of course, lifestyle involves personal choices, so there is an element of willpower there, so let's start talking about willpower.

11. Is the lack of willpower the main cause of obesity? (18:54)

Well, it should be no surprise, I think, that many people think willpower and lifestyle issues are a major contributor. We're bombarded with that message by the advertising industry-- funded by the diet industry-- almost daily. Can we have--run this video? In the form of advertisements like this.

[VOICEOVER:] Are you tired of being overweight? Tired of the latest weight-loss fads? Wouldn't you like a plan that just works? Well, now it's easy. Just follow the Kant-Miss Weight Loss Program, and you, too, can be slim and trim. Just follow our simple meal plans, and your extra pounds will disappear like magic. If you really want to lose weight, decide now to follow the Kant-Miss Weight Loss Program.

[DR. FRIEDMAN:] I should tell you that this plan is not endorsed by the Institute, and the Institute does not have a financial interest in it at all, but the message is pretty clear: Spend your money, take advantage of the opportunities provided by our plan, and you'll be fit and trim. There's a problem with it, though, and that is that that simple notion that you can simply change your intake and change your activity and fix your weight problem ignores one of the most powerful laws in biology, which is the first law of thermodynamics.

12. Obesity as a result of energy input/output imbalance (20:19)

Anybody know what the first law of thermodynamics is?

[STUDENT:] There is no loss of energy. All energy is used.

[DR. FRIEDMAN:] I think--I think that's basically right. It's basically the law of the conservation of energy. So, what does that look like? It means that for any system, which includes living organisms, the amount of energy put into the system is balanced against the energy utilized, and any difference in either direction results in the amount of energy that's stored, and this applies equally well to living organisms based on the amazing work of a Prussian surgeon named von Helmholtz. Well, let's now relate this equation to food intake and people. Your food intake is balanced against your caloric expenditure, and the difference is the amount of calories-- number of calories you store as fat. Now, there are some challenges here. Over the course of a year, you eat a million calories a year, and you need to balance that against a million calories expended, or else your weight is gonna change. And if you actually look carefully, people's weight don't change very much year to year unless they're actively dieting or have some inner current illness. Now, the problem gets even more vexing if you now think about a lifetime of consumption. Over the course of a lifetime, we'll eat tons' worth of fat, protein, carbohydrate. Convert that into CO2, waste, and a small amount of work, and even less exercise, in my case, all the while maintaining a relatively constant weight. In studies in South Africa, Sweden, and elsewhere, it's been observed that weight doesn't change very much more than 10 pounds per decade. This is this increase in weight with age. Now, if you now balance the calories in against the calories out with a 10-pound weight change over a decade, what you come up with is 99.6% precision for this system, and that's pretty-- pretty accurate calorie counting. So, over the course of a decade, you'll take in tens of millions of calories and balance the amount of calories in against the calories out with amazing precision. Compare that precision to the errors on food labels. If you actually do calorimetry-- a way of actually figuring out the energy content of food-- the error rates are astounding. So if you depended on the actual error-- the actual caloric content of the foods you eat, you'd be doing orders of magnitude less well than nature does. Now, this kind of musing has led many people to believe that there's a biological system that counts calories for us and that somehow unconsciously indexes the amount of food we take in against the amount of energy we burn, and that food intake is part of a basic bodily drive. That should be no surprise. Every organism eats and manages their nutrition. And in fact, if you believe that such a system is irrelevant to human behavior, you would have to believe that this basic drive accounts for food intake in every organism up to monkeys and stopped at monkeys, and that somehow, now, it's regulated differently among us.

13. Eating is a basic biological drive and can overwhelm willpower (23:19)

Now, to illustrate this potential tension between a biological drive-- a basic primal drive-- and a higher cognitive wish such as to lose weight, we could do an experiment. And so, oftentimes, I suggest to people that they can get-- make an easy $5 million. The only thing you have to do now is hold your breath between now and the end of my lecture. Well, what does this-- How does this play out, actually? Well, you might be highly motivated to cash in the $5 million check that I just offered you, but you all know innately that the basic drive is gonna win out within a few seconds or, at most, a few minutes, and so nobody even bothered. Did anyone actually bother to try to hold their breath? You did? Well, we had one person. If anybody turns blue, I hope we have a crash cart here. So, what we're talking about is, you have a basic drive to breathe. You might be highly motivated under certain circumstances to hold your breath, but sooner or later, you're gonna breathe. Now, that's the true of almost all our basic drives. They just play out over different time frames: breathing over seconds to minutes. Sleeping over days. You might want to stay up all night for a couple of nights. It's not gonna happen. Drinking, you can probably hold out for days. Sex--I don't think we want to go there. The thing about eating is that this plays out over a longer time frame, so that by the time the drive begins to express itself, because we have calories stored as fat, we no longer recognize it as being the drive, and we just assume it's a problem with our willpower and/or our lifestyle, which we'll talk about. Now, to sort of drive this point home a little more, I'd like to ask the volunteers to come up, please. Were you one of the volunteers? No? OK. We had a few already. So, let's pass these out, and this will be part of our experiment. Did anybody miss breakfast today? Raise your hands. Who's hungry? OK. We're gonna pass these out. These are Twinkies and Ho Hos. You're... Wait, wait. You're not allowed to eat them. You can't eat them until Dr. Evans' lecture is done. Now, the point-- I'm sorry. I'm sorry. It's an experiment. This is all in the name of science. You can look at them. OK, for those of you who are hungry, look at the food and think about the fact that it's hard to resist that. Now, imagine now resisting the food that you might want in the face of a basic drive extended over a much longer time frame. And I'll try to explain to you in the next section what this part of this drive is derived from, but it's this basic drive to eat when you're hungry that leads to most diets to fail within 1-2 years. It's a 70-95% failure rate of dieting. So willpower's not the whole story here.

14. The role of environment as a cause of obesity may be exaggerated (26:26)

What about lifestyle and environment? We talked about this with the poll, and the sort of evidence that you'll see with-- to support the idea that this is a lifestyle problem is calculated here where people index obesity rates over time and see that obesity rates are going up, they say substantially. And people argue that our genes haven't changed... it must be the environment. Our genes don't change over this time frame. Actually, that assertion belies a lack of understanding of how natural selection actually operates, but let's set that aside for a moment. You would imagine from this that there's never been obesity before. In fact, let's go to a quote... “No age has ever afforded more instances of corpulency than our own.” Anybody know who said this? Anybody want to guess when this comes from? This is a British physician-- Thomas Short--in 1727. Well, obesity's not a new problem. The first sculpture ever found, the Venus of Willendorf, is shown here on the left, and there were clearly obese individuals from the 1800s, so where does this disconnect come from? Why is it that we think there's so much more obesity? Well, I think part of the problem comes from the fact that we define it as a fixed threshold. Look here. You're obese if your BMI is over 25, and-- You're obese over 30, overweight over 25, and there's a known phenomenon in epidemiology that when you have a fixed threshold for a trait, a small shift in the average value has a disproportionate effect on the number of people who exceed the threshold. So, the threshold for obesity is a BMI over 30. Here's the distribution in 1990. Thank you for passing out the Twinkies and Ho Hos. This is the distribution. This is schematic. I'll show you real data in a moment. In 2000, the BMI has gone up 1.4. That's 7 to 10 pounds. The threshold hasn't changed. So now more people exceed the threshold. There's been a 50% increase in the rate of obesity, accounted for by a 7- to 10-pound weight gain. Now, here's the actual data corrected for age, which most of the data is not, and it doesn't look that different. Now, I'm not saying there isn't a change. There are clearly more people in the obese range in men and women of this age group than before. Someone eating their Twinkies? Uh-oh. Can we get a picture of

that? That's our next speaker-- is eating the Twinkie. More people exceed the threshold than before. There has been a change, but it's not of the magnitude that you would think if I told you obesity rate increases by 50%, and so I actually think it's much better to look at this problem by exploring distributions of this sort than by simply counting the number of people who exceed the threshold. Now, I don't want to diminish the importance of this environmental change and tell you that if we could roll back the clock and reduce weight on the part of people 7 to 10 pounds on average, that would be a good thing, and public health would improve, and we should try to do that, and actually, lifestyle choices can be effective in many cases for reducing weight in that amount. So I think environment is clearly important, but in a quantitative sense, it's not of the magnitude that you would imagine it to be when you hear rates increase by 50%. Now, there's another question beyond what in our environment is responsible for this increase, and that is, today, where everyone basically has free access to calories, is weight so variable? How is it that in an environment where nobody goes hungry anymore-- which is the case in the U.S., generally-- how is it that weight is so variable and some people can weigh more than 400 pounds and other people less than 100 pounds? And the answer to that question, I'm gonna argue for you in a moment, is genes-- that genes play a very dominant role in explaining phenotypic differences in a population at a moment in time, and that will be the subject of discussion in a moment, but first, I thought I'd stop and take a few questions. So, questions, anyone?

15. Q&A: Why the difference in obesity between the U.S. and Europe? (30:28)

[STUDENT:] If you take into account the potential effects of the environment, how do you explain the differences in the proportion of obesity, for example, in Europe, where the eating environment is clearly different? But I wouldn't think that there would be such a difference in gene distribution.

[DR. FRIEDMAN:] Well, that's a very important question, and I think Dr. Evans will treat that in his lecture and I in mine, as well. Different populations have different propensities for obesity, and it may actually have to do with the selective pressure that each population was under over time. Not every population shared the same environment. Now, with respect to potential differences in obesity rates between obesity in the U.S. versus Europe, there's a rather global assumption that obesity is much worse here and that there's less obesity in Europe. I'm not actually sure to what extent that's the case, because the data are not available for this in Europe of the sort that you would need to draw a conclusion. So people rely-- unfortunately, I think-- on their anecdotal experiences; seeing fewer obese people on the streets, they say, in Europe than they might somewhere in the U.S. I'm not sure that would actually bear out if you did the epidemiologic studies that need to be done. I owe you a T-shirt for a really good question.

16. Q&A: Is obesity linked to depression or other emotional states? (31:45)

[STUDENT:] Do you believe that obesity is caused by more psychological disorders like depression? And genes could lead to depression, so they're all linked together in one way.

[DR. FRIEDMAN:] There are no studies that I know of linking differences in emotional state or emotional inclinations to differences in weight. So I think, clearly, emotional factors can transiently change weight, but I don't think that's the driving force for differences in weight. I think--we'll talk about the physiology of the system that regulates weight in a moment, but I don't think things like psychological factors are gonna be a major influence on it.

17. Q&A: Are there racial differences in the tendency to be obese? (32:32)

[STUDENT:] Have you found certain racial groups to be more obese or less obese than others?

[DR. FRIEDMAN:] Yes. There are clear differences in populations in general, and I'll come to that tomorrow. In general, those populations that carry a hunter-gatherer lifestyle into modernity become the

most obese when then exposed to a diet with ample calories, such as we have today. And we will talk a little bit, as will Dr. Evans, about what those populations actually are, but I think there are clear population and ethnic differences. But remember, of course, what we're talking about is the distribution within populations, and so within any population, there are gonna be heavier people and thinner people. It's just the curve moves slightly depending on the environment that population endured throughout their history. OK. Well,

18. Adoption and twin studies show that obesity is highly heritable (33:28)

I'm a geneticist, so it probably doesn't surprise very many of you that I'm gonna argue that biology and genes play an important role in accounting for differences in weight. So let me ask you all a question. Tell me, how do we know that a particular human trait is genetic? What can we do to try to figure this out? Anybody want to venture a guess?

[STUDENT:] Isolate the genes and then do a PCR on it and take it through, probably, an electrogelphoresis and then compare where you did your base pairs to the trait of the individual.

[DR. FRIEDMAN:] Well, that's what we would do-- and it's actually what we did with the mice that I'll tell you about in a minute-- once you know it's genetic. But let's say, you know, we were starting out, and we didn't even know DNA was the genetic material. So let's take a step 50 years back and say, "Are there ways to assess genetic contributions?"

[STUDENT:] Couldn't you just watch and see if you saw some more traits throughout generations within the same family?

[DR. FRIEDMAN:] Great. That's one way. It runs in the family. And so if you see a trait running in the family, you might assume it's genetic, but then someone skeptical might say, "Wait a minute. "That might be a family that eats a bad diet, "or they have a local environment that leads them to develop, and it's not genetic." Can anyone think of other ways you might go about it to try to rebut that?

[STUDENT:] Nowadays, twin studies can be done where you have identical twins that are raised in separate environments, and you can see whether there's a correlation between how they are raised in the separate environments and whether it's genetically correlated.

[DR. FRIEDMAN:] Yeah. That's the classic way, and you just saved me some time in my next slide, but before I do that, I'll tell you one other way which relates to addressing this family-study business, and that is adoption studies. You can compare adoptive kids, kids who have been adopted, to their adoptive parents and their biological parents, and what you find is that adopted children resemble their biological, not their adoptive parents. Does everyone see why that would be evidence that this would be genes and less environment? And then the classic way was just mentioned-- systematically compare sets of identical and fraternal twins. Since identical twins-- monozygotic twins, said more precisely-- share environment and genes and dizygous twins share environment and less genes, if monozygotic twins are more alike for a trait, we can assume there's a genetic basis and actually quantitate it. So look at this. The monozygous twins are remarkably similar. The dizygous twins come in all different shapes and sizes. And if you actually want to be really stringent, you can do these studies looking at identical twins separated by adoption, and you still find that the incidence of obesity is very highly correlated among the identical twins. Now, using such methods, you can assess the genetic contributions to a particular trait. The actual number here refers to the percent of the variance in the trait that can be accounted for by genetic factors And so what you can see are, a number of traits have genetic contributors-- never, for these conditions, 100%, but significant genetic contributors for height, schizophrenia, diabetes, hypertension, alcoholism, and heart disease, height being the highest. Where do you think obesity falls on this table here-- top, middle, or bottom?

[STUDENT:] Top.

[DR. FRIEDMAN:] Top. Well, top is right. You should get a T-shirt, but I'm not supposed to throw them out if it's not the Q&A session, so we'll give you one later. Obesity--.80 to .90-- as hereditable a trait as has been scored with the possible exception of height. Keep in mind, of course, that height is highly variable in the population but is also different between populations. Some Oriental populations are not as tall as Americans. The average Civil War soldier was 5' 7" tall. So what you come to here is the fact that genes contribute to differences in weight, but not 100% so, and that, in the end, there will probably be powerful genetic influences with certain environmental modifiers.

19. A genetic example of obesity: Leptin deficiency (37:42)

Now, to illustrate the power of these genes, I'm gonna tell you about a case report of a child in England who was of normal weight at birth but began to develop morbid obesity beginning in infancy, and here's a picture of the kid. In addition to being overweight, he markedly over-ate, was prediabetic at the age of 4. He weighed 90 pounds with 57% body fat. His 8-year-old cousin was similarly affected, and this young girl weighed 200 pounds, which is what I weigh. OK. 205 pounds, but it was close. Now, a clue that this might have been an unusual cause of obesity came from the fact that the child came from a highly inbred pedigree. Anyone know what that would suggest?

[STUDENT:] That their family may have had relations within their own family, I guess.

[DR. FRIEDMAN:] Yeah, that there may have been-- Well, a lot of populations don't discourage first-cousin marriages. So in those cases, rare genetic differences often get expressed with a frequency that's not seen in the general population. And that was the case in this kid, who was found to be deficient for this hormone leptin. Anybody know what a hormone is? Can anyone tell me what a hormone is?

[STUDENT:] A hormone is a molecule that is released from one area and travels through the body to affect another tissue.

[DR. FRIEDMAN:] That's right. And so leptin is a hormone I'm gonna tell you more about, but because it's a hormone, it could be made in the laboratory and given back to this kid. And let's see what happens when you give this kid leptin back. He's gotten taller, lost weight. Fat has fallen, and he's much less prediabetic than he was. His insulin levels have fallen. In addition, the people who did this work-- a colleague in England, Stephen O'Rahilly-- gave this kid a test meal before the first leptin injection and gave it to cousins of this child who were similarly affected, and some of these kids ate as many as 2,000 calories at a single meal before they got leptin. That's about the daily caloric intake of an individual my size, and this kid, at the age of 4, was eating it at one sitting. They give the kid some number of leptin injections, and now he eats the correct amount of calories at that single meal. So what's driving appetite in this kid is not lifestyle. It's not willpower. It's the lack of leptin. And you give him the leptin back, and his appetite normalizes, and actually, many of the features of this syndrome are improved. So here's a picture of the kid at 3 years of age. Here's the picture now of the kid at 8 years of age-- 5 years getting these hormone injections. I'd like to ask yourselves to think for a moment about what you would think about a child walking down the street who looked like this and what you thought about his upbringing or his parents' performance versus looking at a kid like this. It's the same kid. And so I think it's fair to begin to ask, might there not be other biological explanations that account for differences in weight similar to this in genes, the identity of which we haven't sorted out yet? And we'll come to this in a moment in this and the next lecture, but before I do that, let's digress for a moment and talk about what leptin is and where it came from.

20. Genetically engineered leptin-deficient mouse (41:19)

Leptin is the defective gene in a genetically obese strain of mouse. This is an OB mouse on the scale being looked down upon by its two lean sibling littermates who live in the same cage with the same amusements that lead this animal to be so obese and the others not. And actually, for those of you who want to look at the mouse at the end of the session, you can come down. I'll show you. There are a couple of OB mice, as they're called, and a lean littermate, and here they are. It's not evident at the moment, but one of the things that becomes obvious if you spend some time with these mice-- and I've spent a lot of time with these mice-- is, the fat one doesn't move around as much. So in addition to eating more, he's rather sedentary. He would be the equivalent of a-- Well, I don't want to go there.

21. Leptin, a hormone secreted by fat, influences appetite (42:13)

Well, how does this system work? What is leptin? Leptin is a hormone made by fat tissue that's secreted into the blood in proportion to its mass. It communicates a signal to brain centers that regulate the basic drive to eat as to what the amount of stored energy is so that adjustments in food intake and energy expenditure can be brought to bear to maintain relatively constant weight. The idea of this system is not to control weight to the pound, but rather to keep weight within a 10- to 15-pound range that allows, in an evolutionary sense, the population to keep weight at, you know, a somewhat optimal level. So if you could roll the tape here, this will sort of explain how the system operates.

22. Animation: Leptin feedback-control system (43:01)

So at equilibrium, at your normal weight, leptin is made, and you're eating different types of food. Now let's imagine you were starving or you went on a diet. Your fat mass would contract, and you would make less leptin. This is now the state that led to the less fat. So you've been eating less. Now the response to low leptin is to eat more. A low leptin level is a very powerful stimulus to eat more, gain weight, and return your weight to the starting point. Now let's imagine instead that you went on a binge of eating. You spent an extended period of time eating at wonderful restaurants. You would get fatter and make more leptin, which would then suppress your intake again until your weight returned to the starting point. Now, by such a mechanism, again, weight can be maintained within a range. I'll point out to you that if you diet and your weight falls, leptin level will fall, and this is a potent stimulus to regain weight.

23. Leptin deficiency causes obesity; leptin replacement cures it (44:00)

It's sort of what's evident in this kid. Let's think about why this kid is obese. The child is morbidly obese. He fails to make leptin. Because of this, no signal is generated that informs the brain that there's adequate nutritional store. So this is a potent stimulus to eat more and burn less, the net result of which is more and more fat which never makes the leptin that signals there are adequate nutritional stores and would suppress the food intake. So leptin deficiency is a very powerful stimulus to eat more. Now, actually, what happens after a diet for most people is quite similar to this. When you diet, your leptin level doesn't disappear altogether-- although it can-- but rather, it goes down. That's a stimulus to eat more, and it's that basic drive-- driven in part by this new lower leptin level-- that leads to the failure rates in dieting over the course of a year or two. Now, what I showed you in the case of the leptin-deficient kid is that leptin treatment improves or essentially corrects the condition, and that's the case for most hormones. In most cases, treating a hormone deficiency is rather easy. You give the hormone back, and people respond to it. And so in addition to the treatment of leptin mutations, leptin treatment has proven to be a very effective treatment for a range of human disorders associated with low leptin levels, including a diabetic condition known as lipodystrophy, certain forms of amenorrhea-- this means failure to menstruate in women-- as well as subsets of the obese, including--perhaps, in time-- people who have lost weight by dieting as a means to prevent the weight regain.

24. In most obese people, leptin sensitivity is reduced (45:49)

Well, what about the rest of the obese population? Is obesity a leptin-deficiency syndrome? Well, here's the data. If you look at plasma leptin levels measured by what's known as arrayed immunoassay and relate it to percent fat, what do you see? Well, there's a pretty good correlation between leptin level and percent fat-- much better, in fact, than BMI versus percent fat, and what you can take away is that in most cases, obese people make more leptin than do lean people. Anybody want to guess what that could mean? What does it mean if you have a lot of a hormone like that?

[STUDENT:] If you have a lot of a hormone, and you're not responding to it, you might be resistant to the effects of the hormone.

[DR. FRIEDMAN:] That's exactly right. High levels of a hormone in a setting where the hormone is not having its normal action would suggest that there's resistance to the hormone. And for those of you who follow it, insulin resistance is the main cause of diabetes, not insulin deficiency. Well, what does this mean at the cellular level? Well, leptin acts on centers in the brain. In the obese, there may be some relative insensitivity to leptin. Somehow, the leptin doesn't work well enough for reasons we don't fully understand, and as a consequence, less effective signal gets through. If less signal is getting through, food intake will go up, energy expenditure down. Fat mass will increase, and now leptin level will increase. What this means is that by dialing down leptin sensitivity, you can change weight in some ways. Now, actually, if you think about the fact that having enough fat is advantageous from an evolutionary point of view in certain circumstances, dialing up or down leptin sensitivity is a very powerful way to change weight. And so one of the challenges that we'll come to in a moment and then in the next lecture is, how can we figure out what the molecular basis of this insensitivity is?

25. Only a subset of obese people responds to leptin therapy (47:44)

But before going into that, we can at least ask the question, What good does it do to treat people who already have high leptin levels with extra leptin? Anybody want to guess? What happens if you give someone who has a lot of leptin more leptin? Do you think it would work, or not?

[STUDENT:] They become more resistant to it?

[DR. FRIEDMAN:] Well, actually, that's a subtle but good answer in that it may be that when you make more of a hormone, sometimes you downregulate the response to it, and there's some evidence for that in animals, but if, on the other hand, you just take naive humans and give them leptin, in the only published paper on leptin treatment of obesity, what you see is that as the leptin dose increases and you follow weight loss, there's a clear dose-dependent loss of weight shown here. Now, this was, admittedly, a small study, but what you can probably glean from it is that some of the obese subjects given the highest dose of leptin lost significant amounts of weight, and others didn't. Now, we now know, based on data that are not completely published yet, that a subset of obesity does, in fact, respond to-- Obese subjects do, in fact, respond to extra leptin, but it's not as many as would be suggested by this slide. It's probably closer to 30%. Well, where do we go from here? Well, for one thing, we'd like to figure out if there's a way in advance to distinguish those individuals who respond to the leptin and those who don't. Anyone have any ideas what one of the first steps would be to try to distinguish?

[STUDENT:] I have been led to believe from psychology class that chemical receptors in the brain are the reason that we perceive certain things. So perhaps finding the chemical receptor for leptin and finding out whether or not it's that receptor, in fact, that is malfunctioning in some way might be a way to distinguish between people who are obese because of lack of leptin and people who are obese because their body is not responding to normal levels of leptin.

[DR. FRIEDMAN:] So we're gonna come to exactly that subject in the next lecture, and I think you alluded to what is the right answer here, which is, the first thing you might want to know is, are the people who responded-- do they have lower leptin levels to start with than the people who don't respond? And you can measure that directly, although these brain chemicals also sometimes give you an indication of how well it's working. And so there's some reason to think that it's worth doing studies in which now we ask, Are those obese individuals who have relatively normal leptin levels the subgroup that responds? What about the rest? For the people who are truly leptin-resistant, we need to understand why they are so, and this means understanding on which cells leptin acts, how it does what it does, what chemicals it might modulate, in fact, and then try to understand what's different about that response in the obese state. And this was our level of understanding about 8 years ago. We now know that leptin acts directly on nerve cells, and I'm gonna tell you in the next lecture something about how leptin modulates the activity of the nervous centers that control food intake and weight.

26. Biology is the main cause of obesity (50:56)

So with that, I think I'll just return now to the picture of the kid and emphasize to you that the previous slides and this one, I think, drive home the point that obesity can be a biological problem. And that includes not only this child, but... I'm gonna tell you about what those causes are in a minute. Now, I want to emphasize something. 5% are caused by a single gene defect. In the rest of the population, it appears to be a combination of genes and environment. But this is a remarkably high percentage of obesity accounted for by genetic factors, and I think it's important to understand that when you look at someone on the street who's overweight, there's no way at all to discount the possibility that they have genetic alterations that make them so. So I thought I would close now with a final poll question. I'm a little nervous in doing this, because I've been told my Hughes support is contingent on more people answering "C" now than at the beginning of the talk, but we'll go for it here. I'm kind of curious if anyone has changed their point of view. I think we have a tape that will record the original answer. So why don't you vote in response to this question, and then I'll be happy to take a few more questions to end the session. Oh! I should have been a lawyer. OK. That concludes what I have to say for today. Thanks a lot. You were really great. Why don't I take a few questions now? OK, questions.

27. Q&A: Are there other hormones that control weight? (52:34)

[STUDENT:] Have you looked at any of the genes or other hormones from different organs, as opposed to, you know, looking at fat and the brain? Are any of the other organs in this system that's regulating our body fat?

[DR. FRIEDMAN:] That's a really good question. It turns out... I may have given you the impression that leptin is the only factor in this system. It's by no means so. There are many other hormones that regulate appetite, at least-- perhaps not as profoundly as leptin regulates weight, and Dr. Evans will talk about other molecules that are also critical parts of this system. Now, if you think about it, the organism really has to devote a lot of attention to getting nutrition just right. So there are lots of cues about how much fat you have, what the level of nutrients in the blood are, and so on, and the brain centers I'll talk about tomorrow basically sense a lot of such cues; integrate them into a behavior. Leptin is clearly an important such molecule, but not the only one.

28. Q&A: Is there a connection between leptin and age? (53:40)

You know, I'm afraid to throw the T-shirt all the way in the back, so-- I'll go for one. How about one person in the back? Let's see if I can do this.

[STUDENT:] I guess it's a common belief that our metabolism will cut out when we turn 30, you know, and we have to really start watching our weight. Would there be a connection between our age and how

much leptin we produce or how our brain has learned or unlearned how to deal with leptin and how it can regulate our weight?

[DR. FRIEDMAN:] There's a clear increase in leptin levels with age that go along with the increased weight with age, as if with age, leptin sensitivity goes down. We'd really like to understand why that is and how that is, but we have very few clues at the moment. One possibility, in some cases, was raised by an earlier question, which is that maybe as leptin levels go up in some people, you start to dial down the response to it, and weight would keep ratcheting up in that way. And that could be a way in which, you know, environment and transient weight gain contributes to the problem, but we don't really know yet at the molecular level, and I think what we really have to do is sort out how leptin and other molecules that regulate weight send their signals and then compare that signal-generator and signal-receptor system in obese or aging individuals to younger individuals. I'm gonna try this, but is there any liability issues here if I try to throw this to the back?

29. Q&A: Have you thought about marketing leptin injections? (55:12)

OK. OK, we have time for one more question-- someone who hasn't asked one before.

[STUDENT:] I was wondering if you guys thought about marketing leptin injections to just normally overweight people and not obese and what the effects are.

[DR. FRIEDMAN:] Well, I should say that these sorts of studies are very comprehensive, intensive, highly regulated, and can only be done by companies. The company Amgen that Dr. Cech referred to has done such studies. You know, there is some evidence to think that moderately overweight people will respond, at least in some proportions. How you then translate that into a drug to the population is a more complicated issue. My own view is that when we think about obesity, we should be thinking about health consequences and less about cosmetic issues. It's the people who are most obese who have the greatest health risk, and I think that's the subgroup we want to focus on. How it might then get used for people who have aspirations that are more cosmetic is not entirely clear. I would like to see a situation, however, where there was less of a premium on being thin for being thin's sake, for its own sake, and more of a premium on being as healthy as you can be and make it about health. I think that would serve a number of positive purposes. So with that, I think we're out of time. So I'll thank you again for your attention, and there will be lots of times to answer questions later today or in the break.

30. Closing remarks by HHMI President Dr. Thomas Cech (56:53)

[DR. CECH:] Thanks, Jeff, for a great introductory lecture. One might even say that your talk was phat. The topic of obesity is complex, but I think we're beginning to see that it can be approached like any other scientific topic. I'd like to thank the students in the audience for your terrific questions, and now we're gonna take a 30-minute break. When we return, Ron Evans will continue our exploration of the science of fat, looking in particular at something called Syndrome X.