The Science of Fat (2004)
Lecture Two—Understanding Fat: Syndrome X and Beyond
Ronald M. Evans, Ph.D.

1. Start of Lecture Two (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 second lecture is titled "Understanding Fat: Syndrome X and Beyond." And now, to introduce our program, the Vice President for Grants and Special Programs of the Howard Hughes Medical Institute, Dr. Peter Bruns.*

2. Introduction by HHMI Vice President Dr. Peter Bruns (0101:08)

[DR. BRUNS:] Welcome back to the Holiday Lectures for this year. As was mentioned before, we've been doing this for some years and have actually collected the lectures and associated materials, like animations and virtual labs, on yet another web site called BioInteractive.org. And if you're interested in these things, I encourage you to go take a look at that web site at your leisure. There are a lot of different things on that. The next speaker is Ron Evans, who is an HHMI investigator at the Salk Institute in La Jolla, California. Ron is justifiably well-known and famous for his work on a family of molecules called nuclear receptors, which are involved in regulating metabolism of a number of things, including the burning and storing of fat. For this work, in fact, he was recently honored by receiving the Lasker Award, which is one of the premier awards in biomedical sciences. In this lecture coming up, Ron will explore how fat is both nutritional and informational and how it can become a toxic substance in the body. Ron's lecture is entitled "Understanding Fat: Syndrome X and Beyond." Now we'll have a short video to introduce him.

3. Introductory interview with Dr. Ronald Evans (02:42)

[DR. EVANS:] I was always good in the sciences. I had no idea what I was going to do with it. I had no idea what research really was. I was, at that stage, just tracking my own strengths, and it's something that I always encourage people to do, is think about what your strengths are and go with them. The goal for my work was to understand how hormones control the genome, and that was a very avant-garde question at that stage. Little was known about how genes were controlled, so when I came to the Salk Institute as a young assistant professor, I knew exactly what I wanted to do and began studying how hormones control the activity of genes, and that directly led to the series of experiments on the area of my major interest, which are called nuclear hormone receptors, and these receptors are small, genetic switches that control the activity of networks of genes. Our research plan is constructed around understanding the mechanism of how these molecular switches work. They're a little bit like software controlling a computer, the hardware, and if the genome is the hardware, the switches are the software. And so our major interest is taking the gene and gene control mechanisms, this operating system, and using it to understand some of the most pressing human problems, such as diabetes, obesity, heart disease. What's the link with our genetic switches, and how can we reprogram the operating system to reset the balance in our physiology more towards the normal range? I like the idea of opening the minds of young people because the future of science belongs in their hands. This is a society that survives on advancing our understanding of the world. Technology, biomedical research. These will change the world, and those students can do it. They're the ones who can embrace the ideas and make the next breakthroughs, and so that's what I want to encourage.

4. What changed in the last 30 years to cause an obesity epidemic (05:09)

Well, thank you, Peter, and welcome to you all. You are the guys that I was talking about. You're the young people who I do want to encourage, and I really am thrilled to see the number of hands that said that you want to go into science. After Jeff's lecture, how may of you still want to go into science? There's still--there's a few of them left. I have my first polling question, which is not part of the script, but since we did pass out those Twinkies, I want to know how many of you actually--raise your hand if you actually ate any of your Twinkie. Oh--oops, oops. Sorry about my hand there. Some of you I actually saw were eating those Twinkies--excuse me. I haven't had a Twinkie in about 35 years. I still have one that was made 35 years ago and looks still pretty good. It's one of the dangers with Twinkies. They stay around for a long time, whether it's on the shelf or in your body, and that's one of the subjects that we have to talk about, which is fat, and fat that starts on the outside of our body and ultimately ends up on the inside of our body. It's part of our everyday conversation, it's part of the stuff we talk about at meals while we're eating it, and it's also part of a medical problem. We as Americans enjoy one of the most comfortable and luxurious lifestyles in the world. Our food is bountiful and our work is automated and our leisure time is carefree, and all of this results in medical problems that's really killing us. And the question is why? I want to talk about that in some detail. Since 1965, the weight of the average American has gone up by more than 25 pounds. Now, you heard from Dr. Friedman about the role of genetics in weight, which is obviously a very powerful factor, yet genetics are not going to change in a matter of years or decades, or even your lifespan, so what is different? What does change during this time span? I'm gonna ask just for the audience to throw out a few things that might be changing in, say, a 10- or 20- or 30-year period. Anyone have any ideas?

[STUDENT:] The chemical additives or preservatives that have gone into food may play a role in how they're turned into fat or other substances.

[DR. EVANS:] Chemical additives in the composition of our food. Any other suggestions?

[STUDENT:] Portion sizes have gone up significantly in the last 30 years.

[DR. EVANS:] Portion sizes have gone up. That's a very good point. There's one back there.

[STUDENT:] Availability of sugar in soft drinks and just, like, food like Twinkies, like that in school and elsewhere.

[DR. EVANS:] Exactly. So, and we can go around the room and I'm sure that there would be many other types of things that would have changed. In my time, some other things have changed besides foods. I started with records for music, and then it became tapes, and then Sony Walkman. Then it became CDs, and now what is it? It's iPods. Music changes. TV changes. Remote controls were invented. Skateboards, rap music. Computers came along during my time. Credit cards, and even crime changes, which affects our lifestyle. Combinations of pop culture, lifestyle, and social issues all blend to interact with our bodies to--when we live in this very complicated environment. And as all this comes together, this changes the way that we act and interact with the world,

5. Food, particularly fat, is irresistible (08:53)

and so part of what is a key feature here is that lording over all of this external environmental change are the foods that we bring into our body. These are the little tasty substances that we all love. And let's face it, that our species wouldn't have survived the millennia if we were not successful at gathering food from our environment. Three billion people can't be wrong. And as food comes into our bodies, it interacts with our genes, which direct its absorption, its storage, its trafficking, and, ultimately, its burning. It's a key part of it. One of the most tasty and powerful regulators is fat, the magical ingredient that is part of our everyday life. I call fat the lord of the genes. Now, sitting up here on the podium--this is just a little

anecdote--is a vegetable. This tends to have a fair amount of fat for a vegetable or fruit, and you are all science majors, and very advanced, I can tell, by the questions you're asking. So how many molecules of fat do you think might be in this particular item I'm holding up? See, now, I'm not getting very many hands here, but I'll tell you what the answer is. It's Avocado's number. OK, I know. That was a really bad--this is a science joke. And you can measure that--the actual concentration measure in the guaca-mole. OK, this is bad. Bad science puns. So I really want to discuss what fat is, what it does, and how all this factors into balancing the fat equation, Syndrome X and beyond. Let's look at a movie clip that gets us in the mood. Can you roll the clip?

[WOMAN:] Fat is the magic ingredient. When fat is used in cooking the food, you get that extra sensory experience. It's what makes things have great texture. It can be a crispy texture. It can be a wonderful fudgy texture in the case of a delicious piece of chocolate cake.

[DR. EVANS:] Oh, yes. You know you love it, and it's true. Fat is something that is really important to our daily lives and it's become a very big business, and it does add a tasty component if we do it correctly.

6. Contributing factors to obesity (11:45)

However, we know that there is an obesity epidemic that is out there, and what contributes to it--Jeff talked to you about biology and genetics and the importance of that in obesity trends. I mentioned the changing environment and social dimensions that are very important here. We've seen how fried foods and some fat-rich foods that were up there also affect this, and so--and layered on top of these components are also the lack of exercise.

7. How many calories are in one ounce of fat? (12:19)

And so how do we get fat? It is complicated, but in the end, you don't get fat simply by looking at movies or advertisements. You have to eat it. And what does eating fat mean? What is energy? Well, we measure energy by the term "calorie." We all use this term. Calorie is defined as a unit of heat equal to the amount of heat required to raise the temperature of one liter of water by one degree centigrade. One C, that's what the calorie is. So let's just ask a question, and this is the first polling question. How many calories are there in one ounce of fat? Now, I'll tell you that in your packet, I had them give you one ounce of fat. This is this guy right here. It is actually a little bit greasy. It's not real fat, but it is so real-like that when you pick it up, it's a little bit greasy. So how many calories do you think are in this? Why don't you take your vote? 9 calories, 137, or 252? And then we'll see what the answer comes up on the poll while we're looking at this. So, about half of you said that it was 9 to 137 and the other half of you said 252. And this is a pretty good group, and the test group was much different. But in fact, 252 is the correct answer for the number of calories in that small sample, one ounce of fat. And that's what a calorie is.

8. Portion sizes have gone up (14:00)

How has the diet trends changed over the last few years? What I show you here is one of the key examples of how this changes, and when I went to a movie theater, this is what we got for popcorn. Now it's called a child's portion, and you have to, like, say, "Oh, it's really for my kid. It's not for me," right? And then we all got used to--this is the real portion that we're supposed to have. And, of course, now you all know that--the trends change, and they don't just change in popcorn, of course, but when I was a young kid, this is what we actually got. You had no other choice. But then they realized that people were licking the bottom of the bag, people like me, and so they said, "Let's, for a small amount of more money, "give them twice as much," because the actual--it doesn't cost them that much for the French fry itself. All the cost's in the building and the people and that sort of stuff, and so they get a lot more money by giving you twice as much. That extra 50 cents is a big deal for McDonald's, in that case. And when I grew up, we had these little bottles, 8-ounce bottles of Coke, and we now have progressed to the Double Gulp.

Sixty-four tasty ounces of that favorite soft drink of yours that could feed a family for a week, I think. And so there's a lot more availability of cheap calories, and there's a number of social reasons for that availability and their cheapness, which I won't go into now, but portion sizes have dramatically changed during our time and part of that is an economic and marketing issue, and so this is one dramatic change.

9. Sedentary lifestyle and marketing are also factors (15:49)

Other changes--we used to play on the playground. Now there's a PlayStation. We're a PlayStation nation. You can see this advertised, and most kids your age, and certainly ones that are growing up now, that's an absolute must-have gift to give to a child who's growing up if you can afford it. It becomes a--almost a measure of status of the family. So PlayStation is a--really changes our behavior, in part because it forces you to sit still in front of a TV for long periods of time, and so you learn from a young age to not run around as much but to entertain yourself by not moving around in a very clever way, however. In addition, Marshall McLuhan said that the true art form of the 20th century is advertisement and marketing. This has truly become an art form, and marketing has moved down from its early years marketing to adults and to women and moved down to children as a major target group, and this has had a profound effect. Kids want the things that they see advertised. Take into account the recent news that the SpongeBob blow-up things on the roof of McDonald's had been stolen all across the country. So SpongeBob, an entertainment cartoon, is linked in to food, so we're using the popularity of SpongeBob SquarePants to sell hamburgers. It's a very sophisticated and effective ploy, and so popular that people want to sell these things from McDonald's on eBay.

10. Obesity trends worldwide and in the U.S. (17:34)

The trend for obesity is not just one that is happening in the United States, but in fact, it is a worldwide phenomenon. We have just some numbers here. If it's green, it's the least percentage of obesity in a particular country, and if it's yellow or very light yellow here, it's the most, and so this is the scale of relative number of people who are obese in a particular country in the world. Now if we just zoom in on some part of Europe, this is Hungary. Hungary and Germany happen to be the fattest countries in Europe. Italy, for example, is much thinner. England's actually pretty heavy as well. I just didn't highlight it up there. If we move on to the Pacific Islands, you'll see that almost all Pacific Islands have rampant obesity, and Jeff will talk about some of this in his next lecture. If we move to Asia, Thailand is one of the most rapidly growing countries. With its successful economy, the population has really acquired a substantial amount of obesity. And bringing it on home, in the United States, there's been an obesity trend that has been going on for quite some time. If we look at our country, the obesity map, and we start filling it in from 1985, about 20 years ago, we can see that there was green and light green coloring in the states. There's a growing trend here in 1990, and we'll move to the year 2000, and you can see what's happening, and before I click onto the last one, there's 4 states that will turn out to be the fattest states, and I'm trying to--I'll ask--does anyone want to guess what one of these or two of these states might be? Ok, there's one back there. Yeah.

[STUDENT:] West Virginia?

[DR. EVANS:] Yeah. Oh, West Virginia. That's very good. That's one of the states. I don't know if I can--That's pretty far back. I'll throw you one of these. I don't know if I can make it. Well, the row before you. That was a good catch, by the way. Another one, right here.

[STUDENT:] Louisiana?

[DR. EVANS:] Louisiana. That is not one of the states, so you're not going to get one. We'll get one more right here.

[STUDENT:] Indiana?

[DR. EVANS:] Indiana. There you go. Excellent. And in addition to Indiana, we have Alabama and Mississippi as the 4 states that have been--and West Virginia--that have been leading the trend. Now, I'll ask one other question. Which is the fattest city in the country?

[STUDENT:] Houston?

[DR. EVANS:] Houston. That's where our president hails from, and... Excellent catch. Houston is the fattest city in the country, yes, and Texas has a fair number of the cities that rank up there. But as a state it's only approaching the top.

11. BMI and its shortcomings (20:34)

As Jeff mentioned, how do we measure obesity and these obesity trends? Body mass index, which is indeed a convenient but imperfect measure of how heavy we are, but it's not bad if you're a typical person with the average amount of exercise, which tends to be not much, then you can use body mass effectively. However, I'm not going to say that either one of these are typical, but for a body mass index of 32, which is definitely obese, if you are a weightlifter or in exceptionally good shape and you have most of your weight in muscle, you can have a body mass of 32 and look like this, or if you do not get exercise, most of your weight will be stored as fat and you will look a little bit more like that. And, obviously, this is a continuum. There is no specific mark, although for medical purposes, you have to choose a boundary to decide when someone is overweight, obese, very obese, or morbidly obese, or thin as well, and it's an entire category, and so—

12. Environment can affect obesity: The Pima Indian example (21:49)

now, what is--I've sort of mentioned already what the contributing factor is for this process, which is environment and diet and food, but I'm going to ask you to take a poll. If you could take a group of people, in this case, and divide--a genetically similar group of people and divide them in two and place them into two different environments, how would the environment play on their weight? And I'm going to ask you, would the genetics hold them to a common weight in two different locations, or would the environment shift their weight because of that change? So take a vote there. And 80% of you say that environment could tip the balance. And we're going to see an example of that in a little video, if you could roll the video. Today, the Arizona Pima share the American culture, the American lifestyle, and the American diet. But in one important respect, they've outdone their fellow Americans. They are now the fattest population group in the fattest country on earth. I have 12:45, 1:45, and 2:45. That's on the 11th. In this state-of-the-art hospital, the Pima cope with diseases that doctors have linked to obesity: hypertension; high blood pressure; several forms of cancer; bone, joint, and muscle strains; sleep apnea, and diabetes. A staggering 60% of Pima adults are diabetic. High in the Sierra Madre mountains of northern Mexico, there's another Pima community of just 700 people whose ancestors separated from the main tribe and migrated here nearly 1,000 years ago. These Pima of the Sierra Madre are, on average, 60 pounds lighter than their American cousins. Diabetes and obesity are virtually unknown here. The only thing that distinguishes the two groups is lifestyle. The Mexican Pima farm and live as their ancestors did. There are no labor-saving devices here, not even electricity or piped water. You walk, you ride, and if you're late for school like Maria and Isidro, you run all the way--three miles. The Mexican Pima spend 22 hours a week in hard physical exercise. In Arizona, the figure is less than two. And here they eat a traditional diet of fruit, vegetables, and corn tortillas high in fiber and low in animal fat. For scientists, the striking physical difference between the two branches of the Pima nation perfectly illustrates the impact of modern living on weight and health. It's a relatively dramatic example of how environmental change can impact on our bodies.

13. Animation: How dietary fat ends up in fact tissue (25:30)

And there's the last couple points that I want to make before we conclude this portion, and that relates to the idea of fat itself. And so there are two kinds of fat: the fat that we eat--and the outside--we take it into our body, dietary fat; and then as fat becomes transformed to be part of us in fat cells. They're shown here. So, I'm gonna take a little journey with you, a video of the late, great Francis Crick. And Francis is known for his discovery along with Jim Watson of the structure of DNA. And he would occasionally indulge in a double bacon cheeseburger from Jack in the Box. And this ultimate cheeseburger contains more than 1,000 calories, 62% by fat alone. And since the requirement for an average person is only 2,000, this would be more than half your daily requirement, not counting the French fries and the Coke that he actually had on his table with him. And that would take you out for the day, that's for sure. Now, food is a mixture of protein, carbohydrate, and fat, and we need the energy from these things to live on a daily basis, but we may not need all of it. And I'm gonna take you on a journey as we take a bite of food and watch as it goes through our bodies from the outside to the inside, and what happens to it. And it goes through a series of scripted events. Here is the bite of food that through chewing is broken up, and then through biochemical events begins to be further processed in our bodies. Here it is in our stomach, where it's beginning to break up into its components. The little yellow droplets there are the lipids that we're gonna track in more detail. And you'll see that these begin to break up into smaller components through biochemical action. And these will drift from our stomach into the intestine where absorption of nutrients occurs. And here are the microvilli in the intestine that take the fat from the outside, repackage it on the inside into something called chylomicrons, which travel through the lymphatics ultimately to the bloodstream, where this fat--this packaged fat now is delivered to tissues such as the muscle, where it can be used to burn energy--this is shown here--or the excess that is not burned--remember the fat equation? The excess will be delivered and stored in adipose tissue. And this shows some cells there. And our chylomicron droplet delivering the excess energy where it's going to be stored in fat. And so I'm gonna basically conclude with this--this is how fat comes from the outside to the inside. And in the next lecture, I'm gonna talk about how we actually become overweight and how we go on this complex journey towards obesity. But before I do that, I'm gonna invite some questions about what we just spoke about.

14. Q&A: Can differences in Pima tribes be attributed to genetics? (28:30)

OK, questions? Um, you.

[STUDENT:] About the Pima tribe in Mexico and America. Could their differences also be attributed to a possible change in genes from their separation?

[DR. EVANS:] The question was could the Pima changes be attributed to a change in genes. And that's unlikely. It could be a little bit of genetic drift in that time frame, but not that many people--it's a clear population effect. Almost 100% of the Pimas in the United States are obese, and that directly correlates to the development of casino life on the reservation and the almost complete dependence on a Western or American diet. And so, it's a very good question, but in that time frame, it's not gonna be a substantial genetic change between the two.

15. Q&A: Have adoption studies looked for Pima genetic changes? (29:23)

Let's see. Next to you.

[STUDENT:] Have there been any crossover studies, say, for taking a Mexican Pima and raising that child, for example, in the American community or vice versa and seeing any differences in weight gain to sort of... offset any genetic differences?

[DR. EVANS:] Yeah, that's a good question. I don't--I can't tell you the answer to that, but I can tell you that in cultures such as Japanese or Chinese that come to the United States, that immediately in the next generation of kids that are raised, they adopt the Western style, and the kids become much heavier. And so there's a lot of examples where changing from a diet... one cultural diet to an American diet will change. Now, yes? I'll throw you a T-shirt. Now, where was the other question that was asked? Here we go. You get a T-shirt, too.

16. Q&A: What do the four heaviest states have in common? (30:15)

Let me--let's get one from back there. It was--OK. Over there in the seat, yeah.

[STUDENT:] The 4 states that were heaviest in the country... is there anything that they found to have in common that's the reason why they're the heaviest?

[DR. EVANS:] The states that are the heaviest, is there anything that they have in common? Well, there is something called an obesity belt in the United States. It's roughly in the south. It does drift up northward, as you did see. And what we track with the obesity belt is the relative number of fast food restaurants. And all of the states that you see there have an increased number of fast food restaurants, an increased interest in fried foods, and also, they tend to be slightly poorer states. So there is an economic issue as well. Calories from fast food are much cheaper than other types of calories. I'll give you--I don't know if I can get this shirt over. That's gonna need a good toss. Oh, baby! One, maybe one more-maybe one more question. Right here.

17. Q&A: Are fast-food restaurants responsible for obesity? (31:29)

[STUDENT:] In your opinion, do you believe that the fast food restaurants are actually out there marketing their high calorie or is it just the fact that fat is cheaper to bring to the public, and that's why they're cheaper? Is it the fast food market trying to make us obese? Or how much responsibility do you put on the fast food industry?

[DR. EVANS:] That's a very good question. How much is on the fast food industry for marketing and how much is just because calories are cheaper and people want something cheap? It's both. You know it's both because, just as I mentioned before, you link a movie and a cartoon that kids love--SpongeBob--with fast food. It's a very powerful link. Kids want to go. They want their toy. And, obviously, you have to buy the food to get the toy. And so it's a very seductive process of getting kids to want to go and eat that type of food. Of course, it's also very tasty. Anyone who's had fast food--even Julia Child loved to occasionally get a Big Mac. She just--it was one of the things that she liked. And so it's hard to escape. The people who develop these things know what we like to eat. They understand our tastes, they're very smart, and they understand the mixture of salt and sugar and fat. And all these blend together to be very seductive. And so it's a social trend that has made calories cheap and high fat foods and calorie dense foods readily available to just about everyone. OK, so I'm gonna move on to the next part of the talk. And

18. Is obesity related to laziness? (33:11)

we're gonna begin to answer some more of these questions by looking at the medical problems that emerge from obesity. And what I show you here is a California young surfer with a nice pattern on a bathing suit, who is young and getting lots of exercise and out in the sun and feeling happy. But with the benefit of our southern California environment and high fat food, and as he ages, reduced exercise and genetics, he goes--the pattern now is on the couch instead of on the suit. And he now instead of a surfer is a channel surfer. And this is now entering into the problem of obesity and what we call metabolic syndrome, or Syndrome X. And I'm gonna talk about this. First, I want to take a brief poll whether you think that the sedentary lifestyle of a heavy person or an obese person is due to the fact that they are lazy

or whether this is some more complicated part of the body physiology. So, why don't you take the--let's take the poll and see how this comes out--where the responsibility actually lies. And the answer is--wow. This is really split. We're gonna have to really work on this. This is interesting. Also, you're very different than the test polls that we took. And we're gonna drill into this question in a little bit more detail. And I'm gonna show you one video that actually tends to address some of these issues. If we can roll this video,

19. Video: Behavior of obese and normal mice (35:07)

we're gonna see an obese mouse and a normal weight mouse in the same cage. And you can see the amount of activity that is expended by the normal mouse relative to the obese mouse. And this mouse is exploring its environment, looking for food everywhere it can, and it is just typical mouse behavior here. Like, "OK, where's the food? "You look like you've got it. "I'm gonna check you out." Keeps coming back to check out why this guy's doing so well. And finally, you're gonna see--oh, he moved. It moved probably because the other one was bugging him so much. So, as the mouse puts on weight, I don't think anyone would call the mouse lazy. As a mouse puts on weight, its need to move around and its spontaneous activity is greatly diminished. And so this is a reality. There's an interaction between our weight and our adipose tissue and our behavior--our interest in seeking out food, actually walking around or trying to get the food. And this changes many parts of our body physiology. So, we have to stop thinking about the heavy person is inherently lazy. There is a very important biological and behavioral component that relates to weight.

20. Health consequences of being overweight (36:31)

But more importantly, what I want to look at now is the health problems that are attendant to the weight gain and what the nature of the growing molecular problem is. And I'm going to do this by taking you down a little trip. And here is our patient again. I'm setting up here a stopwatch, which is the symbol of our metabolic clock that is ticking in all of us. And as our overweight patient goes farther along, the weight is gonna be linked to insulin resistance, hypertension, hyperlipidemia, and heart disease. And this is a metabolic clock that is ticking away. I'm gonna show you a little bit of a video about this metabolic clock. So, if we can roll the video...

21. Animation: Timeline of obesity-related health problems (37:23)

and here we're gonna consider a hypothetical patient that's gonna be destined to develop obesity. And there he is in silhouette. And from early adulthood onward, his metabolic clock is ticking. And this unfortunate patient, as he walks along, with each beat of his heart, does not realize what the danger is ahead. But by the early 20s, there's already evidence in his heart of cardiovascular disease. You can see that in the yellow areas of the heart. And around the same time, our slightly overweight patient now is going to develop an abnormal response to sugar that he eats. And during a carbohydrate load, such as after a meal, resulting in increased levels of glucose and triglycerides in our body. And then during the early phases of this problem, the pancreas will respond by producing insulin--and we'll talk about that in more detail--to help keep the sugar levels at the right amount. But as he get into his mid-30s, the problems get worse. Central obesity will have begun to develop. And as weight goes up, the pancreas has to produce ever more insulin, and it's hard to keep up with the body's demand. So at points along the way, he's developed multiple problems with obesity, hypertension, high fat, diabetes, which are risk factors for cardiovascular disease known as Syndrome X or metabolic syndrome. And he's at risk for a cardiac or cardiovascular event, which is a heart attack, a stroke, which is the leading cause of death in the Western world. That is the ticking metabolic clock. The metabolic clock is accelerated by each of these components: insulin resistance, hypertension, hyperlipidemia, and heart disease. And

22. Animation: How a heart attack occurs (39:16)

on the podium here is an example of a coronary artery. And if you can look into this, you'll see the yellow fatty streaks that begin to develop in the heart. And here's a model of the heart. This is what goes wrong for many people that have metabolic syndrome. And I'm gonna show you a brief video on the next animation here, where we're going to look at what happens in a heart attack, but we're gonna actually go--travel into the heart. And as we go through the process of metabolic syndrome, let's roll the video. We're going in. We're gonna zoom in on a coronary artery. And in the cutaway, you're gonna see LDL cholesterol in yellow--these little yellow droplets that under a hypertension hyperlipidemia are gonna create here the beginnings of a fatty streak, which most of us have. It'll get a fibrous cap to protect it for a while. But the fatty streak will continue to grow, as you see here, under continuing obesity metabolic syndrome. It has--with inflammation, it can begin to rupture, producing a blood clot, disrupting blood flow, creating a heart attack, stroke, and sudden death. And that is what's actually happening. It's rather a gruesome process but is what's going on all the time. So, it's--the consequences of metabolic syndrome are very serious.

23. The role of fat tissue (40:45)

Now, how is fat doing all this? Why is adipose tissue having this effect? Well, first, adipose tissue, it's important to realize, is a living tissue. It both stores energy and releases energy, as you can see here on this balance. So it plays a very key role in the energy balance. In addition, it is a tissue that has the ability to communicate with various parts of our body. It secretes factors which I'll talk about. Jeff spoke about one. It can talk to our brain, as he told you. It can talk to our liver, and it can talk to our muscle. Can you hear me now? So, here is muscle. And here's how fat can talk to muscle. Whenever you look at muscle, you will see that fat is intimately linked with the muscle. All muscle is surrounded and embedded with adipose tissue. And this is where it derives much of its energy. If you do not exercise, you will not burn that fat, and you'll accumulate more fat in the muscle.

24. The link between fat and sugar (41:50)

Now, what is the link between fat and diabetes and sugar? And so, let's look at the other energy source, sugar, that we take into our bodies through this good stuff that we drink. We also produce it in the evening, when we're sleeping, from our liver because we need sugar to circulate. And what we can see is that as the sugar production will cause the--oh, sorry--cause the delivery of sugar, shown here in these little trucks, to go to the pancreas, where it will signal the pancreas how much sugar there is, and that will cause the production of insulin, creating the insulin highway. Insulin is what directs sugar into various tissues throughout the body. So, now we have the sugar going down the insulin highway towards the muscle that's going to absorb and take up this sugar. But then there's the fat to consider. The fat has something to say. "Can you hear me now?" And in normal individuals, it is sufficient to have a balance of fat with insulin, and sugar can get into muscle. But as we increase the amount of fat, we get into glucose gridlock, which is shown here. And that glucose gridlock can progress during obesity to really create the problems of insulin resistance and the beginnings of diabetes.

25. Diet and exercise are key (43:15)

And so, I'm going to conclude just by looking at the potential... within looking at muscle itself where some of the answers might be. Part of that answer is better eating, and the other part is exercise. If you have too much of a bad thing--which is that tasty, high-fat, and high-caloric diet, you will accumulate more fat. If you exercise, you can tolerate much more caloric intake. You'll have less fat stored in the areas of your muscle, and therefore, fewer problems with insulin. And so part of the answer here, and we'll talk about this--exactly what's happening and how this happens at the molecular level in the next lecture. But part of the answer here is in diet and in exercise. And with that, I'm gonna stop, and I'm going to take some questions.

26. Q&A: How long have you been a researcher in fat? (44:13)

OK, let's see. Now, who had--I'll take a question right there.

[STUDENT:] How long have you been researching fat, like, the subject of fat and how it affects the body?

[DR. EVANS:] How long have I been a researcher in fat and how it affects the body? That's a very good question. The last thing I ever thought that I would be studying is fat metabolism. And I started by studying how hormones control gene activity. And as part of that process, we discovered some molecular switches and one of the switches turned out to be the fat switch. And I'll talk about the fat switch. And as Tom had mentioned in the introduction, a part of the mission of HHMI, but also part of my own personal mission, is to try to translate basic science facts into reality. How the discoveries at the basic research level relate to our own body physiology. Can you explain physiology at a molecular level, and can you explain complex disease and use that understanding to... to both explain and treat complex disease? I think it's a problem that we can grapple with. It's a complicated problem, but, you know, as scientists, we like complicated problems. And so, I never thought I would be studying fat, but I am.

27. Q&A: What disease is caused by glucose gridlock? (45:28)

Right there.

[STUDENT:] You said that fat, if it goes too much into a muscle, it causes gridlock. What diseases come from that type of gridlock?

[DR. EVANS:] That's a good question. First, I'm gonna toss the T-shirt up there. See if I can get this... All right. I'll accept that as a good throw, but a good catch as well. What are the complications from gridlock? The initial complications from gridlock is that you need more insulin to drive sugar into, in that case, muscle. And the body will produce more insulin so that it keeps the sugar levels low. But your pancreas cannot forever produce more insulin. It gets tired out, essentially. And so, under years of increased insulin production, eventually the pancreas will fail. In addition, high levels of insulin cause other problems in the liver, where there's increased production, actually, of fat. And so, you do not want to have high levels of insulin for too long. And therefore there's a lot of medicines that are being developed to try to treat increasing insulin levels, but it starts out as insulin resistance and then ultimately becomes diabetes. And that's the real problem that you have to worry about. I'll take the blame for that one.

28. Q&A: What is the difference between good fat and bad fat? (46:52)

Right here in the middle.

[STUDENT:] What is the difference between good fat and bad fat? Like, nowadays, you hear a lot of essential fatty acids. What makes these essential and good for you?

[DR. EVANS:] What's the difference between good fat and bad fat? And that's a very good question. First, there's an assumption that there is good fat and bad fat. And that's a good assumption, actually. So, good fats typically--and I'll show you... I'm not sure that I--we have all the models up here. Good fats are what we call polyunsaturated fats. And so there are two kinds of fat. In fact, we do have some models up up here. The mono-or polyunsaturated fats are fats that because of a molecular change in their structure are liquid at room temperature. Saturated fats... or trans fats... such as... in this good stuff here--that have an exceptionally long shelf life, by the way--these fats, they're equally caloric, but these fats are solid at room temperature. And as you'll see in my next segment... the liquid fats actually have information that

can interact and provide instructions to genes. The saturated fats lack that ability. These fats are much easier to store in our body. Typical components of saturated fats also will include triglycerides of various types, and also they get packaged into a particle called LDL cholesterol. LDL cholesterol is the so-called bad cholesterol. It's the cholesterol that streams through our bodies and is associated with increased heart disease. So-called good cholesterol is called HDL, and that represents the cholesterol that streams away from tissues. So, there's cholesterol that streams in the tissues, LDL. HDL streams away. It's the removal of cholesterol from tissues. And so, if you have high HDL, that's considered good, you'll probably live longer. If you have high LDL, you have increased risk for cardiovascular disease. And so there are things such as good fat and bad fat. That's a good question.

29. Q&A: How are LDL and HDL levels controlled? (49:13)

Let's get someone from the way back. Last row up there.

[STUDENT:] How does HDL control LDL?

[DR. EVANS:] The question was, how does HDL control LDL? So, these are two important components of the dietary fat system. LDL is produced by the liver. It's a particle--actually, there's a couple of particles that are produced called VLDL and then LDL, and both of those deliver energy throughout the body. And they're key delivery packages of cholesterol and triglycerides and fatty acids. And so we need that energy to fuel the body. Too much production, however, is not good, and the excess of those particles will deliver that fat--more fat than is needed into the heart and various other tissues, and that creates the problem. The ability to get rid of that production of HDL is what flows back to the liver. It's the return system. And so there is a balance and a connection between these two, and that's genetically programmed, as a matter of fact. There are some drugs that can influence that balance, such as the statin class of drugs, and these are one of the most widely used drugs in the world. In fact, they may be the most widely used. They are about a $10-billion-a-year annual sales and growing all the time. And these reduce LDL while leaving HDL the same or elevating it. And so the actual production of cholesterol by the body regulates the balance between LDL and HDL. And also, your genetics are very important in that process. That's a good question. You know, I have to give you a T-shirt. This one, I don't know, getting the last row is not gonna be easy. Well, I got right next to you. So, I'll take that.

30. Q&A: Why is adipose tissue in the muscle? (51:05)

Up there in the blue shirt.

[STUDENT:] If we can't spot-burn fat, then why is adipose tissue in our muscles? Like, why can't it be elsewhere?

[DR. EVANS:] Well, adipose tissue is else--so, if you look at this diagram that's over here... you'll see. You'll see muscle and you'll see fat, which is in the obese and the less--and the normal person here. And so, fat is distributed everywhere. It's under the skin. It can be in our stomachs, in our hips, in our butt. You can have, basically, fat everywhere. You will always have fat interspersed in the muscle as well. And so it's not only stored in muscle, that's for sure. It's stored in many different places. So it's distributed throughout the body. And particularly as you gain weight, you can see how that fat distribution tends to change.

31. Q&A: How does the body decide where to store fat? (52:05)

[STUDENT:] How does the body decide where to store fat?

[DR. EVANS:] How does the body decide where to store fat? That's a very good question, and that is genetically programmed. And so it's going to store fat--it will distribute the storage of fat into various adipose depots or fat pads. And each animal, including humans, has characteristic fat pads in different locations. And also it depends a little bit if you're male or female where those locations are. For example, as you enter obesity, men tend to store much more fat in their stomach. Women tend to store much more fat in their hips. And that's how the initial fat distribution works, and that's genetically programmed in terms of that distribution. There's a lot of variation that relates to that. The other depots... subcutaneous fat, that is fat under the skin, is common for all of us. And you'll--you can feel that fat and you kind of get a sense of how much fat you have by pinching yourself. And so fat is really, if you look at it, distributed almost everywhere because it's an energy source that is providing information and signals throughout the body and instantaneous energy to proximal tissue, such as muscle, where it's being burned. And so it's a very--it's a very good question. But when you look at it, there's a complex genetic program that we're very interested in studying as to how fat forms, why it forms, and why it does what it does. OK, we have time for--and I'm gonna give you, let's see, the last... a little overtossed there.

32. Q&A: What are the effects of gaining fat centrally and elsewhere? (53:46)

Let's see. Where can we get... right here in the front row. Haven't gotten down to the front row for a while.

[STUDENT:] What are the effects of, say, a woman gaining fat in her stomach and a man gaining fat in his hips?

[DR. EVANS:] The question was it could--does it switch back and forth? In fact, it does. There are plenty of women who have central adiposity. And I have to say that central adiposity generally is the worst place to store fat. And we don't really understand why that is. But it may be a hallmark of other events that are going on in the body. Central fat is amongst the hardest to get rid of. It's not very close to muscle groups, and so it takes a bit of effort to get rid of that fat. You have to burn down a lot of energy. But in the end, when you start expanding, you have to store it somewhere. And I have to tell you that fat has almost an infinite capacity to expand. It's individual cells--and we'll see that happen in one of the next videos--but it has quite a tremendous capacity to store ever more energy. Ok, so

33. Q&A: What research is there relating depression and obesity? (54:47)

one last question. Right here.

[STUDENT:] With movies like "Super Size Me" drawing attention to, like, the direct correlation between obesity and depression, what research is under way to determine if depression creates a chemical or releases a hormone that might increase the appetite or be related to gain--gaining weight?

[DR. EVANS:] What research is available to see if...

[STUDENT:] I was wondering if there's any research under way that's trying to draw that link between depression and weight gain.

[DR. EVANS:] There... it's a good question. Eating is often linked to our mood. And that is a complicated question as to how you link the psychology, especially depression, in weight gain. Now, oftentimes, there's sort of a sense that people who are depressed will eat more. It's not an absolute fixed reality, however. And I'm not sure of all the studies that link depression and hormones. But I can tell you that simply said, there are many hormones that are changed during depression. Some of the hormones that we study, for example, cortisol--and I'll talk about that briefly in the next segment--change during depression. And that, the hormonal change that goes on will have a pervasive effect throughout the body.

And for some people, that can manifest itself as weight gain. Thank you all.

34. Closing remarks by HHMI Vice President Dr. Peter Bruns (56:26)

[DR. BRUNS:] Well, thank you both, Ron and Jeff, for what were, I suppose, really weighty lectures. But--and it brought out the complex nature and active nature of fat in our metabolism not just as a passive player. There have been a lot of questions, both here, and I suppose people who are watching this on the Web now and in the future will have questions on this. And we have a solution to that. That web site called BioInteractive.org has a section on it called "Ask a Scientist." And if you go there at any time, you can ask a question, and we have a panel of scientists who will answer your question for you. So that's worth remembering--not only on this subject, but on other life science subjects. So we will continue this tomorrow. And in the next lectures, Ron will explore the intimate relation of fat and muscle, and Jeff will take us on a global journey to understand more about the genetics of obesity. Thank you for coming. See you tomorrow.