Jeffery M. Friedman

Nobel Conference 46

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Well, thanks, Mike, for that really lovely and generous introduction. It’s difficult to segue from that into my talk but I will. [laughter] Some of the students and I were talking before and I promised two of them that I would use the word segue at the earliest possible opportunity. [laughter]

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Well, I’d like to begin by first of all thanking you for giving me the opportunity to visit. This is really a lovely college and a wonderful event. It occurred to me looking through the previous 45 such conferences that one could get a wonderfully broad and interesting education simply by watching the videos of all 45 of those that range among a set of topics that are interesting, pressing, and reflect, I think, the presence [sounds like] of this institution to bring big questions to campus with an opportunity for certain, for people to discuss them.

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Now the topic that I’m going to speak about today really focuses not at the larger level that, such as you’ve heard about in the previous two talks, but really focuses on at the level of the individual. And shown here are images of, two images of individuals who obviously differ with respect to their body weight. And before even beginning, I’d ask each of you to reflect for a moment and think to you yourself, or ask yourself, why are these two individuals different? How is it that one individual has so much more adipose tissue than the other and what does this mean?

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And think also about what judgements you might or might not make about that person. Because if asked why the individual on your, well, your left is obese, most people would I think correctly say, well, the child eats too much and exercises too little. But that I think ignores the deeper and more important question which is why is this so? Why is that individual eating more and perhaps exercising less? And so what I’d like to try to do today is answer that question by deconstructing obesity and at least presenting for you a scientist view on this condition.

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And so today I’ll just talk about two topics in turn. One is just in a general way the causes of obesity and then I’ll follow that with a discussion of how the identification of Leptin has informed our understanding of how body weight is regulated.

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Now this is a challenge. In part because if I were talking to you about any of the conditions listed on this slide, chances are most of you would accept what I have to say at the outset and if pressed, you would simply, with a specific set of questions, if pressed, you would probably defer to the experts. That actually isn’t true about obesity. Everyone has such an intimate connection to food and their own personal experience eating, dieting, trying to maintain their weight, that everyone has a deeply held set of beliefs about this topic. And for the most part very few people have any great interest in what I have to say at all. [laughter] In part, I think, because everyone has their own set of convictions that range greatly in terms of what they are. And this range of opinions is reflected in the press where there are innumerable articles sort of elaborating on why it is weight is so different.

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Now whatever one’s opinion about the causes and potential remedies of this treatment, there’s no question that it represents a significant public health risk. For reasons we don't fully understand, obesity increases the risk of diabetes, high blood pressure, heart disease, fatty liver, some forms of cancer, a set of diseases that in aggregate are the principle causes of morbidity and mortality in the developed world and are growing problems in the developing world. Now there’s one important fact here, which is that while obesity increases disease risk, it is also the case of the severity of these conditions is ameliorated even with modest weight loss.

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So modest weight loss, so one doesn’t have to normalize weight to improve health, and I’ll come back to this and emphasize this at the end of the talk. And so the point here, however, is that it is intrinsically difficult to take weight off. Now the severity of these conditions is illustrated in this slide, and I just want you to focus on this magenta line here in women and in men, which shows that when you look at relative mortality or relative risk of death over time as a function of body mass index, an indicator of adiposity or obesity that I’ll have more to say about, the relative risk of death increases as soon as you increase above a threshold 30 BMI as weight over height squared.

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And so as body BMI rises, so, too, increases the risk of disease and death, and so, too, increases the social stigma that lead obese people to earn less than no better talented people and be promoted less readily. So here again, one might ask the question, if you’re up here and suffering health effects and potentially social stigma, why don't people just lose the weight and come down to the flat part of this curve and live a life of health? Well, it’s not so easy. And so given the fact that body weight is quite stable and that most diets are unsuccessful over the long term in effecting weight change. One, I think, might ask the question, why is it that the obese can’t typically reduce their weight to that of the average weight individual?

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Well, there are three general explanations for why it is that obese people remain so. One suggestion is that the obese lack a level of willpower that’s normally exercised by lean people. I find this point of few is more often favored by lean people. [laughter] A second possibility is lifestyle and environment, that we live in a modern “toxic” environment and in this environment, obesity becomes rampant. And then the third possibility is that there’s a biological and genetic basis, that biology and genes account for differences in weight and difficulties in changing weight away from some homeostatic so-called set point.

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Now when I used to give talks, I would sometimes ask people to vote their preference for each of these three before and after I spoke. I stopped doing that when one day more people vote, fewer people voted for biology and genes when I finished than when I began. [laughter] I do want to emphasize, however, that in a sense this is a false choice. And most people feel compelled when asked to pick just one of them. I think for any other condition but obesity, if asked what’s the relative importance of each of these factors, biology, environment, higher cognitive factors such as willpower, people would say, well, it’s plausible to suggest there’s a biological system that can be modulated by behavioral and environmental factors. But for reasons that we could talk about, I think debate on, or discussion about this subject is really polarized. I think in a manner that’s often at odds with the scientific evidence. So what I’d like to do for a few minutes now is share with you my point of view about the relative importance of each of these components, as a prelude at the end of trying to unify them or at least suggest to you that they’re not mutually exclusive contributors.

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So what about willpower? Well, this is a message that obese and lean people hear all the time. Obese people are advised to eat less and exercise more. And that message is relayed in any number of settings, partly is illustrated in this sort of mock infomercial that the people at the Howard Hughes Institute made for me. So I’ll play this for you now because you’ll all recognize this. [video plays][laughter]

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So the operative word there is decide now. The idea is that you can voluntarily control what you weigh. All you have to do is decide. What flashed at the bottom is a requirement now of the FDA of all diet plans, which is that the success rate be made public. And the success rate of these plans is actually quite dismal for effecting large degrees of weight loss over the long, the long term. Now why might it be that voluntary factors have limited potency for effecting weight change in anything other than a minority of individuals. And we can talk about that minority in a moment.

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Well, for one thing, there’s pretty good evidence that there must be a biological system for regulating body weight. Body weight is remarkably stable in individuals who are not actively trying to change their weight. This has been established in studies all over the world, in Sweden, South Africa, Israel, and elsewhere. If you’re not actively trying to change your weight, year on year, one’s weight naturally changes very little. It’s within just a few pounds.

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Now all living organisms obey the laws of thermodynamics and if you extrapolate from that, what it simply suggests is that if your body weight or the amount of energy you have stored as fat has not changed in that year, then the amount of food you’ve eaten had to have been perfectly balanced against the number of calories you’ve burned. And that’s a tall order considering that over the average year an adult will consume approximately a million calories. And so that, those million calories would've have to been precisely against energy expended or your weight would've changed, and for most people it hasn’t.

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These numbers get even more profound if you now consider consumption over a lifetime or a decade. Over the course of a lifetime, we’ll consume tons worth of fat, protein, and carbohydrate, convert that to waste, heat, and a small amount of work, all the way maintaining a relatively constant body mass. Now if you extrapolate from this into a back-of-the-envelope calculation, keeping, assuming that weight would change less than 10 pounds per decade, which is what the evidence would suggest, what you’re left with is the notion that the number of calories in had to have been balanced against the number of calories out with approximately 99.6 percent precision. This exceeds the ability of dieticians to actually surmise the calorie content of food that you might begin to eat by several laws. Which means that if you just have a plate of food in front of you, you can’t really tell how many calories there are. And you could not do as well as nature appears to do quite naturally.

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This situation is evident even if you are diligent about looking at error rates on food labels, where the error rates can be quite staggeringly high. In fact, ironically here, the error rates are highest among organic producers or smaller producers who don't have the resources to as assiduously count or monitor calories as do bigger growers.

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Now the idea here that somehow energy that we eat is balanced against the energy that we consume is suggested for than 100 years that there must be some basic system or basic drive that regulates food intake and that essentially counts calories for us. That somehow there’s some natural means for inventorying calories. And it’s very easy to see evidence for this sort of self-monitoring of calories in animals. In this classy experiment by Wilson et al, what was done was to take animals and overfeed them through a tube. This is something called gavage feeding. And so over that interval, you see while the tube is in place, the food that, the voluntary food intake of the animal decreases. It’s not hungry because it’s eating all the time. And its weight increases. But the second you stop overfeeding this animal, its food intake remains low compared to a control group until such time as its weight returns to that of the control group.

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As if the animal somehow knows that it’s been overfed, and it’s going to make adjustments until such time as its weight returns to that of its control group. And the same can be seen if you food restrict an animal, the animal will lose weight but as soon as you restore the food to that animal, it goes right back to that of a control group and it will overeat during this interval. As if, here again, the animal somehow knows that it’s been rendered thinner and is making adjustments in its energy balance to return to some starting point.

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What this begins to suggest is that there must be a biological system that’s sensing our calo-, that’s taking an inventory of number of calories stored and changing behavior is a consequence, at least in animals. Now what this would imply is that perhaps there’s a basic system in all of us that’s similar to that which I just described for animals. And that it’s in opposition to a conscious drive. And there are lots of examples of basic drives being imposed by higher cognitive wishes. And it’s very easy to demonstrate this even in this audience in an experiment. I mean, basically you could decide to stop breathing, but sooner or later the basic drive to, will be to, basic drive to breath will win out. Same for all these other traits. It’s just that in many cases they play out over a long period of time, so we no longer recognize the potency of the basic drive.

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And there’s a simple way to sort of emphasize this point further. The notion that our basic drives cannot be so easily overcome in all cases by willpower. Sometimes when I give talks, I’ve offered to give students 5 million dollars if they stopped breathing through the end of my talk. [laughter] And I stopped making that offer when one student stood up and said, ‘Does it count if I’m dead?’ [laughs][laughter] So the offer does not stand. But it’s this idea that there's a basic drive to eat that overcomes the con-, that ultimately overcomes the, maybe the higher cognitive wish to eat less that I think is the subject actually of the talk I’ll give today. And that explains the fact that most diets are ineffective. So that 95 percent of individuals who lose substantial amounts of weight, more than let’s say 25 pounds or more or even great degrees of weight loss, return to their pre-dieting weight within a couple of years. Most diets fail. And I would propose to you it’s because while willpower can effect changes over the shorter term, eventually the basic drive wins out.

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What about lifestyle and environment? Well, you might see this quote in many different places or quote like it, ‘No age is every afforded more instances corpulency than our own.’ This was Thomas Short in 1727. [laughter] So we hear this even more frequently today than I quite sure Thomas Short did. So where does the idea come from that obesity is increasing to the extent that it is? And what do the data really mean?

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Well, the sort of data that’s been presented to defend this point of view or similar to what you saw earlier, it was basically estimated that 15 percent of the population was obese in 1980 and now that number, well as of 1999 that number had doubled. And people then argue that our genes haven’t changed in this interval, so it must be the environment. Well, first of all, that statement is not true in terms of how natural selection actually works and this was eluded to in the last talk. Natural selection is most powerful over the short term in selecting among preexisting variants that are better suited for changing environmental conditions. So the notion that natural selection can’t be used to evoke changes in pop-, in allele frequencies over the short term is not correct.

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But there’s another reason actually why this statement is wrong and that the environment, the statement that the environment has to be accounting for all the changes we see over time and it has to do with the way we measure body weight. As I mentioned before, body weight is at adiposity or fat content is measured by a metric known as body mass index. That’s weight over height squared. And what’s shown here are the approximate BMIs for 5 foot 10 inch men who would be either 167, 202, or 242 pounds. If your BMI works out to be over 25, you’re considered to be overweight. And if your BMI is over 30, you’re considered to be obese. The point here is that we define overweight and obesity as a fixed threshold. Under you’re not, over it you are. Now there’s a problem when you define a continuous trait, such as BMI or body weight, with fixed thresholds. And that is that the distribution doesn’t have to change very much over a period of time to get a disproportionate increase in the number of people who exceed that threshold.

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So let me explain what I mean. Here’s the threshold for obesity. BMI over 30. And there’s a hand-drawn scheme of the distribution. In 1990, our BMI on average was 26.7 and 23.3 percent of the population was obese. In 2000, the average BMI was 28.1 and now 30 percent of the population was obese. So we saw about a 33 percent increase of the incidence of obesity over the course of a decade, this is true, but it was associated with on average 1.4 BMI unit increase, or 7 to 10 pounds. Now I’m not here to argue that 7 to 10 pounds average weight gain is not important from a public health point of view. It’s very important. And it would be very useful to try to reduce that average weight gain. It would improve public health.

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But I’d also like to suggest to you that you get a very different impression of what’s been happening over that decade if you hear average weight increase 7 pounds, to 7 to 10 pounds, versus hearing 33 percent increase in obesity in a single decade. Now what’s shown here is the actual data, which was provided to me by Katherine Flegal, and if you correct for age and sex, which is not typically done when such calculations are made public, the difference the distribution in 1991 versus 2000 are even less dramatic. Now it’s absolutely true that there are more people who are obese now, at that point in time than previously and there’s probably more skewing, and I don't mean to minimize the possibility that there’s been a secular trend towards more obesity. And we definitely would like to understand what in our environment is responsible for this increase to try to figure out remedies for it.

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But there’s another question that we can ask at any moment in time. In an environment where everyone has unlimited access to calories, we can all in this country at least by and large eat as much or as little as we choose to, why is weight so variable? How is it that in a relatively uniform environment people can be different by hundreds of pounds as you saw in one of the images a few moments ago. And the answer to that to a very large extent is genes. There are a number of ways to assess the genetic contribution to a human trait. One is by asking, does the trait travel, segregate or run in families? Another is to ask, do biological parents, do adoptive children tend to resemble their biological parents or their adoptive parents? And the last is to look at twin studies and ask are monozygotic twins more alike for the trait than are dizygotic twins? And in all cases for obesity, the conclusion is the same. There’s a very substantial genetic contribution to differences in weight.

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In fact, if you look, obesity is as or more heritable than any trait that’s been yet studied with the exception of height. Approximately 75 percent of the variance in body weight can be accounted for by genetic factors. So genes explain a lot about why individuals weigh disparate amounts in a relatively uniform environment. Now to emphasize to you the power of these genes, I want to tell you of a case report provided by Stephen O’Rahilly colleagues in Cambridge, England. This young body, this is the image I began by showing you a picture of, was of normal weight at birth but he became to develop morbid obesity in infancy. He was extraordinarily hyperphagic. The family reports have to padlock the refrigerator and it’s almost as if the child became a safe cracker. He was so determined to eat. He was already pre-diabetic at the age of 4, when he weighed 90 pounds and had 57 percent body fat. Now this child came from a highly inbred pedigree, the product of first cousin marriages, and he had a similarly affected 8-year-old cousin, a girl who weighed over 200 pounds, which is what I weigh. All right, 210, but it’s close. [laughter]

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Now when you see an extreme phenotype in a highly inbred or consanguineous family, the cursory conclusion is that this might be genetic. And Steve O’Rahilly reasoned that the phenotype of this child might be similar to that of a mouse strain that we had been studied and that you heard about a moment ago, the ob mouse. This is a pictures of an ob mouse. It was identified at the Jackson Laboratory in 1950 and the only difference between this animal and its sibling litter mates is a defect in a single gene.

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These animals live in the same cage with the same free access to food. And yet, this animal weighs three times as much and has five times as much fat as his sibling litter mates. And so we were captivated by that question in my laboratory and set out to identify the defective gene in these animals, and in 1994 identified it as encoding a protein hormone which we call, called Leptin. Now as you know, hormones are molecules made in one part of the body that signal information to other parts of the body. And this particular hormone is made by fat tissue in proportion to its mass. So if you have more fat tissue, you have more Leptin. If you have less fat tissue, you have less Leptin. And then Leptin sends a nutritional signal to the brain, in particular a region of the brain known as the hypothalamus, which controls most basic behaviors, to regulate food intake or body weight.

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And so we identify this hormone and have been studying it in animals and because it, it is a protein, we can make it in the laboratory. And what’s shown here is a picture of ob mouse given either saline or a different mouse given Leptin. So this hormone had the ability to reduce weight of animals by sending its nutritional signal. And in addition to affecting one of the two things that people suggest the obese should do, eat less, this hormone could accomplish in these animals. It also changed their activity. So this is an ob mouse given saline and an ob mouse given Leptin. As you can see, this animal moves around very little at all. And this animal moves around normally. And indeed, we could see this dramatic behavioral difference even before any weight was lost. In fact, we could see changes in activity even before the animal began to eat less. The point here is that this hormone in this system appears to play a role in regulating the levels of not only food intake, but activity, the two things the obese are advised to do more of.

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Well, anyway, O’Rahilly reasoned that perhaps this child was deficient for this hormone Leptin, similarly to these mice who carry a mutation in it. And so he set out to give the child this hormone in the blood by injection. And here’s what happens. The child gets older. This has nothing to do with Leptin. That’s just the way things are. But despite getting taller, he became thinner, less diabetic, lower fat content. Now early on, before the first Leptin dose, they even gave this child the test meal and this 3-year-old child ate in a single meal 2,000 calories, which is the number of calories an adult of my size will eat typically in a day. All right, 2,200 calories, but . . . [laughter] After a few Leptin injections, the child now ate an age-appropriate number of calories, 180. So it was driving appetite. And this child was not lack of willpower. It was not the environment. It was the lack of the hormone Leptin.

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Now what happens in this child is that there’s a mutation that disrupts the expression of this hormone. So no Leptin is made. This is interpreted by the brain as meaning that there’s no available fat stores at all. It basically signals that the child is starving. The child eats more, burns less, makes more and more fat but it’s to no avail. He can never generate the signal that shuts the system off. And now here’s a picture of the child at the age of 8. This is the same child I showed, the same child, this is the same child just before and after Leptin therapy. I think this is a really important image because it emphasizes that the judgements you might make about children or adults who are very obese are as often as not going to be incorrect. And I’ll come later to explain to you that at least 10 percent or more of morbid human obesity is the result of single-gene defects. The rest being some combination of genes and environment.

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Now in aggregate, this new information has established the following. That body weight is regulated by a homeostatic system. So at each individual’s stable weight, a certain amount of fat is carried and a certain amount of Leptin is made. And at that level, food intake equals energy expenditure. Now image you diet and fat mass and Leptin level falls. Similar to the child who makes no Leptin, this will be a stimulus to eat more. And such individuals will continue to eat until such time as fat mass and Leptin level return to the starting point.

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Now imaging for a period of time you go on a binge of eating and you are a Leptin-sensitive individual, fat mass and Leptin level will increase. This will in turn suppress appetite again until such time as fat mass and Leptin level return to the starting point. Now what this sets up in a sense is a biological system that seeks to maintain relative constancy of fat and a biological force that resists weight change in either direction. Doesn’t mean that weight can change or can't be changed voluntarily. It does, however, mean that that voluntary wish will have to contend with a very powerful biological drive that opposes it.

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Now this also has evolutionary implications in so far as if there’s if there’s a homeostatic system of this sort, it would suggest that there’s a good reason not to be too fat or not to be too thin. And that this system sort of seeks out a happy medium. In the course of our own evolution is a species, both obesity and leanness carried with them certain risks. Leanness carries with it the increased risk of a starvation the next time there’s a famine. But obesity increases the risk that we will be susceptible to predators and so the system probably evolved to balance the relative risks of these two conditions. And without going into any detail about it, I’ll simply say that those two relative risks of leanness and obesity are still evident in our population, though the relative potency or severity of those risks has changed and the cause of it has. So in any environment I’d like to suggest to you that there’s probably an optimal amount of fat. And that this system sort of seeks out the balance between the two sub-optimal extremes.

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Now in a sense one of the explanations here is that a biological system has emerged to avert the risk of starvation. And that explains something important about these children because ironically, despite the fact that they’re obese, they manifest a whole set of biological abnormalities that are normally evident not with obesity but with starvation. So these children often have insulin resistance and diabetes. They have infertility. They have thermoregulatory abnormalities, thyroid and immune problems and so on. And ironically these are typically the abnormalities you see in starved individuals. All of them have been corrected by Leptin and this and other data has suggested, in fact, that when fat mass is reduced and Leptin level falls, the readout of this includes not only a stimulus to eat more but what we might refer to as a starvation response with alterations to perhaps every biological system, the net effect of which is to try to conserve energy. So these are all energy, these systems all consume energy. And when Leptin level falls, a set of biological responses are elicited that seek to conserve energy. Now this data has established in fact that Leptin is a bonified hormone and fat tissue is a bonified endocrine organ and it, the connection between Leptin and other systems establishes it as, I think, a key mediator of nutritional information. Everyone accepts axiomatically that nutritionally changes effect physiology. It’s pretty clear now that a key means by which this happens is through the change in the levels of this hormone.

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There are also a number of Leptin deficiency syndromes that can be well treated with Leptin much the same as was the case for the Leptin-deficient child. And a partial list of these increasing number of syndromes is shown here. I’ll mention to you, however, that mutations in the Leptin gene causing obesity similar to other hormones are quite rare. And so there are only about two dozen cases worldwide with a syndrome similar to that of the child I showed you a picture of. Now this is important information physiologically. The nature of the condition in these children tells us a lot about what Leptin does in humans. But it doesn’t have much explanatory power for telling us what causes obesity.

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So the next question is, what are the levels of Leptin in obesity? And that’s shown here. If we now relate percent fat in humans to plasma Leptin concentration in nanograms per mil, what you’ll note is that as a general rule, the more obese individuals become, the higher their Leptin levels, not the lower. Now this is not uncommon in endocrinology. When we see high levels of a hormone, such as Leptin, in the absence of a hormone effect, in this case to reduce weight, it commonly denotes what’s known as a hormone resistance syndrome. And the classic example of a hormone resistance syndrome is Type 2 diabetes, where most Type 2 diabetics actually have elevated, not reduced levels of the hormone insulin. And so here, too, obesity appears to be a Leptin-resistance syndrome. What does that mean?

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Well, imagine we have a Leptin system that’s configured something like this, and for some reason there’s a block to Leptin action at the site of action in the brain. Well, less effective signal will get through. This will provide a stimulus to eat more, burn less, deposit more fat, and make more Leptin, as if you can dial up or dial down body weight by changing Leptin sensitivity. In fact, I think there’s reason to believe that changing Leptin sensitivity could be under selective pressure during evolution so you can dial up the weight or dial down the weight of a population dependent on the relative risks to it.

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Be that as it may, the available evidence from animals and now humans suggest that in most cases of obesity for reasons that are not well understood but that are beginning to be gleaned, the ability of Leptin to act on key neural centers that regulate weight are slightly abrogated. So the next question is, if you already make a lot of a hormone, what good does it do to give extra hormone? Might do some good sometimes but in other cases, it doesn’t.

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A partial answer to that question was provided in the last 1990s by Steven Heymsfield and colleagues at, publishing in a journal called *JAMA*. And what they were eable to show was that if you jack up the Leptin dose really high, at this dose, .3 milligrams per kilogram, in a small number of patients at least, you could see a statistically significant effect to reduce weight. The problem was this dose of Leptin was just too large to administer to large numbers of people and the lower doses didn't appear to have much of an effect. And so while there did appear to be some promise of efficacy for Leptin by itself, it was not a commercially viable project and there it languished.

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Now in such circumstances, there are a few different approaches one can take to try to develop new therapies based on a hormone. One possibility would be to ask, or is there a responder subset? Is it possible that some individuals will reduce, lose weight even with a relatively low dose of Leptin, and indeed that’s the case. About a third of obese subjects will lose a significant amount of weight, getting even a lower dose of Leptin. And there’s reason to think that this is the subset of obese individuals who start out with lower Leptin levels.

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There’s another possibility that’s become especially popular in the treatment of diabetes which is to develop a hormone sensitizer. And so one other possible approach would be to see if there is some way to re-sensitize individuals to Leptin. Now it does appear that there is a Leptin sensitizer but to tell you about that, I need to say a little bit more about the complex systems that regulate food intake and body weight.

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Food intake and body weight are regulated by overlapping systems. One is a long-term system that maintains homeostatic control of fat mass and Leptin is a key player in that system. A second system controls what’s known as meal pattern. These are the factors that make you feel hungry in between meals and feel full or satiated as a meal is concluded. A whole host of hormonal and neural signals mediate these short-term signals. And they include the hormone insulin, peptide YY, GLP-1, ghrelin and CCK as well as vagal afference. Many of you may have heard about some of these other signals.

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Now both these systems talk to one another and it’s been reasoned for some time that if you affected only the long-term system, the short-term system might compensate and vice versa. And so this has underpinned the notion that one might need to treat obesity with combinations of age and to hit multiple pathways simultaneously. And so the brief story I’m going to tell you about now is a combination of Leptin and this hormone Amylin, marketed by a company known as Amylin Pharmaceuticals, which in the interest of full disclosure, I should tell you I consult for. Now this molecule Amylin is currently an anti-diabetic therapy. It’s administered to diabetic patients as an adjunct insulin because it has several desirable features.

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It suppresses glucagon secretion. It suppresses gastric absorption of glucose and it also acts on the brain stem as a short-term signal to reduce weight. Amylin in human has been reported to have a 5 percent weight loss that’s durable in patients receiving it. And so Amylin Pharmaceuticals wanted to ask, what happens if we combine this short-term signal, Amylin, with the long-term signal, Leptin. And in two separate studies, the data appear encouraging in so far as the combination in this case led to about a 13.5 percent weight loss that was more than 10 percent reduced compared to placebo. So there is promise for this combination, although I don't want to say anything other than there was enough efficacy to motivate these companies to maybe perhaps do larger trials to really establish whether the combination is safe and efficacious.

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What’s important here, however, is that metabolic signals can and are likely to be used in the future, be used to manipulate weight. And that the sort of basic research that one does to code these signals I think inevitably will lead to new therapies. Now there’s a final question, which is the one that captivates our lab today which is to try to understand why Leptin resistance develops in the first place. What’s the molecular basis of Leptin resistance?

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Since Leptin acts on groups of neurons in the brain, this will require that we understand much more about how a peptide hormone can change the activity of a neural circuit that regulates behavior and then what’s different about its ability to activate this circuit in the Leptin resistance state. There’s already a partial answer to this question in the form of key sets of neurons that respond to Leptin in the brain. In the hypothalamus, one class of Leptin receptor neurons expresses a peptide called NPY and when these neurons fire, feeding is activated. A second class of neurons in the hypothalamus also expresses the Leptin receptor but in this case expresses a different peptide known as MSH and this peptide acts on its receptor, the MC4 receptor, to inhibit feeding. Leptin works in part by inhibiting these neurons and activating these neurons.

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So if this was the case in the child, you make no Leptin. These neurons are maximally active. These are off and you eat more. With extra Leptin, these are maximally active. And these are off and you eat less. And moreover, the system is said to be tuned, which means that quantitative changes in Leptin concentration will change the relative balance between these pathways and influence whether you eat more or less as Leptin levels change.

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Now these neural pathways have been attracting a great deal of attention in recent years, in part because they’ll form, I would hope, the basis for new therapies in time. But also because mutations in it cause human obesity. These include Leptin, the Leptin receptor Alpha MSH, MC4 receptor, BDNF-TrkB and other genes in this circuit, and we now know that more than 10 percent of morbid human obesity is a result of defects in one of these genes, most commonly either the Leptin receptor or this MC4 receptor.

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So more than 10 percent of human obesity, morbid human obesity is the result of a defect in a known gene. And there’s very good reason to believe there are additional genes that cause obesity that we don't know about. And there’s also reason to believe that there are in other cases combinations of genes acting together with environment to change, to lead to obesity. I think this is a very important number to keep in mind if and when people might be inclined to make harsh judgements about the obese. Now there’s a deeper basic science question that underpins this. Because no one actually believes that the decision about whether or not to eat is initiated in the hypothalamus. Clearly there are other parts of the brain. And as a basic science exercise for future years, I’d like to suggest that here we have Leptin, this hormone, acting on a discrete number of responding cells in the brain and a measurable behavioral output in human, and so the deep question for the decades to come is going to be what happens in between? How is this information decoded? How is behavior really controlled?

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Feeding is what’s known as a classic complex motivational behavior. This is in contrast to a reflex, in which case a defined stimulus gives an invariant result. Here a defined stimulus changes the probability of the behavior but doesn’t guarantee it. So Leptin levels and these other metabolic signals influence the likelihood that you’ll eat but don't guarantee. The same is true of sensory factors, smell, taste, and vision. Emotional factors are important in influencing whether or not you intiate feeding, as are, as I mentioned, higher cognitive factors.

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Now this sort of reasoning has led people to believe for many decades that there must be some integratory centers in the brain that process complex information of this sort and convert it into a behavioral response. Not only do we not know how complex behavioral, complex sensory information of this sort is processed in the brain. We don't even know where it’s processed in the brain. And so a deep question for the coming decades that I think will prove trackable, will be to understand how a diverse set of relative inputs are integrated and lead to adaptive behavioral responses.

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Well, the elements of this complex neuro circuit are years away, although they’re under study in our laboratory and other places, I want to close by telling you that while we don't know very much yet about the real key elements of this neural circuit, we have in recent years developed a better understanding of a physiologic circuit. The physiologic circuit is comprised of a classic, constitutes a classic feedback loop composed of an afferent signal in Leptin, integratory centers in the brain that respond to it, and a set of end organ effects that regulate food intake and metabolism. Think of this in a way as a thermostat of sorts. You have a set point for fat mass. And a signal. And if the signal doesn’t match the set point, adaptive changes are developed.

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Now this framework, I think, has important explanatory power for telling us why some people are obese and others aren’t. I think it’ll provide the basis for new therapies. But it’s also a platform with which to better understand how environmental factors and psychological factors work. After all, these are not metaphysical entities. They act on biological systems. And so I think the sort of framework that’s been developed in the last decade and a half will help us in time better understand how environmental and behavioral factors exert their effects as well.

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Now I think this is also important as we move forward and thinking of therapeutics, as Dr. Ferragamo told you. The advice the obese currently get is that they should basically eat less and exercise more and as you heard, this was the advice of Hippocrates 2000 years ago. And I’d like to suggest to you that perhaps advances in medical science will allow us to do better than simply reiterate a nostrum that was no more likely to work 2,000 years ago than it is today. Rather, we should approach this, as you also heard, in the same way as we would approach any other biological condition. Understand the molecular components of that state or the physiologic state that regulates the parameter, in this case body weight. Understand what’s different about that circuit or these molecules in the path of physiologic state. Of course understand how environmental and behavioral factors and developmental factors influence these pathways. And from this will come rational therapies.

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Now I’m quite optimistic that there will be therapies to emerge in the coming decades with a caveat I’ll come to in a moment. I think the caveat is that we will be able to reduce weight and improve health. I’m less optimistic that we’ll be able to normalize weight in people who feel they should have an average weight, although I’m not sure that’s a worthy aim in the first place. However, the development of these therapies is still probably years away. And in advance of that, I’m often asked to give people advice about what they might do if they do find themselves with health difficulties and overweight.

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And so I’d like to close by providing to you the advice I give obese people who ask and everyone else in advance of better medical therapies. Here again, focus on improving health. The cosmetic aspects of this are not what’s important or at least not what should be important. What’s more important is to improve your health. And remember, it doesn’t require normalizing your weight to see an improvement in these comorbidities. Exercise and eat a heart-healthy diet. Do your best to lose some weight. There’s a disproportionate health benefit to a modest achievable weight loss, 7 to 10 pounds. The system I’m talking about doesn’t control weigh to the pound. It sets a range for weight and simply states that the further you go outside that range, the harder it will be to use cognitive measures to achieve it. But 7 to 10 pounds is well within what I believe to be the achievable range. Don’t berate yourself if you cannot normalize your weight and most people can. This is a very powerful, age-old, evolutionary-selected basic behavior, and don’t berate anyone else either. And I’ll point out to you that this is the same advice I would give anybody. Improve your health, exercise, eat a heart-healthy diet. Try to stay at the leaner end of your range. And don't judge yourself or anyone else more harshly than can be defended by our understanding of biology.

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Now I’ll close with two other slides. And tell you that I put forth this set of ideas in a Newsweek editorial about a year and a half ago. I think it was a year ago last September. And you can read the headline, The Real Cause of Obesity, it’s not gluttony, it’s genetics. Why our moralizing misses the point. Now for a period of time on Newsweek it was quite extraordinary because it was only posted online, it was the most talked about article on the web in Newsweek. It was number one on their most circulated, most commented on articles. In fact, there were chat rooms that sprung up in Yahoo about this article. And so I wanted to close by reading you some selected comments of what turned out to be about 40 pages of them that make some points that I think illustrate the range of opinions about obesity. ‘This is crap.] [laughter] ‘What a complete load of aplogistic crap!’ Crap was a popular word on this site. ‘Not only am I supposed to forget the genetic defect or know what a person puts in their own body is clearly their choice, but I’m also supposed to brainwash myself with some PC notion that disgusting, oil fat is somehow attractive.’ Not my point exactly but, OK. ‘Ditto to the hogwash. Empowering obese people with yet another excuse is reprehensible. How many before and after ads for weight loss, diet, and exercise are there? Do they work? Sure if you want to. Fat is as fat does.’ This is my favorite. ‘I smell smoke.’ Goes by the name smoke. ‘I’ll bet Dr. Friedman’s buddies don’t call him skinny.’ And it turns out you end up with defenders on the web and so my defender, tmassan said, ‘And I bet smoke’s buddies don’t call him smart.’ OK, another. ‘I don't think how I live my life is anyone else’s business. My obesity is not hurting anyone else.’ Another, ‘I often wonder if people vilify obese people because they’re so visibly obvious and nothing makes you feel better than pointing out the mote is someone else’s eyes.’ And then finally,’ Are we animals or do we have an intellect and the ability to choose how we behave?’ Actually, I think this is a core point. I think as humans, we want to believe we’re in control, even in cases where our control may be limited. And I think the notion that some people find it difficult to consider the possibility that aspects of our behavior are at least completely or partially beyond our ability to control them. After all, no one asks the question, why is it that every living organism up to and including non-human primates seems to manage their weight just fine without passing judgement on the heavier or thinner among the chimp community. And I think we could ask ourselves why we feel the need to make judgements when quite obviously the same biological system that’s evident in all these animals still resides within us. So with that I’ll stop and thank you for giving me the opportunity to visit this wonderful place and I hope to visit again someday.