

Harvard - Interviews - David Ludwig Office

Jonathan: So, when you combine diabetes and obesity; diabetes, statistically it is the leading cause of medical problems, suffering and death in the United States. What have you observed over the course of your career in terms of the rates and impact of diabetes?

David Ludwig: Well my career and the diabetes epidemic in a sense evolved together. I started medical school in the 1980's when childhood obesity was first getting started. Rates of obesity in youth and in adults were going up by 50 percent a decade. But it takes several years perhaps even a decade for increased prevalence to translate into serious complications like diabetes, fatty liver, kidney problems. And we've seen the second stage of this epidemic over the last 10 or 15 years. Type 2 diabetes in children was previously unprecedented. I don't think I ever saw a case of that when I was in medical school. And now it's becoming relatively routine in pediatric obesity programs around the country. But then it takes a period of time for these complications to translate into a life-threatening event like a heart attack, stroke, or other serious problems, and we're just now entering this stage of the epidemic. In fact, in the last two years, life expectancy in the United States has decreased basically for the first time since the Civil War. Primarily owing to obesity related complications.

Jonathan: So, it sounds like one of the things I would imagine is difficult in terms of your personal mission to help combat this epidemic is that delay, because if you touch your hand to a stove it burns immediately there's immediate pain there's immediate consequences. So, coaching someone to overcome that could maybe be easier. Since we're seeing such a long-term delay from lifestyle choices to the diabetes epidemic, what can we do to help people to understand the scope and severity of this problem, to merit the large actions that would seem that need to be taken to reverse it?

David Ludwig: Well childhood obesity has a variety of immediate complications which can affect many organ systems of the body and also not to overlook the psychological impact. You know most children with obesity experience varying degrees of teasing, abuse, bullying and adults face stigmatization. In fact, in today's environment we don't tolerate discrimination based on race, sex, sexual orientation, but somehow body shape is still you know fair game for jokes on late night TV. So, people with obesity typically

carry a big physical and also emotional psychological burden. But, the Problem isn't that people don't recognize the burdens of obesity, it's that the treatments that have been offered lack effectiveness. You know people struggle with the calorie-in-calorie-out approach to weight loss, just eat less move more. You know people can do that for a while but over time the body tends to fight back with increasing hunger slowing metabolism and That Takes a toll on willpower it erodes our discipline and erodes our ability to stay on a diet over time. In the battle between mind and metabolism, metabolism usually wins, and so people wind up gaining weight, falling off a diet, not for lack of motivation but because we've asked them to do something that's fighting against their biology. We need more effective treatments. The problem isn't that people don't understand the complications of obesity, the problem is we haven't offered them an effective treatment option.

Jonathan: You mentioned fighting against your biology. Beautiful term. How analogous...if I were to go see a clinician and I was struggling with either diabetes or obesity and that dietitian or professional told me simply to eat less and exercise more. How analogous would you say that would be to tell a person to just say use the bathroom less or a depressed person to frown less and smile more. Like is there is any merit to that kind of instruction or is it simply an almost moralistic trivialization of deep metabolic problem?

David Ludwig: The conventional approach to weight control is based on a law of physics which we interpret to mean that if you want to lose weight you have to eat less or move more. You have to change your calorie balance. And of course, that will work over the short term. But there are a few problems over the long term. First, very few people can continue to stay on a low-calorie diet for more than a few weeks or a few months. And we know that the long-term studies show initial weight loss, but then very consistent weight regain after three or six months. Why is that? Well conventionally we think it's just a problem of willpower, that people lose the ability to just say enough is enough in our modern food environment but there's evidence that things aren't that simple, that biology plays a fundamental role in determining and controlling body weight. So, you know our approach, our conventional approach, to weight control doesn't work over the long term. Secondly, in a sense, it can't work. You know a difference of 200 or 350 calories a day would mean the difference of remaining lean or becoming massively obese over two or three years and very few people can accurately assess their calorie

balance. In fact, not even a trained nutrition professional could do it without very sophisticated technology. For that matter, how did people ever manage to control their body weight before the very notion of the Calorie was invented about 100 years ago? Another problem with the calorie-in-calorie-out model is that it tends to blame people for this failure. You know if losing weight is simply a matter of eating less moving more everyone should be able to do it and if you can't there must be something the matter with you according to this way of thinking. You must lack willpower or discipline. We know that body weight is controlled by biology that when we cut back on calories you start losing weight, but your body fights back with predictable responses hunger increases and hunger isn't just a fleeting feeling. It's a primal biological signal that your body is crying out for more calories and even if you could ignore hunger over the long term which very few people can. Your body has other tricks such as slowing down metabolism and producing what's called the starvation response. This is a very difficult situation to manage over the short term, let alone for the rest of your life. So, our conventional approach doesn't work in a sense can't work because it's too difficult to accurately assess calorie balance and it blames people for this problem. We need a much more sophisticated approach to weight control that will help people succeed over the long term.

Jonathan: To illustrate one distinction that, in my mind like five years ago, to really illustrate what you just described in terms of this is a much more complicated problem it can't just be calories-in calories-out. Say we have an individual, her name is Mary-Beth and Mary-Beth at her Healthy weight would be 160 pounds. Mary-Beth weighs 260 pounds, so her body has one-hundred surplus pounds of fat on it. And she's ravenously hungry. How can a body that already has 35,000 excess units of energy already inside of it still vociferously crave more energy in. I mean she's already eaten it, that food is there...it's waiting, but she is as hungry as always, she's always hungry. Why is that?

David Ludwig: You know, according to the conventional view of obesity Weight is simply a problem with calorie balance. Now of course we know from a century of research that it isn't so simple that there are a variety of hormones, organ systems, and biological systems that also control body weight. But recognizing this doesn't seem to translate into clinical treatment in the weight loss clinic because despite that knowledge, we don't have a good explanation for the obesity epidemic. If body weight is controlled mainly by biology, why is it that a typical man say, five feet nine inches happily

defended a body weight of 160 pounds in the 1960's and today that person's body wants to weigh 30 or 35 pounds more. What's caused that shift? We know that genes haven't changed over that period of time. Something has undermined our biology and caused body weight, in effect the body weight set-point, to shift up year after year. Based on the latest data we haven't even reached a plateau. There's the prevalence of obesity continues upward. What's messing around with our biology? So, the conventional view keeps, will recognize that biology is important but then comes back to willpower because they lack a good explanation for what's changed. So, they say well you know all these delicious foods are causing people to overeat. But that's not really a satisfactory explanation. You know if you take someone in a classic overfeeding study, that researcher, this research was done 50-60 years ago. You take people and you overfeed them by 500 or a thousand calories a day you know that might sound like an enjoyable study to participate in but then after a few days what happens? You know people quickly lose all interest in food they become really satiated and uncomfortable and their metabolism speeds up and the body's attempt to get rid of those extra calories people in forced feeding studies who are gaining weight feel as uncomfortable as people in starvation studies who are losing weight. The body fights back in both directions. Why is it that those control systems that limit weight gain, after all populations haven't always gained weight year after year when they had plenty of food around? Why are those systems that limit weight on the upper side suddenly defective? Why are people gaining weight year after year? The conventional model of obesity based on calorie balance offers no explanation and thus has no new treatment options in the clinic other than ultimately resorting to the advice eat less and move more.

Jonathan: It sounds like we need a fundamental paradigm shift in how we think of both obesity and diabetes as they are so tightly related, and later I want to talk about how tightly related they are, because if we continue to think of the body as fundamentally stupid and it's just a balance scale and you have to manually balance calories then we will continue to treat this as just eat less exercise more. But you continuously talked about imagining what your body wants to weigh. I love that. You mentioned what your body is defending either up or down. We've heard people call this term a set-point meaning that you have a weight that your body wants to weigh. Can you explain what is the body weight set-point? What are the components of it and how, if you could wave a magic wand and get everyone to understand that body weight is homeostatically

regulated... hormones, brain, gut. How would that change our treatment of obesity and diabetes?

David Ludwig: Well many of us have a sense of a body weight set-point which is a body weight that our body, based on our genes, other biological factors, just seems to want to be. So, we all know somebody for example who weighs 250 pounds is struggling to keep that weight off it seems to gain five pounds just walking by a bakery. Whereas another person looks like they can eat all they want and never gain a pound. So, we know that genes and other biological factors play an important role but that's not the whole story because the set-point can explain why people are defending. People's bodies want to be an ever-increasing body weights over the last 30, 40, 50 years. What's causing the set-point to move up? So just thinking about body weight as calories-in calories-out misses the story. Let's take an example let's think about fever. Now 100 years ago the biological origins of fever were known, they could take temperature. So, imagine you went to your doctor with a fever and your doctor said, 'Okay your temperature is too high'. This is really just a question of heat balance, too much heat going into your body not enough heat coming out so it's simple we just need to reverse that. Get into an ice bath and you'll draw heat out of your body and the problem will be solved. Now, if you could be convinced to go into an ice bath with a fever you'd break it. But what would happen? Your body would fight back in predictable ways. Severe shivering, blood vessel constriction and you'd feel an overwhelming desire to get out of that ice bath. So, for that reason ice baths aren't very popular treatments to fever today. We have a more effective approach you know, you identify the source of the fever and treat it or use aspirin. What aspirin does is it lowers the body temperature set-point and you take it your body goes from wanting to be 104 degrees to being ninety-eight point six. So, over the next half hour or so you naturally throw off your blankets, you start sweating and your temperature declines naturally because your body temperature set-point has changed. You don't have to work to do that. In fact, when you change biology, behavior follows we've sort of reversed that. We're trying to change behavior and hope that biology catches up. That isn't the case. So, our challenge with obesity is to figure out what's causing this apparent set-point to have climbed up so much over the last 30-40 years. Identify the source of the problems, reverse them so that we can lower the body weight set-point. And once we do that hunger naturally declines, metabolism speeds up and you lose weight with your body's cooperation not with your body kicking and screaming.

Jonathan: You mentioned a couple times how overfeeding studies just absolutely fascinating because many people today, like you said, that sounds like an enjoyable...that's a study I would want to participate in. So, there was a study that Dr. Levine at the Mayo Clinic did where they overfed participants 56000 calories over eight weeks, and according to calorie math, everybody should have gained 16 pounds...by the definition of calorie math. Nobody gained 16 pounds, the most anybody gain was eight pounds and a couple of participants gained a little less than a pound. How can human beings, let's call them lucky naturally thin people, because we've all met them, how can some people eat 56,000 surplus calories over the course of eight weeks with no other major lifestyle changes in a very controlled environment and not gain statistically significant amounts of fat?

David Ludwig: The beauty of many biological regulatory systems is that it can maintain fairly stable internal conditions amidst a range of varying environmental conditions. So, let's take fever. You know if you're sitting quietly your body generates very little heat and your temperature might be around 98.6. You can engage in an iron man contest and generate a tremendous amount of heat, but your body responds by vasodilating, opening up blood vessels, radiating heat, you sweat, and these adaptive mechanisms keep your body temperature from shooting up in line with all that heat you're producing. So that's a regulatory system that keeps things within a narrow range and body weight is very much the same that we can adapt to relatively low physical activity levels and high activity levels without very much change in body weight. In fact, that's unfortunately why exercise alone, short of marathon levels, is not a particularly effective long-term treatment for obesity. Exercise is great, it helps body composition, you feel better, but it produces very little weight loss by itself. The bottom line is that until we figure out what it is about our body weight set-point that's shifting up year after year that's causing people to want to defend or protect a higher body weight than 30 or 40 years ago. We're going to be struggling against our biological systems and ultimately failing to successfully maintain weight loss over the long term.

Jonathan: We're going to be forcing people into ice baths and then shaming them and mocking them and criticizing them when they want to step out because they're in pain. Is that fair?

David Ludwig: Yeah. You know the conventional...an implicit assumption in the energy balance model of obesity is that the individual has control over their calorie balance that if you just eat less and move more, as if those are voluntary behaviors over the long term, you'll solve the problem. But we know that's not the case. We know biology determines in large measure our hunger and metabolism and that efforts just to eat less are antagonized by other biological responses, that the body pushes back against calorie deprivation. Somehow just eating less puts the body into starvation mode and that makes it increasingly more difficult to keep losing weight. Think about this as you cut back calories you get hungrier, but your metabolism starts slowing down so you have to keep cutting back calories more and more as you're becoming ever hungrier just to keep up with that slowing metabolic rate. But why is that? Why are we...why does so many people's bodies want to be much heavier than was the case in the 1960's and 70's? One alternative idea is that it's the quality of the calories we're consuming. Something about all of the processed carbohydrates in our diet that's programming the body to want to be at a higher body weight. And if that's the case simply cutting back calories without changing the quality of what we're eating is a losing proposition.

Jonathan: So, let's continue, let's continue down the calorie quality track. And there's four factors let's say that we've seen individuals and we've seen in myriad studies test in terms of varying between different types of foods. One is that certain foods, like Pringle's for example, literally advertise once you pop you can't stop. So, you can eat 200 calories of Pringles and literally be hungrier than if you would have consumed no calories. You contrast that to salmon and asparagus, eat 200 calories of salmon and asparagus you will experience satiety. How, calorie for calorie, how is it, or is it, that certain foods will fill you up faster and keep you fuller longer than other foods?

David Ludwig: Right. Satiety or, how full you are and how full you stay after a meal, is a complex concept. There are many things that affect it you know, the volume of food or energy density, the amount of fiber, the relative proportions of protein, fat and carbohydrate. But according to the carbohydrate insulin model of obesity insulin levels play a critical role in determining hunger and satiety. So, you know you can think of insulin as the Miracle-Gro for your fat cells just not the sort of miracle you want happening in your body day after day. We know that in states of excess insulin action weight gain inevitably occurs such as treating people with diabetes with too much insulin, that's a well-known complication. Or rare conditions in which people have insulin

secreting tumors that causes people to get hungry, eat too much and gain weight and gain excess of fat. And the opposite is also true, when the body doesn't have enough insulin weight loss is inevitable such as a child with Type 1 diabetes first coming to attention. That child can't produce enough insulin, that's an autoimmune problem involving the pancreas and without enough insulin that child will be losing weight whether he or she is eating three, five or seven thousand calories a day. Without insulin you can't store body fat. Now if you don't have diabetes the most potent determinant of insulin levels day to day is the amount and type of carbohydrate you're eating. All of the processed carbohydrates, we're talking not just sugar, but refined grains, potato products all of those low fat processed carbohydrates that flooded our diet during the low-fat years. These foods raise insulin more than would ever have been the case throughout our history, throughout our evolution. And that insulin, according to this carbohydrate insulin model, is programming fat cells into a calorie storage feeding frenzy. So they take in too many calories, unfortunately there are not enough calories left for the rest of the body and the brain perceives, that the brain sees that there are not enough calories in the bloodstream. And that's why we get hungry and if we resist the urge to eat that's why our metabolism slows down.

Jonathan: So, it sounds like satiety is not, it's not only a function of the types or quality of calories eating but you could have a body that will perceive any quality of calorie as more or less satisfying based on hormonal, neurological or gastrointestinal differences. And maybe this is, would you say, part of the cause of an elevated set-point?

David Ludwig: So, the brain in determining our hunger and our metabolism cares about two things. One, is how much fat is stored on the body. It wants to make sure that we've got enough fat that can make it through a famine if there isn't enough food for a while. But everyone other than the most extremely thin people have enough fat in their body to last for weeks without food. The other thing that the brain cares about is how much or how many calories are in the bloodstream to fuel metabolism at that particular moment. So, you know we all know that experience of like, hitting the wall sometimes in physical activity or just going too long without eating. You feel this drop in your metabolism, extreme hunger in a sense that you really can't think about anything else until you get food. That's your brain saying we have a metabolic problem. We need food in order to run metabolism in states with too much insulin around in the body, we get into that metabolic problem too often, too quickly. Calories that we eat enter the body,

help us feel good for a while but then quickly gets stored away in fat cells or elsewhere. We run out of fuel and get too hungry too soon after eating. That's a function not just of the number of calories we eat but the type of calories we eat. Simply cutting back calories if they continue to cause these swings in our blood sugar and insulin levels isn't going to solve the problem.

Jonathan: You mentioned types of calories. I want to laser focus on this because similar to defending the body, understanding the concept of homeostasis, how the body is going to work to balance itself out, if you're fight that you're fighting a losing battle. It does seem, and I don't want to oversimplify things, but we've already used these terms so far; that you can say it's a calorie quantity problem just eat less and exercise more primarily, or it's primarily a calorie quality problem that if you get the calorie quality right quantity will take care of itself. Could you speak to calorie quantity preferably using that term because I really want to hit the difference between quantity and quality, quantity, quality. And so, a quantity-based approach...what that is, why it doesn't work in brief, and then a quality-based approach. What that is and why it works?

David Ludwig: Well what are the fundamental problems in obesity, let me try that again. One of the fundamental questions in obesity is why do people who are heavy overeat? And the most common response is that they're hungry. So, think about it, people are overeating because they're hungry and what's the most common approach to treatment? Eat less. What does that do to your hunger? Makes it go up more. So that's the disconnect, that the conventional approach has no solution. In effect it's saying you've got to spend the rest of your life dealing with this excess of hunger and it offers all sorts of behavioral and psychological techniques to distract you, to take your mind off your hunger, maybe you eat on little plates to make it look like your food is bigger than it really is, you drink a lot of water to temporarily fill up your stomach, when you're hungry go out and exercise. But none of these behavioral approaches solves the basic problem. What is driving hunger? So simply cutting back on calories, simply eating less doesn't change your set-point. In fact, it sets up a battle that you will have to deal with the rest of your life, excessive hunger. So, what does change set-point? Research over 50 or even 100 years suggests that the quality of the foods we eat can play a fundamental role. That by altering the way that blood sugar and hormones change after we eat we can change how fat cells behave how many calories they store versus how many calories go to the muscle and the other organs of the body to be

burned. Once you make that change set-point can decrease and when set-point decreases then hunger and metabolism naturally adapt without the struggle without requiring willpower.

Jonathan: Can you speak to how...so what you just said may sound like a miracle or too good to be true. Because what I heard you just say is that your body can start to pursue being lean as robustly as it is currently pursuing being overweight. That sounds like the magic miracle solution. Can you speak to, one, is that a miracle or is it proven science? And two, what you have seen that do for people once their body makes that change?

David Ludwig: We can see this change in set-point in the animal research laboratory in black and white. If you make a certain change in diet, give a certain drug, alter some other environmental conditions, give a specific hormone you can cause a lean rat to suddenly gain weight and double its weight. Reverse those changes do some other interventions and you can cause that weight to drop right back down to where it was. So, in a sense you could look at that heavy rat and say this is a genetically predisposed rat to obesity. But if you didn't know that you'd made those specific environmental changes you wouldn't have access to these other treatment options. In the animal laboratory we can make changes in diet, hormones or other environmental exposures and adjust body weight set-point up or down. This is standard science, easily accepted. That you don't have to change genes to change how biology controls body weight. There's very strong evidence that that's happening in humans as well. In fact, how else do we explain the obesity epidemic among genetically stable populations? You know people are gaining weight year after year something is causing that set-point to shift upward. And, while there could be many things, environmental toxins, contaminants, other exposures, diet is the most likely player here. And it's surprising that that gets denied so commonly with the conventional calorie-in-calorie-out mindset. It's a mindset that the food industry loves because it means there are no bad foods. They can market as much sugary beverages, processed junk food as they want and put the responsibility on to the public to just eat less move more. That hasn't worked. We have an epidemic that is out of control despite a focus on calorie balance for the last 40 years. I mean you can't buy a processed food packaged without seeing the calorie count on label. Somehow that's not helping us. So, what have we missed? The obvious player here is food quality. And, research from my group and many others around the country around

the world suggest that the worst players now are the processed carbohydrates. We're talking not just sugar but refined grains, potato products, anything that breaks down into sugar quickly, the technical term for that is high glycemic index. So, let's walk through what would happen after a conventionally recommended breakfast say a bowl of cornflakes, fat-free milk and orange juice. You know that's low in fat, so-called complex carbohydrate but it also digests very quickly. So, within 10 or 15 minutes after that meal blood sugar is going to be shooting up and that's going to cause a lot of the hormone insulin to be released much more than after a meal with you know such as scrambled eggs and vegetables. That insulin is going to be directing the glucose and other calories from the meal into storage. Some of it is going to get locked away in fat cells, some of it's going to get locked away in the liver and you may feel fine for an hour or two. But what happens later in the morning? Blood sugar starts coming down rapidly, in fact we've seen in our research that it comes down so rapidly that it causes the body to release stress hormones, hormones like adrenaline...that's an emergency stress hormone. It's your brain's way of saying 'Houston we have a problem, we're running out of calories'. So, it's not an hour after eating processed carbohydrates that's the problem. It's after three or four hours when the calories have been absorbed, locked away, and the body runs out of fuel. It's at that time that we either feel satiated, good, high energy, clear thinking or we're starving, poor energy. Can't take our mind off of food and are either going to have an extra-large snack or extra-large meal. That difference can make for the difference between weight gain and weight stability. Even before we bring in metabolism which also changes.

Jonathan: So, let's talk a little bit about that specific example say we have two breakfasts, isocaloric so the same number of calories one is cornflakes, toast, juice, fat free milk conventional, 400 calories. And then we eat 400 calories worth of scrambled eggs with vegetables. We talked about how the brain perceives energy or glucose in the bloodstream and we talked about how with the high glycemic breakfast after three or four hours there's perceived starvation. Possibly there's perceived starvation because we are not, the body is then not able to release more energy into the bloodstream because of the impacts of insulin is trapping fat in the fat cells. But if I ate a lower glycemic or a higher quality breakfast what would happen after three or four hours to prevent me from feeling hungry, to prevent that dip, to prevent the release of adrenaline. What is different three four hours after eating a high-quality meal then eating a low-quality meal?

David Ludwig: Back in the 1960's we ate more than 40 percent of our calories in fat but because of concern for saturated fat which quickly generalize to all fat, the public got the message year after year to cut back on fat. So now we're down to about 30 percent, close to the government recommended 30 percent carbohydrate increased. The obesity epidemic unfolded during those years. Could there be a relationship? One thing about fats, things like olive oil, nuts, avocado, even dark chocolate they don't raise insulin essentially at all. When we eat them, the calories take longer to digest, and they stay in our blood circulation longer and that Promotes Longer satiety. You don't have the same surge and crash in blood sugar and in hormones on a higher fat lower carbohydrate meal compared to the typical processed carbohydrates were eating so much of today. To look at this we did a study actually, this was a double-blind study, which is kind of hard to do in research. We gave our participants on two separate days one of two milkshakes. One milkshake was made with fast digesting carbohydrate the other with slow digesting carbohydrates but otherwise they were same had the same level of sweetness. So, we first we followed their blood sugar and we saw as expected that after the fast digesting carbohydrate blood sugar surged and then crashed, insulin surged as well, people got hungrier four hours later. They reported that despite the same calories, four hours later they were hungry. When we looked into their brains with a new technique called functional MRI you can actually look at the brain areas that are that are getting active. We saw one area lit up like a laser. This area is called the nucleus accumbens. So that area which is deep in the brain is considered ground zero for the classic addictions like cocaine, heroin and alcoholism suggesting that these highly processed carbohydrates are hijacking basic pleasure and reward systems in the body producing something like food addiction. It's not that these foods are inherently so tasty. When we looked at brain function it was already four hours after the meal and the two milkshakes tasted the same. After all, are potato chips, popcorn, you know all these other binge foods really so tasty? It raises the possibility that we're craving these foods not because of their tastiness but because of how they're affecting our metabolism. They're causing changes in our blood sugar and our hormones that make us crave them a few hours later. And then when we crave those foods and eat them it raises blood sugar, we feel better for a while, but it sets up the next surge crash cycle. That sounds like an addictive cycle and in my experience the fastest way to get off it is to cut back on the processed carbohydrates and replace it with healthy fats.

Jonathan: Cutting-edge, breaking news FDA approved a new weight loss drug. Interestingly enough the active ingredient in that weight loss drug is the same substance given to heroin addicts. Do you have thoughts? I mean food addiction is a hot topic but now the FDA says one of the ways to treat obesity is to prescribe the same medication we give to wean people off of heroin. I would love your feedback on that because that just seems like a big deal.

David Ludwig: Well of course there's been a long and sorry history of drug treatment for obesity. There are a few basic problems. One, is that you were trying to alter primal biological regulatory systems, systems that have evolved for hundreds of millions of years to try to keep our weight in a healthy range. We don't want to weigh too little because then we can't survive a famine, we also don't want to weigh too much because then we're going to be probably the most attractive to the nearest saber-tooth tiger and weighing too much also affects other important biological systems it can influence fertility, can create complications in childbirth. So, there's nature wants us to be in the healthy normal range. And these systems have evolved to do that. Coming in with a drug to try to change these systems is really risky because we don't know what other systems are going to respond and what the side effects of those are going to be. In addition, any drug treatment is going to have to be used for your whole life because once you stop taking it, it stops working. So, do we want to address this major public health crisis involving most of the country, more than two thirds of adults have excessively high body weight. Do we want to be treating that mainly with drugs that people are going have to take for the rest of their lives? Every drug tried to date has either been taken off the market for side effects or is proven to have very limited long-term effectiveness. There may be some new drugs that can do better but if you look back over the last century the story has been very depressing. And, you know ultimately our biology is not defective. You know it's not like humans struggled to keep a healthy body weight 50, 100, 200 years ago without these drugs or without bariatric surgery. Something is causing the set-point to creep up year after year, we need to identify that and then target our solutions at the underlying problem.

Jonathan: So, I just want to talk about the massive scope of both obesity and diabetes and then also if possible, how deeply related these things are, because I'm seeing data that suggest that if you're obese your likelihood of becoming diabetic is astronomically higher. If you're diabetic because of insulin treatment and so on and so forth. So, I

mean are they different things are they the same thing? How big of a problem is it? Does one lead to another? So, size of problem and relationship of two conditions.

David Ludwig: Diabetes is not a new disease. But what we sometimes lose amidst the current epidemic is an awareness of how rare it used to be. Very few people, just one or two percent, would have gotten diabetes 100 years ago or before and today one in three people are predicted to develop diabetes at some point in their lifetime and diabetes reflects the ultimate metabolic meltdown. It's basically the fundamental systems that control blood sugar, this critical fuel for the body breakdown. And without treatment you know diabetes can be either rapidly fatal as is the case with type 1 diabetes or very severe cases of Type 2 diabetes, but also will develop severe complications over years. And fortunately, we're able to prevent many of those complications with modern drugs and technology. But the diagnosis of Type 2 diabetes, it still carries a tremendous consequence to both the quality and the length of life. We have to ask why has this condition become so common? What's going on that has caused our bodies to basically lose the ability to manage blood sugar? We know obesity is a big part of it but not the whole story. The quality of our diet and other lifestyle factors importantly influences risk at any body weight.

Jonathan: If you are diagnosed with cancer, another deadly horrific disease. It seems like that diagnosis is treated so much more differently than, I think the American Medical Association now calls obesity a disease diabetes is a disease. Why are the diseases of obesity and diabetes seemingly treated almost like it's just a new normal? Like, it's just like having a sunburn or having a cold, like we can manage, it's not a big deal. Why does it seem like these two potentially fatal diseases, diabetes and obesity which have reached epidemic levels, that are affecting children are not treated like other fatal, potential fatal diseases?

David Ludwig: Obesity and also to a considerable degree adult type diabetes which we now call type 2 has conventionally been viewed as a lifestyle problem. Question of personal choice, eating too much, not getting enough physical activity. It's your fault if you develop obesity and diabetes. And this way of thinking I think permeates treatment and even how we invested in research into the condition. We somehow blame people for these conditions more than we would for cancer, heart disease, rheumatoid arthritis, all conditions that also have some interplay between biology, behavior and environment

that we know that obesity and diabetes are importantly affected by biology. We've lacked the deep understanding as to how our environment is causing these epidemics and once we identify more accurately what's driving the diabetes epidemic we'll be able to de-stigmatize the condition. we'll be able to say you know rely less on exhortations to eat less and move more and more on sophisticated approaches that target the underlying drivers of these conditions. You know we also have the new phenomenon of childhood type 2 diabetes. It's one thing for an adult who'd been gaining excessive weight to develop Type 2 diabetes at age 50 and suffer their first heart attack or stroke at age 60. It's a very different thing if the clock starts ticking at age 10.

Jonathan: It's fine to love your body and to accept your body. I don't want you to have diabetes though. And how do we help people to see the profound connection between carrying excess fat, which you could be very healthy and carrying excess fat hypothetically, but if it then turns into diabetes you're not going to be around for your grand-kids or, your ability to be around for your grand-kids it's going to be very limited. How do we help to bridge the gap between obesity and diabetes? Because they do seem so tightly related.

David Ludwig: Well the key step is to understand that obesity and its complications are not simply a problem of poor character, lack of willpower, lack of discipline. Unfortunately, that's a mindset that evolves directly out of the calorie-in calorie-out approach to obesity. Now if all calories are alike and you just have to eat a little less and move a little bit more, anybody should be able to do it. And if you can't it must be your fault. We now understand at least in the basic laboratory in the science laboratory that bodyweight is controlled by our biology and yet that knowledge is not getting into the weight loss clinic it's not getting into the Diabetes Care Clinic. We have to understand what's driving the epidemic beyond lack of willpower. Once we do we can destigmatize this problem. If having people feel badly about their weight were going to be an effective cure for the obesity epidemic, it would have been solved years ago. You know, blaming people you know, not only doesn't help it actively hurts. You need a lot of support and self-confidence to make a long-term change in lifestyle. And simply blaming people for the problem undermines their ability to make those changes.

Jonathan: Do you see there being any difference between the causal factors of obesity, from a lifestyle perspective, and the causal factors of diabetes?

David Ludwig: I think an underlying driver of obesity, diabetes and what's called the cardio metabolic syndrome. You know a constellation of high insulin, insulin resistance high triglycerides, low HDL or good cholesterol, chronic inflammation. All of these circle around insulin resistance and one of the obvious drivers is processed foods but specifically processed carbohydrates. Now, these modern industrial high carbohydrate, low fat foods that have flooded or diet are driving metabolic dysfunction and that's resulting in obesity, it's increasing the risk of diabetes, it's arguably fueling cancer, neurodegenerative diseases. What else, what other change in our environment could be plausibly causing this epidemic of chronic degenerative conditions? You know the prevailing explanation that we just lose our ability to control ourselves and show discipline in the modern environment somehow just misses the mark especially in light of the well demonstrated fact that our weight is strongly controlled by biology.

Jonathan: I would say just from a high level it seems like the message of calorie quality, eating higher quality food, is leading to higher quality health is so straightforward and simple but there still seems to be either confusion or refusal to adopt that mindset. Why?

David Ludwig: Well in medical school I sat through hundreds of hours of study into drug treatments for chronic disease. I might have had five hours of nutrition and the nutrition I had was probably wrong for the most part. We have this mindset in the health care system that usually patients won't want to embrace lifestyle change and so we like to prescribe drugs and surgeries and other technology-based interventions. There's no question there's an important role for these but for the most part those technologies don't get at the underlying problem. Now what would it take to truly change lifestyle in the clinic. You know we need more than six minutes reimbursed with patients to have a hope of changing lifestyle and we need more than just doctors, we need integration with dieticians, psychologists. We also need to be thinking about this from a public health perspective. If the easy inexpensive choice is processed junk food kids walk home from school through a gauntlet of junk food both in school, after school and at home. It's going to make significant long term change very difficult. But if at the same time we ask what does it take to recreate a society where the healthy choice is also convenient and affordable and easy? We need to develop models of treatment that support lifestyle change in the clinic. And also, be thinking from a public health perspective for how to

make the healthy choice also easy, convenient and affordable. Today we've basically done the opposite. We've given all of the incentive to drugs, technology and basically giving a pass to the food industry to continue to market atrocious quality food including directly to children. So, you know if you think back to the 1960's when JFK, when Kennedy said we need to put a man on the moon. If you said instead how do we make America the fattest country in the world rife with chronic disease. You know what would you do? Well you'd say we're going to you know place farm subsidies and other incentives on high calorie low quality commodities like corn for high fructose corn syrup. We're going to heavily advertise junk food to children on TV, video games. We're going to give them atrocious quality school lunches you know, at a dollar twenty-five a day reimbursement. We're going to cut back physical education in school and afterschool recreation. We're going to design our cities to make physical activity inconvenient possibly even unsafe as it is in the inner cities to some degree. You know. And we're going to create a political system in which the food industry can give millions of dollars to politicians to undermine meaningful regulation. Well, guess what it worked.

Jonathan: Did you abstain from saying the low-fat sort of push in there?

David Ludwig: Well that's another part about it is getting the science right. All low-fat foods aren't a problem. Apples have very little fat but aren't driving the obesity epidemic. It was a combination of having the wrong science focused obsessively on reducing all fats including many very healthy ones. And the partnership with the food industry that endorsed the marketing of highly processed, high calorie, low quality junk foods. So, we got products like the fat free Snackwells and the low-fat Twinkies advertised as health foods when they're really nothing different than an oral glucose tolerance test

Jonathan: That's very powerful. There's a lot of talk about fat and carbohydrate. Could you talk a little bit about the role of protein and fiber in food quality? Let's do protein first. What is the role of protein, high protein versus low protein, in food quality treatment for obesity, treatment for diabetes?

David Ludwig: Well one of the big problems with the food supply today is all the processed carbohydrates that have flooded in during the low-fat years. This not about just one nutrient. The quality of the fats we eat are very important we know that trans fats are the nearest thing to poison in the food supply. Fortunately, they're being

removed through regulation, and let's not overlook the importance of government regulation, but other kinds of fats are exceedingly healthy like nuts, olive oil, avocado, even dark chocolate. Beyond fat the amount and type of protein is very important protein balances carbohydrate. It causes a little bit of insulin secretion, but it also causes secretion of a hormone called glucagon. Glucagon is sort of like the yin yang with insulin whereas insulin promotes calorie storage, glucagon helps pull calories out of storage so it's available to fuel metabolism. So, we want to get that right combination between protein and carbohydrate and then beyond that fiber and other critical substances of food play a role especially in feeding or gut microbiomes. So, the gut microbiomes are the microbes that live in the intestinal track and play an important role in not just body weight regulation but general health. We have to think in terms of prebiotics, probiotics and polyphenols. So, prebiotics are things like fiber that we don't directly digest, it enters into the colon and it serves to stimulate growth of healthy bacteria. Probiotics are those healthy bacteria themselves. We can get them from fermented real fermented foods like yogurt or we can take probiotic supplements. Traditional cultures would have eaten lots of naturally fermented foods sauerkraut, all sorts of pickled dishes would be regular parts of traditional cuisines. So, prebiotics, probiotics and the third is polyphenols which are typically plant substances. Oftentimes they're colorful and they have interesting strong tastes and they serve as a form of weeding. They specifically inhibit the growth of unhealthy bacteria so that the healthy bacteria can take over and not be pushed out.

Jonathan: Is metabolic dysfunction synonymous with an elevated set-point?

David Ludwig: The term metabolic dysfunction implies that there's some problem in your biology that's predisposing to weight gain quite apart from willpower and the amount of food that we intentionally consume. We know that many causes of obesity in the animal laboratory, and some human genetic causes of obesity, have metabolic dysfunction at the source. It's not primarily a problem overeating. It's where those calories are being stored. Over overeating, in many of these experimental models of obesity, comes second.

Jonathan: So, it's not that overeating doesn't happen by definition overeating is happening, but overeating is caused not by a lack of willpower but rather by blank.

David Ludwig: So, if somebody is going to gain weight they have to either eat more or expend fewer calories than at neutrality. But that doesn't tell us anything about the cause. Is it that we are just somehow unable to control our behavior? We eat too much and that leads to weight gain? Or is it there's some basic problem involving fat storage, metabolic dysfunction, or body weight set-point that's programming the body to weight gain and that leads to overeating and that leads to a problem with calorie burn. Which comes first? Answering that question makes all the difference in how we approach the problem.

Jonathan: Can you speak to the fact that we've all met people, every person who watches this will know somebody who eats whatever the hell they want, doesn't exercise and doesn't gain weight? We call these people naturally thin people and they themselves might be the opposite of a naturally thin person. Naturally thin people seem to be the embodiment of a low set point and people who are less fortunate do not have that. Can you speak to naturally thin people? What does the research community have to say about are they freaks or are they proof for this more reasonable hypothesis of the underlying cause of diabetes?

David Ludwig: You can take a naturally thin person or for that matter animal in the laboratory and convert into a naturally obese individual through a variety of exposures, changes in diet and hormones. For example, just giving rats moderate doses of insulin on a daily basis will cause a shift in metabolism toward more fat storage. Over time that animal is going to start eating more and gaining weight. If you then cut back calories, you put that rat on a diet, you can prevent weight gain, but that animal still has too much fat that insulin has caused excess fat storage at the expense of lean body tissue and muscle. So, simply considering calorie balance misses all of the biology that's happening inside the body that determines whether or not we're hungry, whether or not our metabolism is speeding up or slowing down, whether or not we're storing fat we're building lean muscle.

Jonathan: When you speak to all the other beautiful complexity that's taking place in the body so that the term insulin has been used a lot, I think a lot of people are becoming familiar with the term insulin and there could be some risk that people just say 'OK it's just insulin so I'm going to go on a ketogenic diet for the rest of my life and eat less than 20 grams of net carbs forever because before I thought it was calorie problem.

Now I think it's just an insulin problem we solved the problem. Can you speak to the interplay of hormones other than insulin? Can we speak a little bit of the gut and can we speak a little bit about the brain and their combined interplay to determine the set-point weight or their combined interplay when affected by metabolic dysfunction?

David Ludwig: Well there's no question that obesity and body weight control more generally is complicated. There are hundreds if not thousands of genes that to some degree influence body weight. We now know that there are dozens of hormones and other biological signals that play a role. There are a few dominant players. One is insulin, because insulin directs the storage or burning of calories after we eat and that is a critical determinant of how hungry we get soon after the meal. Other players are leptin, leptin's a little bit more of a long-term player that reflects how much fat is stored in the body. And, you know a relatively new player on the block is ghrelin which is made from the stomach and that's considered the hunger hormone. When we go for a while without eating that rumbling in the stomach feeling you know that comes from ghrelin.

Jonathan: Why is it that, for example leptin therapy, hasn't been an effective obesity treatment?

David Ludwig: Right. Because body weight control is so complicated we have so many interacting hormonal, neurological, and fuel signals involving multiple organs of the body changing just one component of that system typically doesn't lead to a long-term cure. That's why you know drug after drug tried over the last century has failed to be effective over the long term either causing life threatening, in some cases, side effects or loss of effectiveness over the long term. And that's also true with leptin. Leptin was discovered about 20 years ago and initially there was hope that this would be a miracle cure because animals lacking leptin become massively obese, you give them just low doses of leptin and you can cure the obesity. The problem in most varieties of obesity is not leptin deficiency, leptin levels are actually high. We have what's called leptin resistance which is similar to insulin resistance that occurs in obesity and diabetes. So, if leptin levels are already high and you just give even more leptin you don't get much effect. And for that reason, despite dreams of a blockbuster drug, leptin has not panned out for obesity.

Jonathan: One of the reasons, in my experience, that helping people to understand the impact of the brain in everything. Is that clearly starvation? Just the deprivation of calories is not going to have a therapeutic impact on the brain whereas certain substances such as omega 3 fats can have almost dose dependent, at least in rodent models, positive impacts on appetite regulating centers of the brain and other things found in processed foods like MSG caused tremendous amounts of inflammation of the brain.

David Ludwig: The brain is centrally involved in body weight control. There are more genes that can go wrong in the brain leading to obesity than anywhere else in the body. But that's been falsely interpreted to mean that it's all about hunger. And food intake. In fact, the brain controls metabolism just like it controls hunger. Changes in the brain, genes in the brain or activity in the brain influences biological systems throughout the body. The brain directly communicates with fat cells directly, communicates with the cells that make insulin. As well as other critical hormone systems in the body. So, while everything does ultimately go through the brain, that doesn't tell us what the fundamental problem is.

Jonathan: It sounds like to understand the underlying cause of dysfunction and thing that we need to heal requires an understanding of hormones would require an understanding of neurological function.

David Ludwig: So, the brain controls metabolism and hunger as well but it in turn is influenced by many factors in our diet and our environment beyond what we eat. Levels of sleep, stress, physical activity all get integrated into the brain to determine, in effect, our set-point at that particular point in our life. Some key factors as we've discussed are the amount of protein, fat and carbohydrates in the diet. Other qualitative aspects of diet fiber, polyphenols, prebiotics. Types of fat are also important especially polyunsaturated fats like Omega 3 fatty acids. These play a critical role in calming down inflammation in the body, inflammation in the brain and especially the hypothalamus can produce biological dysfunction, can cause insulin resistance, leptin resistance that leads to weight gain and that adversely affects metabolism. The brain integrates many aspects of our diet and our lifestyle and determining what the set-point of the body will be at that time. Beyond just the ratio of fat, carbohydrate and protein, the quality of the fat that is also critically important. Omega 3 fatty acids calm inflammation, inflammation in the

hypothalamus can exacerbate hunger and adversely affect metabolism. In fact, we know that dysfunction or damage to the hypothalamus leads to a very difficult to treat form of obesity.

Jonathan: And what would you say the relationship is between inflammation of the body and the brain and the set-point?

David Ludwig: One of the potential exciting areas of research linking the gut microbiomes to weight control goes through inflammation. We know that the type of bacteria and the relationship between the bacteria and the lining of the gut determines inflammation not just in the digestive tract but potentially throughout the body. Having a healthy gut microbiome, a high-quality diet feeds those good bacteria but also can calm inflammation throughout the body plays a critical role in affecting the brain and helping the body to achieve a healthy body weight.

Jonathan: If we if we can for bringing together almost like a master thesis of you've got your brain, you've got your gut, you've got hormones which essentially, in oversimplification, facilitates some communication there. Can we talk about how the brain, gut and hormones work together to determine set-point and how eating high quality diet affects each of those factors?

David Ludwig: When humans are eating a natural high-quality diet of mostly unprocessed fruits whether it's relatively high in fat and protein you know if you were Inuit, living in the Arctic, or relatively high in natural carbohydrate if you were living around the equator eating a lot of fruit. The body is able to integrate these signals, hormones, into the right level of appetite and metabolism to keep body weight set-point at a healthy level. We know that our modern diet and environment is upsetting this and causing set-point to be ticking up year after year. And so, we have come about this to try to impose conscious control either by willpower to cut back or cut back calories, or the willpower to cut back calories or other simple interventions, a specific drug, even surgery. You know these aren't holistic approaches they may work in the short term, but they have long term side effects. So, we really want to create a situation where our biology, our brain, as it has evolved over hundreds of millions of years gets the right inputs that involves the quality of our diet also feeding our gut microbiome, the right amount of sleep, stress relief physical activities. And when these are in place the brain

and the biological systems that control body weight do their job without requiring conscious control.

Jonathan: What I'm trying to help people to see is that part of the reason that starvation is so toxic and ineffective is that just the absence of food does not cause the changes that we're after here.

David Ludwig: There's a raging debate as to how much carbohydrate and fat we should have in the diet. The pendulum had been at one extreme during the 70's, 80's and 90's with the low-fat era. And now many people are suggesting that all carbohydrates are an issue especially for people with metabolic dysfunction, type 2 diabetes. Get rid of all of it, eat a ketogenic diet. But there's a middle ground that most people can live in which is to pay attention to the quality of the carbohydrates keep those carbohydrates natural, minimally processed so they digest slowly they don't raise blood sugar and insulin levels very much. In that situation people have a little more freedom to eat a bit more carbohydrate or a bit more fat if that's your culture, you don't have to count calories we don't have to count carbohydrates. So quality carbohydrate is the first step second quality fats. You know for many years we were told to fear all fats in the diet and it led us to banishing some of the healthiest foods in existence...nuts, olive oil, fatty fish, avocado even dark chocolate. These are slow digesting very nutritious foods, they're not associated with weight gain consistently in studies in fact quite the opposite. And it seems the more you eat of these healthy high fat foods the lower your risk for diabetes, heart disease and, according to one recent study, the longer you live. Then we need to get the right amount of protein. Which can be vegetarian, or animal based there are plenty of plant-based sources of protein and there may be some advantages to be getting those plant proteins regularly. Plant proteins tend to stimulate less insulin than animal proteins. Then we want to get plenty of fiber and polyphenols to feed our microbiomes, and that natural diet will also automatically carry along rich levels of vitamins minerals and other protective plant substances.

Jonathan: So, it sounds like a high-quality diet is satisfying, does not cause a tremendous amount of aggressive issues with hormones, provides high nutrient density and does not facilitate an efficient storing of fat in the body. Can you help to sort of help us find some common denominators of what a high-quality diet looks like?

David Ludwig: Cultures around the world have eaten diets that differ quite dramatically in the relative amounts of protein fat and carbohydrate. But there's some similarities. They tend to be minimally processed a lot of, if you're eating carbohydrates they would be natural, slow digesting whole fruits, legumes, grains ideally in their least processed state possible. Healthy sources of fat in the Mediterranean that was of course olive oil, adequate amounts of protein, which can come from animal sources but also plant sources. In Asia soy products like tofu or fermented soy products like Tempe play an important role in the diet.

Jonathan: Whether you're phase one Atkins or T. Colin Campbell, talking about the China study you both agree those two people agree that eating not starchy vegetables, green leafy vegetables is important. What is the role of the consumption of non-starchy vegetables in the treatment or prevention of obesity and diabetes.

David Ludwig: Well human requirement for carbohydrate is actually zero. People can live indefinitely on no plant products at all. And that was simply demonstrated by the Inuit's or the Laplanders who spent most of the year where no plants or carbohydrate would be available. But that begs the question which is, what's the optimal diet for people and what's a sustainable diet. Clearly, we've got too many people in the world approaching 8 billion for us all be eating diets consisting entirely of animal products. And so, we have to have plant products to feed the world and many plant products are very healthful and delicious. Non-starchy vegetables are rich in micronutrients, phytochemicals and antioxidants that calm inflammation in the body, they typically have the carbohydrates and non-starchy vegetables are very slow digesting. And they also make a wonderful vehicle for healthy fats so if you're going to eat spinach don't boil it, sautéed in olive oil add a little garlic and salt. Now that's a dish that people would pay a lot of money for in a French restaurant or an Italian restaurant. You can make it yourself.

Jonathan: I think that that's a huge breakthrough that I would like to talk about more which is potentially the stigma around vegetables that they're disgusting because people think they need to eat them raw or they think they just need to steam them. But once you overcome your fear of fat, if you see vegetables as a fat delivery mechanism almost it can make them extremely palatable and transform your diet lifestyle. Can you talk about that a little bit?

David Ludwig: Many of us and especially kids have paired vegetables with bad taste, and that's unfortunate, and it's a reflection of our cultural unawareness of the potential of vegetables. Around the world you know kids have traditionally eaten and liked vegetables because they were prepared in tasty ways. Make a rich sauce to pour over vegetables either cooked or raw. You know, if you're having salad throw away the fat free dressing loaded with sugar and other artificial flavors, make a real oil and vinegar dressing and use it liberally, that's a healthy component of the salad. Sautéed vegetables in a healthy oil make a rich sauce to accompany vegetables at the table and you win twice.

Jonathan: As you discuss all these complex mechanisms and how everything within your body sort of interacts in a complicated way to keep the body working well. Like how you just said you can't just introduce leptin and expect it to fix things. Can you speak to the fact that, for example the polyphenols help other things and when your hormones are out of whack that affects all sorts of other things, and having inflammation here and there? So, in broad terms without discussing any of those specific things. Say, when you eat high quality foods that has myriad effects that help everything work better rather than only those are better higher quality calories and so it's better because it's less bad qualities.

David Ludwig: If we view obesity just as a calorie balance problem then the solution is just to eat less and move more and it doesn't matter so much what you eat less of. That has not worked out well. People can't stay on low calorie diets the obesity epidemic has continued to emerge despite an overwhelming focus on calories. But if we think of obesity and related chronic disease as metabolic dysfunction it opens up an entirely different view and solution. In my perspective two things underlie most chronic disease. One is insulin resistance and the other is chronic inflammation. I call these the twin metabolic trouble makers. They underlie excessive hunger, poor metabolism, weight gain, risk for diabetes, heart disease potentially some of these feared neurodegenerative diseases like Alzheimer's as well. If that's the case then diet, lifestyle interventions are opportunities to calm down chronic inflammation and lower insulin levels. From that perspective we want to eliminate the processed carbohydrates they're the chief problems in insulin resistance. We want healthful fats digest very slowly, you want the right amount of protein enough Omega 3 fatty acids which are anti-

inflammatory and then plenty of polyphenols, prebiotics and probiotics so that the gut microbiome works with rather than against us. By focusing on these two problems, chronic inflammation and insulin resistance, a variety of complicated and seemingly unrelated health problems can be addressed at the same time.

Jonathan: How does it light you up inside when you think about how all that stuff interacts without discussing anything specific? Does that make sense to you? Like when I talk about a movie and I talk about the theme and the plot...

David Ludwig: One of the things that really attracted me to medicine specifically but also researching obesity and nutrition is the extraordinary interplay of hormone, genes, metabolic factors of the body much too complicated for anybody to ever totally understand. But the beauty is we don't have to understand everything. Traditional cultures maintained excellent health, low chronic disease rates by simply eating a high-quality diet and living in tune with their biology, enough physical activity, sleep, stress relief. By getting these basics right we've kind of forgotten them in our modern society but by relearning these basic principles. We can address and change this extraordinary internal biology without having to understand it.

Jonathan: If those are both so causal, I'm using that term intentionally (you can refute it) in the development of obesity and diabetes. Why do some people develop obesity and not diabetes even though they're chronically inflamed and have high insulin levels and some people develop obesity and not diabetes, some people develop diabetes and not obesity and some people develop diabetes?

David Ludwig: Think of it this way, weight gain is the price you pay for not getting diabetes. As long as you're able to store the excess calories consumed, safely into body fat, there's no problem. The body can function metabolically perfectly well. It's when the fat cells reach their tipping point. Where they can no longer safely store that calorie excess. Now for some people that happens at a relatively lean body weight other people can gain massive amounts of weight and still not reach that tipping point. When you reach that tipping point fat cells start to become inflamed. And they spread that inflammation throughout the body by secreting toxic substances, inflammatory mediators, that affect the pancreas, the liver, muscles, even the brain. In addition, those excess calories that can't be safely stored in fat starts building up elsewhere. When they

build up in the bloodstream they're called triglycerides, high triglyceride level, that's one of the problems in metabolic syndrome. When they build up in the pancreas around the beta cells that make insulin it causes those beta cells to more easily fail leading into the process of diabetes. When they buildup in the liver we get what's called fatty liver which is such a problem today. And when they build up in muscle they cause insulin resistance in muscle which further accelerates this descent into diabetes.

Jonathan: Part of what we're trying to accomplish with this movie is almost everyone in the world they say 'Hey you have diabetes', perceive that differently and would be more motivated to do something then if it is just like 'I've got an extra 20 pounds but that's OK because I'm fine', but what they don't understand is that extra 20 pounds...it doesn't matter if you're fine with it because you're biology isn't fine with it. You know, and we don't ever want to shame anyone, but we do...it's not just that your child is a little bit chubby. It's that your child's likelihood of having a really bad quality of life because obesity is a symptom.

David Ludwig: Weight gain is the price you pay for not getting diabetes on a poor-quality diet. As long as you can store excess calories safely in fat the body can do relatively fine without developing diabetes. It's when those fat cells reach their tipping point, which comes at a higher level for some people, relatively lower level of body weight for other people. When those fat cells reached their tipping point they can no longer safely store the calorie excess, so they spill into what's called ectopic fat, fat gets stored in places it shouldn't like the liver and the pancreas and the muscles and even in the bloodstream called triglycerides. And these promote metabolic dysfunction. In addition, fat cells beyond their tipping point become inflamed and spew inflammatory chemicals throughout the body that can lead to inflammation in the brain that accelerates this process. So, some people can continue to gain weight on a relatively unhealthy diet without immediate consequences like developing diabetes, some people can gain massive amounts of weight. But over time weight gain for most people will ultimately manifest in chronic diseases like diabetes. So, for most people there's no such thing as metabolically healthy obesity. It's a temporary state, eventually a tipping point will come.

Jonathan: It sounds like that temporary stay is, is it a healthy response? Is it your body trying to delay...like delaying the development of these diseases by temporarily storing fat in these cells but is just delaying the inevitable?

David Ludwig: Think of what kids are eating these days. You know the massive amounts of junk food, items that had never been in human diet until really the last 30, 40 years. And yet most kids can you know do pretty well for a while, not developing diabetes, not developing other severe medical problems. True, the rates of asthma and other inflammatory conditions are increasing in kids. We know that they're suffering from a severe obesity epidemic. But for the most part the consequences of even the atrocious diet being consumed today are not immediate. So, the body can handle these dietary insults for a remarkably long time. But sooner or later those dietary choices catch up with most people.

Jonathan: And they catch, it sounds like, in the forms of obesity, diabetes or myriad other chronic...

David Ludwig: Based on one's individual biology and genetics, sooner or later insulin resistance and chronic inflammation build up. Once the tipping point is reached, chronic diseases begin to emerge most notably type 2 diabetes. Now some people can gain a tremendous amount of weight and not yet have type 2 diabetes but that's a small minority. That eventually chronic diseases emerge for most people with continuing weight gain.

Jonathan: So is it almost like, assuming you are eating anything close to the standard American diet, which most viewers of this movie are. Even if they're not currently obese and not currently diabetic, if they have these twin metabolic troublemakers. Is it just a matter of time unless they intervene?

David Ludwig: Obesity is a major risk factor for diabetes but not the only one. We know that some people can develop diabetes at remarkably low body weight maybe just 10 or 20 pounds above ideal because their capacity to store safely those excess calories are limited, perhaps you know for genetic reasons. Without those genes that cause that effect in another environment might have some benefit. But in this environment that leads to increased risk for Type 2 diabetes. That's especially a problem among some

Asian populations. The tipping point into metabolic dysfunction in type 2 diabetes occurs at a significantly lower body mass index for Asians and some other ethnic populations than it does for many Europeans.

Jonathan: In your book you say some awesome thing about cornflakes with sugar, or sugar with cornflakes.

David Ludwig: All carbohydrates break down into sugar ultimately. But when grains are highly processed, as they are in so many of the low fat high carbohydrate food products today, that process happens literally in minutes after eating. So, after having a bowl of cornflakes blood sugar rises very rapidly for 10 or 15 minutes. Insulin surges and a few hours later blood sugar crashes you get hungry and tend to overeat. So, from this perspective you can have a bowl of cornflakes with no added sugar, or a bowl of sugar with no added cornflakes. Below the neck they're going to do the same thing. We've been told for many years that that breakfast of so-called complex carbohydrates, low in fat, was the best way to start the day. And so many mothers thought that by giving their kids cornflakes with fat free milk and maybe a glass of juice they're doing the right thing. The problem is all those foods break down very quickly into sugar leading to a surge and crash and blood sugar, overeating later in the day, and untold effects on you. So, parents were told that that breakfast of complex carbohydrates would be healthy support your kid's metabolism through the day. So, they gave cornflakes with fat free milk and juice. But what happens? Blood sugar surges for about an hour and then crashes a few hours later, your kid, 10:30 in the morning is going to be hungry, blood sugars crashing...what's that going to do to cognitive function? The ability to concentrate on studies. Compare that to a vegetable omelet with fruit. You eat it, those nutrients are absorbed more slowly blood sugar and hormones stay stable. Ten thirty in the morning your kids metabolically in a better state and brain functions better.