OZEMPIC: The Brain and Obesity: Are We Wired to Eat More? | Stephan Guyenet, PhD | The Proof Podcast EP #260

There's been an enormous increase in obesity rates It's been kind of increasing gradually over a long period of time However the pace accelerated sometime between the 19 mid 19 seventies and mid 1980 s And so at this point in the United States 43% of us adults have obesity And that doesn't include people who are overweight that is just people with obesity body mass index over 30 Yes Welcome to the Proof podcast A space for science based conversation exploring the health and longevity benefits that come with mastering nutrition physical exercise mindfulness recovery sleep and alignment facts nuance and trustworthy recommendations minus the hyperbole In today's conversation I sit down with Stefan G A phd a neuroscientist with a deep interest in the neuroscience of obesity and eating behavior and the author of the best selling book Hungry Brain Obesity is an extremely complex and multifactorial condition So while I do think you'll find this episode incredibly interesting I do want to emphasize that the intention here with this exchange was to simply open the door to the topic of hunger and obesity rather than being intentionally exhaustive It's a topic that I have many more questions about And thus in due course one we will no doubt revisit and expand upon Please enjoy You have been thinking about obesity uh eating behavior um why it's so difficult to lose weight and and keep it off et cetera for for quite some time at this point I'm interested in kind of starting here with how all of that started for you So maybe you could take us back to your early days as a a scientist or even prior to that What got you interested in neuroscience first and foremost and why did you sort of decide to direct your attention to the various things that drive hunger Yeah So my parents are scientists My dad is technically a pharmacologist but essentially a neuroscientist And uh so I always had it around me and I've always been very interested in science And uh growing up I also had a major interest in fitness and health just you know a personal interest And you know I played sports in high school So I was interested in in fitness and performance as well as the health aspects And really you know I kind of always knew I wanted to do something with science and there were a few things that were particularly interesting to me The biggest one was the brain and the reason is that the brain is first of all one of the great remaining scientific frontiers you

know we there are still things to be learned about muscle There are still things to be learned about the liver but there's a lot more to be learned about the brain in terms of you know the percentage of understanding that we have of the amount that we could have for the brain It's probably lower than any other organ And so it's this huge remaining frontier scientifically And furthermore it is the organ more than any other that makes us who we are So to me it's it's a really fascinating topic and it always has been So I ended up going to grad school at the University of Washington in Neuroscience And at the time I didn't really I didn't really have um an idea of what I wanted to go into what field I wanted to go into but I was interested in neurodegenerative disease And so I worked in a lab for my graduate studies that studied a neurodegenerative disease called spinocerebellar ataxia type seven And this is a really rare neurodegenerative disease It's related to some less rare diseases But um it was interesting work and you know contributed to the body of science in that area But I eventually became dissatisfied by you know the kind of impact that my research was having I wanted to have more human benefit And you know I I kind of joke that there are probably more people studying that disease than there are people who actually have it Um which is an exaggeration but probably not by much around that time I got interested in obesity and I started to see links between obesity and neuroscience I started learning a little bit about that and I thought it was really fascinating And so I decided to switch topics for my post doc And uh I did my post doc with Mike Schwartz also at the University of Washington studying the neuroscience of obesity particularly brain particularly regulation of body fatness by the hypothalamus Kind of what happens in that brain region when animals get fat That was really a way to bring together my interest in fitness and health my interest in you know human impact human benefit and my neuroscience background And so that was a really good fit for me Once I got into that field my interest in it continued to grow because it's really fascinating And the thing that was really amazing to me is there was all this information that was incredibly informative about how eating behavior works how body fatness works and you know why people have so much trouble losing weight and keeping it off And that information mostly was not making it to the public at the time And so I felt like you know in our field we had all this really cool information really impactful information that people just weren't hearing about And you know part of the problem with that is people aren't you know getting that interesting and useful information and the other part of it is that that vacuum that information vacuum kind of

allowed all kinds kinds of other hair brained ideas to proliferate And so yeah so that is kind of the reason why I wrote my book I felt like I was the right person to do that because I had the knowledge from being part of this field And and by the way you know the book almost nothing in it is new ideas that I thought of myself This is it's just a collection of the work that the field has done And um you know being able to have that knowledge and have the ability to communicate I was just the right person at the right time to write that book And I think that was really cool to to have been the person who got to do that you mentioned impact there in your story in terms of you sort of cut your teeth with that that rare neurodegenerative disease And then you were thinking about how you could make more impact So to sort of I guess contextualize this conversation how how prevalent is being overweight or obesity or being obese today Like how widespread is this issue and and how has that sort of changed over recent times Yeah so I can speak most authoritative authoritatively about the United States my country Um both because I live here and you know I'm most familiar with the data here but also because the United States has better data than a lot of other countries or more data I should say But you know that said the trends have broadly been the same in affluent industrialized countries So even though the United States tends to be fatter than most other affluent industrialized countries the trends are still pretty similar most countries aren't that far behind And so in the United States what we see is that you know the the data get more and more sparse as you go back But we do have data stretching back to the late 18 hundreds in the United States late 18 hundreds 1900 And what we see is that in middle aged white men at that time middle aged white civil war vets at that time there was very little obesity it was like one in 17 people middle aged white men had obesity at that time If we compare that to today middle aged white men it's basically fif it's around 50% So you know it went from one in 17 or so to one in two So there's been an enormous increase in obesity rates and it's been kind of increasing gradually over a long period of time However the kind of the pace accelerated sometime between the 19 mid 19 seventies and mid 19 eighties We see that the the rate of increase accelerated and that's what we refer to as the obesity epidemic So we had been slowly getting fatter for a long time before that But you see this kind of rapid uptick and it's just kind of been skyrocketing ever since You know it's still going up in the United States We're in 2023 now So you know it's been more than 40 years since the obesity epidemic started and it's continuing to increase And so at this point in the United States 43% this these are the latest CDC data

43% of us adults have obesity And that doesn't include people who are overweight That is just people with obesity body mass index over 30 And what percentage would be considered overweight Yeah I don't know the i off the top of my head I don't know the exact number but it's something like 30 It's in the thirties I think And so really you know people who are lean are only making up something like a quarter of the adult population now And and by the way not all those people are actually lean That's just what where they are categorized on the body mass index scale Those people still might be carrying excess fat Um and and conversely some of the people in the overweight category might not have excess fat as well Do we have any sense for the kind of time scale at which an individual puts on body body fat Is it a very slow incremental thing Over years and years and decades are we seeing it as an even sort of distribution over the year or is it more during the festive hair periods over December January The most interesting study I've seen on this um looked at really high frequency weight data I think it was from like uh wireless scales that people had I'm not I'm not sure exactly but really high frequency And they looked at it in the United States Germany and Japan And those are three locations that both have temperate seasonality So they have summer uh fall winter spring yet they have different holiday periods So they have different periods of fasting or feasting and celebration So in the United States we have this kind of six week holiday period starting with Thanksgiving ending with the New Year in Germany Um There it's more Christmas and New Year and then Easter and then in Japan they have the Golden Week is the main one which is later It's it's um it's not during the US holiday period I forget exactly when it's like February or March or something It doesn't overlay with uh the same period in the United States And basically what you see is people gain weight during the holiday period no matter when in the year it occurs So if it occurs you know between if it if it occurs between Thanksgiving and New Year's that's when people gain weight If it is Christmas and Easter that's when people gain weight If it's the Golden week That's when people gain weight And so it doesn't seem that my perception you know people say like and you know obviously there are animals that gain fat seasonally There are you know deer are extremely fat around here in the in the fall bears are extremely fat They're preparing for hibernation or for a lean long lean season But uh you know humans we're tropical animals originally right Like we're only really recently introduced into temperate climates and in in the tropics you don't need to have that kind of seasonal changes in body fatness And so I just really haven't seen strong

evidence that there is a seasonal change in human body fatness that is independent of holiday feasting What I see is evidence that when we get into this period where you know we have these celebrations that revolve around food calorie dense food typically people are bringing you know giving each other treats cookies things like that We're having things between meals we're eating huge meals That's the period of the year alcohol Thank you Um That is the period where that's what I see in the data that that's what's really associated with weight gain And by the way people gain weight during these periods and typically they don't lose all of it after that So you know we have our New Year's resolutions or whatever or we go back to our typical eating habits and most people on average will lose some of that excess weight but only about half of it So each year they just they're kind of ratcheting up a little bit higher Yeah that seems like a really important piece of of information It's almost like a kind of holiday hypothesis But I I'm sure the answer is not to scrap the holidays So maybe maybe we can we can uh explore some of the potential solutions as we move through this conversation But um from a a health point of view so we're we're talking about we're talking about the kind of incident or prevalence of being overweight or obese What is it about excess fat or adiposity that is problematic for a for a human's health Like why are we actually interested in exploring this and and helping people better manage their body weight or body fat That's a big question I think there are multiple domains that we can consider You know often people look at this only from the medical dimension like how is this going to impact people's health But I also like to think about it from the the individual's perspective I mean when you think about why people want to lose weight there are a lot of different reasons often why they want to lose weight People want to have better mobility they want to feel better they want to look better And you know those are the kinds of motivators that I think are the most prevalent among the people who are actually affected There there's the health concerns as well So I don't want to minimize that But you know often when we're talking about this from like a scientific or medical perspective we're really focusing on the health outcomes But I'm just trying to illustrate that there are there's a broader set of things that are important to the people who are actually affected And um yeah so if if we're if we move from that to the health outcomes um there are a couple of different ways that obesity can affect uh health and physical function One of them that is there but I'm not gonna dwell on is the the actual mechanical aspect of it So for example osteoarthritis of of the knees and hips is something that can be

caused or exacerbated by having a lot of weight on your body But most of the problems that I think people are most concerned with are metabolic and cardiovascular And in in terms of the health the health piece of it And what I think is that essentially most of that is driven by what I call energy poisoning And what I mean by that is exposure of tissues and cells to more energy substrate So that's fat glucose um amino acids then they can safely metabolize So energy containing molecules in the blood from the food that you ate and from your fat tissue more of it is circulating in your bloodstream than your tissues can can constructively handle So your you know your liver your pancreas your muscle tissue those are three key tissues and essentially what we see Um Yeah so I'm trying to think how how deep do you want me to go into this Because there's a lot of evidence I don't need to review it all But do you want me to get into some of the details Some of the evidence I think just the the kind of high level I guess link between excessive adiposity and perhaps where people are storing it Because I understand there could be a difference whether someone is more preferentially storing that as visceral fat versus subcutaneous and just so that the listener appreciates how that could increase their risk of say cardiovascular disease or type two diabetes or whether it's fatty liver or even certain types of cancer at a high level I think a good way to do this is to go through kind of the the process of going from a lean person to a person with obesity And we can kind of walk through how that proceeds and how it impacts the body metabolically You you start gaining fat Um for whatever reason your calorie intake goes up whether that's due to a change in environment due to aging due to you know change in diet you start gaining fat And what will happen is initially that extra energy that you're taking in will be absorbed by your fat tissue your adipose tissue and it will be fine Your adipose tissue is a professional energy storage organ It is designed to store energy in your body and up to a certain point it can do that efficiently it can whatever energy you're not burning that day it can take that it can trap it and it can hold on to it in the form of fatty acids and that's fine when it's doing that it is effectively protecting all of your other tissues from that extra energy But what you see is as that proceeds at some point if you continue to gain fat you will hit what's called your personal fat threshold And I'll give credit to Roy Taylor for this concept He was the one who came up with it and who's made a lot of the evidence for it Um And once you hit your personal fat threshold that is basically the amount of fat storage that you can safely handle before your fat just your tissue just can't hold on to all that extra energy anymore And what you see at that point is

that people are not if you look physiologically metabolically at what's going on in their bodies they're not trapping fat as well So after they eat a meal and those Kyla micros with fat go from the gut and start circulating in the bloodstream they stay in circulation for a long time they're not getting cleared as quickly as in a lean person who has well functioning adipose tissue And you also see elevated triglycerides fats in the bloodstream in the fasting state they're just not getting cleared as well And furthermore you see that the fat tissue is releasing more fat into the bloodstream in the form of free fatty acids It's not necessarily that they're um concentration of free fatty acids is higher but the turnover is higher You you have more release of fatty acids and more take up of fatty acids by the other tissues And so what you're also gonna start to see when that storage capacity gets exceeded is you're gonna start to see deposition of fat in other organs in other tissues You're gonna see deposition of fat and muscle tissue in liver tissue and pancreas And that is is a really strong marker of energy poisoning that those tissues are not supposed to have fat in them And so when you see that that's a sign that there's way too much energy circulating in the body And and that's very common by the way you know fatty liver I don't remember what the prevalence is in the United States I think it's over 25% or something in adults So it's very very common Um But you know we live in a saturate in a society that's absolutely saturated with energy And so um so once that starts to happen you start to get physiological changes you're you're gonna get um your your tissues are gonna start refusing energy And one of the ways they do that is by causing insulin resistance So insulin resistance is saying to the insulin molecule insulin would normally tell your tissues to take up glucose One of the main energy substrates insulin resistance is saying no I'm full I already have too much energy It would be physiologically dangerous for me to take up more energy I can't handle this So I'm saying no I'm creating insulin resistance and you can you know in cells in a Petri dish you can make them insulin resistant by exposing them to elevated levels of fatty acids glucose or amino acids And you can do it in people too You just put an IV and you elevate any one of those and you will cause insulin resistance very quickly So that's one of the things that happens you get insulin resistance and that causes all kinds of problems that contribute to cardiovascular disease and contribute to diabetes risk And then for diabetes it's really a two hit thing So you have to have the insulin resistance typically But the other thing that that energy poisoning does is it hits your pancreas and it starts degrading your beta cells your beta cells there are very unique cells They um because

of their key role in metabolic regulation they have to be very sensitive to circulating metabolic fuels And because of that they have to they take up those fuels to sense them So they're very sensitive to to energy poisoning If if you have this energy poisoning process and a marker of it of course is fat deposition in the pancreas What will happen is eventually those beta cells their function will start to degrade First You see a degradation of what's called first phase insulin secretion which is that first bump you get when you first eat food that'll kind of flatten out and then eventually you just get insufficient insulin secretion to control your your sugar at all And then you have diabetes So essentially if you know insulin resistance alone is not enough to produce diabetes If you have a robust pancreas you can just keep creating more and more insulin to overcome that insulin resistance But when you get that second hit of beta cell failure that's when people go downhill into insulin resistance in excuse me into type two diabetes That's kind of uh yeah what I just explained is kind of what I believe is the main path to cardio metabolic disease not to say it's the only contributor But in our current environment I believe that that is the the primary way that it goes down Only Uh last thing I wanna mention is that I think physical activity is really important in this regard because for tissues to be overwhelmed by energy poisoning it's not just about the amount of energy they're being exposed to It's how much energy can they dispose of as well And if you have a massive energy sink in the form of muscle contractions and liver having to supply that as well then you're you're creating a sink and you're not gonna get the same kinds of uh energy poisoning that you would get if you didn't have that physical activity just on this personal fat threshold And that what you just summarized was really beautifully said And it actually ties together a bunch of concepts from previous episodes I've had with Doctor Thomas Day Spring with Lane Norton So I think um the listeners will really really appreciate that and I have Roy Taylor actually coming on So all of this is coming coming together quite nicely Um But I have a question So is it the personal fat threshold and the kind of um inter individual variation as to where that threshold is that would explain why you can have two people who are both obese one develops um type two diabetes and gets in insulin resistance and type two diabetes and the other doesn't Yeah I think it's probably a key variable that explains the development of that insulin resistance Um Yeah and and probably the beta cell failure too So yeah I do think because you know it's basically if you have if your adipose tissue is functioning well even at a high level of fat mass it's still gonna be effective at containing that

excess energy So you're not gonna get energy poisoning and there are people who are like this typically what you'll see is they have a lot of subcutaneous fat fat under the skin and not a lot of visceral fat fat in the abdominal cavi cavity under your abs And the the former category the people who have a lot of subcutaneous fat some of those people are actually quite insulin sensitive So they just have a really high personal fat threshold they can keep gaining gaining gaining gain gaining and it just never Well I don't wanna say never but they just have a much higher tolerance for that before they hit metabolic consequences And on the other side of things you have people who have lipodystrophy which is a condition where you actually can't put fat on your fat cells are just genetically dysfunctional and those people get insulin resistance at a very lean level of body fatness So they could be have extreme lean leanness and yet have a lot of insulin resistance and diabetes And there it's a little bit more complex because it also involves leptin levels But I think that is an example of people who have as low of a personal fat threshold as you can get and they are extremely susceptible to insulin resistance and type two diabetes And then in the middle you see that common genetic variation in the human population impacts uh the likelihood of getting insulin resistant So basically genetic variation related to adipose tissue storage capacity how good is your your fat tissue at expanding when it needs to expand and continuing to hold on that fat Those genes are related strongly That's actually the main genetic signal that relates to insulin Um insulin resistance in the general population Does this uh sort of tie into the idea of um being sort of uh metabolically healthy obesity Is that something that that you feel exists that you could be obese and be metabolically healthy I asked this question to a previous um guest of mine Professor Susan Davis and she she seemed to think that it doesn't really exist but I understand that there are quite a few different views out there I mean now that you say that now I'm now I'm questioning what I'm gonna say because I I would be curious to know what she would say Um But I you know my opinion is yes there are metabolically healthy people with obesity Um There are papers on this where they you know screen people with obesity and identify a subset of them maybe five maybe 10% where you can do rigorous metabolic testing on them Like what's called a hyper insulin mic U glycemic clamp which is the gold standard measure of insulin sensitivity And you can demonstrate that they're just as insulin sensitive as a lean person And yet you look at photos of them and they're very obese I would say that Yeah I think it can exist I don't think it's it's certainly not typical And the other thing is 11 caveat is that you can

be metabolically healthy today and not be metabolically healthy in five years from now So you know I think obesity is something that predisposes people to be metabolically unhealthy in the future even if they aren't right now So I'd be interested in hearing what your other guest said Um but my opinion is yes there are people at least some people who are metabolically healthy and it you know probably a lot of it is genetics probably some of it is physical activity and other lifestyle related factors Yeah I think in speaking to her about this both on and off air I think she was some overlap in the way that you're thinking about that And she's mentioned you know she feels there's a sort of transient nature I guess and it can be hard when you look at something at a single point in in time Um going back to this idea of where you're sort of storing fat mattering And you you spoke about there's this different threshold and really the problems arise When you get excess energy in the blood you get excess energy being deposited into organs like the pancreas and the liver and muscle tissue And then there's downstream metabolic cardio metabolic consequences of this If someone's kind of thinking wow I wonder you know where my personal fat threshold is is is waist circumference a kind of good way of of gauging um where you're storing body fat Is that why waist circumference is used within the kind of metabolic syndrome cluster instead of BM I yeah that's a good question So um I don't have a quantitative answer for you and probably Roy Taylor is a better person to ask this question But yeah I mean it is part of the metabolic syndrome cluster and it does correlate with insulin resistance So I would say you know having high abdominal adiposity which is reflected in waist circumference is yeah that should correlate with um being above or near your personal fat threshold You know I wanted to mention one other thing I'm sorry to kind of barge in here But there's one other thing that I think the audience really should understand and that is that there you know the evidence that energy overload and excess body fat excess energy intake are the are the main drivers of type two diabetes is incredibly strong I just want to emphasize just how strong it is We have massive randomized controlled trials multi-year trials with actual type two diabetes as the outcome not surrogate measures actual type two diabetes diagnoses such as the diabetes prevention program trial that showed a 58% reduction in transition from prediabetes to diabetes and uh through a diet and exercise weight loss approach And it was a you know pretty like old school calorie restriction low fat diet It wasn't that modern in terms of the intervention that they it was in it was modern in terms of the intensity of it and the uh the amount of

interaction that there was with with the the researchers But um not the diet itself was pretty old school And you know there are other trials multiple other large multi-year trials like this that have replicated that finding There's also you know Roy Roy Taylor's work has shown that you can take people who already have type two diabetes and have had it sometimes for years and you can reverse that diabetes if you can get them to lose enough weight And so he puts them on these really low calorie temporary low calorie diets for I think like a three month period and then once they've lost weight they try to keep them on a maintenance diet Um and then they can show that even after they're off this super low calorie diet at the 12 month mark Uh a large proportion of these people like over half I think if I'm recalling correctly in the direct trial uh actually no longer met diagnostic criteria for type two diabetes So the evidence for this is incredibly strong I mean in terms of diet and lifestyle causation prevention reversal of uh noncommunicable disease I'm I'm not sure that there's any other disease that we have stronger evidence for than type two diabetes What are the the kind of long term success rates I guess um when I say long term and we may not even have that data but I'm thinking out you know 45 10 years So following kind of extreme interventions like that that seem to have very high success rates How able are people to keep that weight off and um and stay in a sort of state of remission Yeah it declined sharply and I don't know if you saw it but just recently there was a I think it was a five year follow up from the direct trial And caveat here is I haven't read the paper yet I don't know what kind of maintenance intervention if any they had after the initial 12 month period So I don't know whether people continued you know intensive weight maintenance efforts or whether they just kind of went back to their normal lives However I think if I'm recalling correctly the top line figure was that about a quarter of the people who initially went into remission at 12 months uh were still in remission And so you know that's a pretty sharp decline over time in in the number of people who stayed in remission And what you see is that most of them regained a lot of the weight And so this is typical you know this could be an entry point into talking about the difficulty of losing weight and and keeping it off because you know the direct trial did a pretty good job actually of causing people to lose weight and maintain that loss Uh I don't know maybe people were more motivated because they were seeing these incredible results But um you know in typical weight loss trials people will lose if you if you follow up at what you'll see is a weight loss curve So max weight loss is usually around six months and then they start typically to

regain on average around that point And by a year if you weigh those people and then this you know applies to almost any weight loss diet I shouldn't say almost any applies to the more effective weight loss diets that have been repeatedly studied I should say what you find is that at 12 months usually people have regained 50 70% of the weight that they had initially lost and then you follow them out for five or 10 years A few studies have done that including the diabetes prevention program trial you're gonna see a gradual convergence between the weight of the intervention groups and the weight of the control groups that did not to a significant weight loss intervention So how do you kind of explain that there's a bunch of questions I have that are coming to mind here and maybe I'll make a statement and then we can work out which direction to to go from here But um I guess my my first kind of thought around what you just said there about the the weight loss at six months And then what happens after that is that the the body is kind of you know fighting its way back to get back to where it was pre intervention And I think that's interesting to explore um if there's any sort of explanation for for why that may occur Um But I think people may also just be interesting and this might seem like a silly obvious question but when the body has excess energy available so we have become overweight or obese And I think I'm I'm sure you'll explain this from an evolutionary point of view But you used the word design before And if I was designing this system today in the food environment and the environment we're in I would probably think about putting a negative feedback loop in there So that as you're laying down excess fat in particular if you're starting to to detect excess energy in the blood and going into to organs you're saying OK let's let's drive hunger down We don't need to to seek out energy at this point in time Um So perhaps you can kind of comment I guess on the on the way that the that system is designed what is the system that we have sort of inherited here the brain and in particular a part of the brain called the hypothalamus contains a regulatory system for body fatness The first evidence of this was published in 18 40 there was a woman named Eliza Moser who uh developed rapid onset obesity And uh a German physician named Bernard Moore did an autopsy on her brain and found that she had a tumor in her hypothalamus And today we call that hypothalamic obesity And it's it's pretty well known uh clinical entity but that is the part of the brain that regulates body fatness And when it gets scrambled you the result is extreme obesity And uh so yeah so we have this regulatory system and it's really complicated but I'll give you I'll give you a uh a kind of like broad outline of it It is a negative feedback system So

it it uh so-called homeostatic or negative feedback system Uh The analogy I like to use is the home thermostat So your thermostat at home has a thermometer in it and that measures the temperature in your home And then it compares it to the value that you've set in the thermostat the set point And let's say it starts getting colder in your house Let's say you have um your thermostat is set to I'm gonna I'm gonna do this in Celsius 24 °C And uh it goes down to 23 Well your thermostat detects that and it engages a response to bring that temperature back up and the response is turning on the heater and then as soon as it gets back up to 24 it it shuts off So that's a negative feedback or homeostatic system And you know similarly it could do protect against increases using air conditioning And we have a system like this in our body that regulates body temperature to you know really precisely too And it engages physiological and behavioral responses that oppose changes in body temperature And so the physiology of it would be like vasoconstriction on your skin and sending you know allowing your limbs to get cold to preserve warmth in your core brown fat activation The behavioral side would be putting on a sweater going inside et cetera And we have a lot of systems like this in our body We have a lot of homeostatic systems that try to regulate around a specific a specific level of a variable to maintain that internal stability our body needs And you know blood pressure ion levels uh breathing rate which regulates carbon dioxide and oxygen levels And one of the things the brain regulates is body fatness And it shouldn't be surprising The amount of energy that your body contains is super super important for your survival and reproduction right So the body cares a lot about this The brain cares a lot about this And so we have this negative feedback system and there are a lot of different signals that converge on it But one of the most important ones is leptin and this is a hormone that's secreted by your fat tissue in proportion to its size So the more fat you have the more leptin you secrete and that is the signal that your brain is measuring to measure how much fat you have on your body So in the same way that your thermostat measures temperature with the thermometer your brain is using leptin to measure your body fat level And once that body fat starts to drop if you're going on a diet for example that starts setting off alarm bells you activate this homeostatic response which like the body temperature response is a suite of physiological and behavioral responses And so and basically it's trying to get more energy in and allow less energy to be burned So you get hungrier you get more interested in food Your attention is biased toward higher calorie items You have a reduction in metabolic rate If you lose enough weight it's

not just that your body is smaller per unit mass you're actually burning less per unit lean mass Your body is just kind of turning down metabolic rate But the main thing the main lever is the food intake the energy intake that is the main lever that the brain is using to to regulate body fatness Yeah So we have the system and you know it evolved a long time ago probably you know hundreds of millions of years ago probably more than 100 million years ago The system was probably mostly in place It's kind of the one of the tiers of the body's energy regulation system And it's very important for your body to have enough energy so that you can survive so that you can reproduce But you know in an ancestral environment having too much fat on your body is not really something that happens very often I mean if you think about the ancestral context people were basically their full time job was getting food If you have to do all that work to get your food every day you know if you're well enough fed why would you want to go out and do all that extra work to work Five extra hours to get more food even if it was available it just doesn't make sense from a cost benefit perspective You know and if you look at hunter gatherers obesity is like as far as I can tell basically nonexistent there is no evolutionary incentive to evolve a really strong protective mechanism against fat gain And so it really looks like we at least most people there's an asymmetry where the system works really well at defending against fat loss not as well against fat gain That said it does defend against fat gain to some degree and in some people more than others So you know you probably heard of you probably know about so-called hard gainers people who just can't gain muscle or fat no matter what they do Um And there are researchers who are studying people like that trying to understand the genetics of it and the genetics of it are related to the genetics of obesity So it it looks like you know in some of those common genetic variants that make people fat If you get the opposite versions then it makes you lean and it makes you more resistant to gaining fat So there's there's certainly some genetics involved and some people are highly resistant to gaining fat um trying to understand their secrets so we can you know figure out how uh everyone can benefit from that someone who is overweight or obese Let's let's focus on obesity here for for a moment Um And based on what you just said then they're going to so they have excess fat their leptin levels would go up from what I heard Um My initial thought or response to that would be that their desire for food should be less than someone who has less body fat but that's not always the case from what I understand So so what's happening to I guess the in the in the brain with regards to receiving this information via leptin and down

regulating hunger So I think we need to really carefully parse this word desire to answer this question Um But before I get to that there's actually a really important piece that I left out to my previous answer that I just wanna make sure to to add people with obesity What we see is that their set point appears to be increased So their set point is at the obese level And so that is seems to be a key reason why it's hard to lose weight is when you start to lose weight you start setting off those alarm bells associated with the starvation response And then you're having to fight this these nonconscious brain regions that are activating this behavioral and physiological response trying to get you to regain that fat So it's this it's a very similar response to weight loss that we see in people with obesity and in lean people So that's kind of the cruelty of this thing is that once you get up there it's really hard to get back down It kind of locks you in that's what appears to be the case And I don't know why that is I don't know what the evolutionary you know reasoning for that is but just appears to be the case So coming back to this issue of eating desire in people with obesity versus lean people I think you know that word desire kind of covers a lot of ground And so I think it would be helpful to dissect what um that could mean So if we look at it from an energy balance perspective people with obesity generally eat more calories than people who are lean So on average if you're matching sex and age and roughly physical activity level people with obesity will typically eat somewhere from 20 to 35% more calories per day than a lean person And so you know there's some kind they are eating more they are engaging in more eating behavior So there is some kind of motivation on some level that is causing that to happen right Um And so whether that corresponds to the word desire I think is another question And I think that there are multiple reasons why you could imagine a person's calorie intake could be higher And I think probably it's a combination of of things with some people falling more into one category some in another category So the two big buckets that I like to think of that drive food intake One is homeostatic eating So this is eating because your brain perceives that you need energy So your brain it's it's like hunger would be uh a way to put it So your brain thinks that you have an energy deficit and it is trying to correct that energy deficit So that's like you feel hungry you would eat just about anything that has some calories in it You're not feeling picky but you're just feeling hungry you want to eat some food And then on the other side we have non homeostatic eating and this is kind of a catch all term for all the other reasons that we might eat So there's reward driven eating where a food is really seductive and we're eating

it We might not be that hungry Maybe it's the end of a meal and the ice cream comes out and suddenly ok we're ready to eat some more calories It might be We're drinking a beer You don't drink a beer because you want because you're hungry you want the pleasure value of it It might be because we're you know it's noon and we always eat at noon whether we're hungry or not So there's a lot of different things that can fall into the non homeostatic eating category And so I think that different people have different contributions from each of those So some people are consuming excess calories because they just are hungrier They have a higher just hunger based desire to eat And we see in the genetics of it we see that common genetic variability some of it is related to the body fat regulation systems and the appetite regulation systems in the brain things like Melani cortin and leptin receptor Yeah especially the Melani Cortin pathway which is part of the leptin signaling pathway And so there are I believe people who are just hungrier and that causes them to eat more And probably a lot of those people were born hungry you know like they just genetically have a higher desire to eat food in the homeostatic sense And then on the other side you have a lot of variability in um reward driven eating So uh Leonard Epstein has done a bunch of work on this where they um they use this concept called the relative reinforcing value of food So essentially they have people play these little video games It's like a gambling game on a computer screen and they're uh they have to do a certain amount of work like do a certain number of clicks to get a reward And that'll be like a little candy bar or some soda stuff like that And critically they feed them a snack before this experiment So the people are not hungry they're not like feeling like they need to eat something This is really desire for a highly uh seductive food And then what will happen is they'll progressively increase the work requirements and they'll keep increasing and increasing and increasing You have to spend more time and more clicking to get the reward until finally you hit the break point where the person says nads just isn't worth worth it anymore And they do that for food items and for non-food items And they say how hard is somebody willing to work for these seductive foods relative to a nonfood item like a magazine or something And what you see is that that relative reinforcing value of food that ratio I just described varies tremendously between people And furthermore you see that people with the higher relative reinforcing value of food tend to gain more weight over time if you measure their weight now and their relative reinforcing value now and you look at them A few years later people with the high value will gain more weight And

there's really a a major analogy with uh drug addiction here too Drug addiction research What you see is that the people who are highly susceptible to addiction are the people who have both high reward drive for that drug and low inhibitory control So they have a really strong craving for the drug and they have a weak ability to control that impulse once it arises those are the people who are really susceptible to drug addiction And you see the same thing with food Leonard Epstein calls this reinforcement pathology or lead foot worn breaks They have some people just have a really strong drive for this highly palatable seductive food and they have a weak ability to to inhibit that impulse once it arises And you know it's like a lot of this is genetics Like you can't really blame people You can't really say it's personal responsibility Like a lot of this is just luck of the draw What cards were you dealt when you were born And so yeah So I think there are a lot of um I haven't described a lot I've described two different ways that one could end up over consuming and and gaining fat Um but I think there are probably other things that you could imagine Um and but those are two that I think are particularly evidence based Yeah I'm glad that you have kind of emphasized the genetic component and I guess that that that sort of leaves me thinking there's that saying that genetics load the gun and lifestyle pulls the trigger And it sounds like with regards to obesity some of us have a more loaded gun than than others which is affecting whether it's that homeostatic um sort of eating or some of these more reward based kind of desires with the seductive foods So would you posit that if uh there was a way of going back 10,000 years in and getting one of our ancestors and bringing them into today's environment that many of them would have the same struggles I think if you took our ancestors let's say yeah you could take them at birth It would probably be even worse if you took them at you know adolescence or adulthood because at that point they would already have all of their behaviors and norms stamped in that are appropriate for their environment And what you see in hunter gatherers is they absolutely stuff their faces when they have the opportunity to And there's no it's really interesting because now we have these concepts of this concept of gluttony and that gluttony is a bad thing that we shouldn't overeat and we feel guilty about it And we think about it If you if you look at hunter gatherers at least according to the anthropologist I've spoken to they don't have any concept like that stuffing your face as much as possible is good in their context That's what you wanna do If you have the opportunity to get calorie dense to easily get your hands on calorie dense easily digestible food you should eat as

much of it as possible because that means you won't have to go out as much tomorrow and maybe you you know you're not gonna come across something like this every day So basically you know so for example uh some of these anthropologists described to me hunter gatherers eating £5 of fatty meat in a sitting or I think it was 30 oranges that are wild oranges that are basically similar in size and sweetness to grocery store oranges in the Amazon and just drinking a liter of honey So I mean when they had the opportunity they would absolutely stuff their faces and it was good for them that helped them to survive and reproduce And so you know imagine a person with those kinds of social norms now gets put into the into the modern industrial environment and doesn't have any of the culture any out of the inhibition around you know viewing gluttony is bad And then he walks into the grocery store I mean it would be a total disaster But I think you know the genes as well which is I think is what your question really was about Our genes couldn't have changed rapidly enough to explain the the rise in obesity that we've seen So even though genetics are very important to create susceptibility to obesity they're not the thing that changed over time that created societies with high rates of obesity Speaking of hunger here I did want to ask you about the carbohydrate insulin and energy balance models to opposing models that different researchers have put forward to explain what they think is leading to overconsumption of calories and obesity How would you help someone understand the differences between these two models The carbohydrate insulin model there are about as many versions of it as there are stars in the sky And so um I'm gonna pick one and and go with it and I'm gonna pick the one that is most prominent which is uh most prominent in the academic community I would say which is the one that uh has been developed by David Ludwig and his colleagues That model um suggests that high levels of insulin impacts the body in various ways but particularly fat tissue causes fat tissue to take up energy from the bloodstream And that fattening process of insulin hitting your fat tissue and your other tissues kind of sucks energy out of your bloodstream making you feel starved So that makes you eat more And so basically in this model the fattening process is upstream of the overconsumption So the overconsumption is not causing fat gain it's actually a result of the fattening process So it kind of turns the causality around And then the energy balance model is more what you probably are familiar with which is that the causality is in the you know more commonly assumed direction which is you eat too much and then you gain fat so that extra energy gets stored extra energy that you consume gets

stored in your fat tissue And the energy balance model as it's been formulated you know there are also many you know variations that you could call the energy balance model But the the version that's been formulated and that has kind of been portrayed as going head to head with the carbohydrate insulin model is is most associated with Kevin Hall um NIH researcher and and also with some um contributions from um uh Speakman John Speakman and myself as well And the energy balance model as formulated by Kevin really revolves around the brain So it is saying that our intake and our body fat regulation the seat of that calorie intake and our body fat and regulation the seat of that is the brain the brain is deciding those things and the fat is more just like a passive organ that if there's excess energy around it will take it up If there's not enough energy it will release it as opposed to it playing kind of the central causal role in the process in uh the carbohydrate insulin model Is there a a good I guess evolutionary explanation for the carbohydrate insulin model that you've seen put forward No I don't think it makes any sense from an evolutionary perspective And let me just tell you you know just just so everybody knows where I'm coming from Um I have been a an advocate of the energy balance model So that's kind of the the side that I'm on Um I you know I don't view science as a team sport but I'll just say that that's what I've argued for Yeah No it doesn't make any sense Why would you want an organism's physiology and its energy balance to be controlled by this you know random environmental variable of how much carbohydrate there is in the environment that doesn't make any sense you know especially for a tropical species where it's not really seasonal it's not like you're trying to store fat at a certain time of year that corresponds to you know maximum carbohydrate availability that could be argued for temperate climates But we're a tropical species at least originally we were a tropical And so if you're an engineer trying to design an organism to survive on the African Savannah you're not gonna allow such an important variable as body fat to be you know you're not gonna allow random environmental variables to to take the reins on your physiology like that doesn't make any sense So if we look at obesity through the lens of the energy balance model and then start to think about the I guess energy balance equation of the energy that we're consuming what we're expending and consider current lifestyles and and the different sort of drivers or or different things that could affect that equation How how well do we understand this problem Uh What I'm what I'm getting at here is do we have enough information right now as it stands today that if we were able to actually implement it and and perhaps

change our society and ways of living we could completely squeeze obesity out of out of society or is this still very incomplete And there's a lot more to the puzzle to kind of piece together Oh I think we absolutely could But the means to do that are would just be completely unacceptable Um You know like if you put a gun to my head and told me to reduce my calorie intake by 30% I could do it And I you know I would do it and I would lose weight but that's not an acceptable means to induce someone to lose weight right Um So you know is it like theoretically possible Yes Is it practically possible That's a more difficult question Um And I would say you know when we talk about potential solutions to obesity and excess body fatness I really like to divide it into what we can do as individuals and what we can do as a society And I'm a lot more optimistic about what we can do as individuals for example you know the subset of people who are engaged and motivated listening to this podcast I'm a lot more optimistic about you know those people being able to modify their body fat trajectory than entire societies You know if you look at the United States we're probably eating like 250 plus more calories per day on average than we did in the seventies You know that probably even saying it that way doesn't even reveal the full scope of it because some people are lean now and they would have been lean in the seventies Their calorie intake is the same probably as it would have been in the seventies So it's really the people who are fatter than they would have been where all of that increase has fallen or most of it I should say And so probably you know the people who have obesity probably eating you know four or 500 calories more than they would have in the seventies And so that's a huge amount of behavioral change that you have to roll back on a societal level That's immense And so even if it was 250 calories that's like 10% of people's calorie intake and to have that kind of impact on a societal level I do think it's theoretically possible So you know we could make drastic changes to the food environment and you know strictly regulate the types of foods that are available in grocery stores change food advertising uh you know eliminate food in places where it doesn't need to be like outside of grocery stores and certain kinds of restaurants Like there are things we could do I just don't think that any of it would be publicly or politically acceptable because it's just too intense People don't want the government controlling their food to that degree that this to the degree that I think it would require And in this context you know I want to mention this study that was just published on obesity control intervention in Chile Chile has one of the most intensive public health anti obesity efforts in the world Possibly the most intensive it

involves controlling food advertising to Children It involves these pretty intense front of package warning labels related to calories and salt saturated fat and sugar And it involves regulating school the food that's available in schools All that you know very logical makes makes good sense to me But if you look three years into this intervention the data on weight change are not very impressive Young Children are continuing to gain weight become more obese and then there might be some signal in adolescence maybe they have the prevalence may have decreased a little bit of obesity but overall not a very encouraging picture And that's basically the best that has been done on a societal level so far globally So I think societally it's a pretty grim picture You said theoretically it could be done And you and you also spoke to the excess calories that people are now consuming So perhaps we drill drill in on that I'm interested in in terms of if you could change the environment what would you target So if you jump on Twitter you might see one person pointing the finger at seed oils and they'll show a graph and seed oils have gone up and and as as obesity right So there's AAA correlation there But then the next person might show sugar uh sugar and then there'll be a conversation around uh ultra processed foods and and hyper palatability What have you kind of settled on as to what are the primary drivers or changes in the the food environment that would be leading to the excess calorie consumption Yeah this can get really complicated and I think that it um can also get really controversial And so I like to take it back to the basics to the real basics and ask the question what can you feed to animals like rodents when you have complete control over their diet and their environment What's the most fattening thing that you can give to a rodent And the answer is human ultra processed calorie dense food So if you take just a group of normal rats and you give them a variety and the variety itself is important too you give them a variety of calorie dense highly palatable foods Anthony Scni first did this in the 19 seventies And on top of that you give them healthy pelleted rat chow the kind of thing that's actually good for them They will ignore the healthy pellets and they will stuff their faces on the calorie dense highly palatable ultra processed human food It you know it doesn't even have to be ultra processed It's more like calorie dense highly palatable Some of it's ultra processed some of it would not fall into the ultra processed category nova category But you know things like cookies salami chocolate uh French fries uh sweet breakfast cereal sweet condensed milk They'll completely ignore the healthy food that would keep them lean and healthy if that's all they ate and they will stuff their faces on this delicious

human food And it's not just rodents Like you know you look at animals and tourist spots like raccoons and monkeys They often will get tremendously fat eating human foods You look at bears who raid human garbage cans can can get very fat So it's not just rats And as it turns out you know there's pretty good and accumulating evidence that human you know delicious calorie dense human foods has the same effect on humans You have this randomized trial really rigorous so-called uh metabolic ward or domiciled study that Kevin Hall did where he fed people uh ultra processed diet or he and his team fed people an ultra processed diet or a minimally processed diet People ate 500 calories a day more on the ultra processed diet than the minimally processed diet And the diet periods were only two weeks and pe and that was enough to see a divergence in weight The effect on appetite is huge And another point I wanna make here that's really critical You can't replicate this effect by only modifying one thing So you cannot make rats as fat as that by just adding fat to their diet you cannot make them as fat as that by just adding sugar In fact sugar isn't even that fattening especially solid sugars in rodents there's nothing you can do nothing to a rodent pellet that will make it as fattening as a constant buffet of highly palatable calorie dense human foods The same is true in humans sugar You can modify sugar doesn't do it you can modify fat doesn't do it You need that whole collection of properties that are present in those foods So what's happening Is there a potential explanation for what's happening in the hypothalamus and in the brain that is distinct between say you know I think most people could appreciate it You probably could but it would be difficult to overeat A lot of calories of butter You probably just start feeling sick right And similar story if you just ate straight sugar But when um are the reward centers I guess for or or where when sensing fat and sensing carbohydrates in the brain are they separate Does something um happen when we combine these that then leads to what you're describing as delicious or hyper palatable The brain is hard wired to respond to certain um stimuli certain goals that would have been valuable to our ancestors And we describe those as the technical term is unconditioned stimuli Brain is hardwired to want those to respond to those And there are certain food properties that are unconditioned stimuli So fat carbohydrate sugar and starch salt protein and glutamate which is that meaty umami flavor in soy sauce and cooked meat and other things and those things the brain is wired to have a motivational response to those and that involves dopamine spiking in the brain So dopamine generates that motivational response and reinforces behaviors related to acquiring foods that contain those nu- those

nutrients So you get that and with all foods this is not I'm not saying this is a bad thing This is a very natural process It can just be overstimulated And so uh but what seems to happen is that you get uh the highest the greatest response when you combine those dopamine stimulating nutrients So particularly combinations of carbohydrate and fat and that can be either in the savory realm like French fries or it can be in the sweet realm So the the savory realm that would be fat and carbohydrate and salt And then the sweet realm would be the fat and sugar together and sometimes salt Um So like cookies or cake or ice cream and those what you see you know we don't have like nobody's stuck a probe in the human brain and measured dopamine um to see how high it goes But what you do see is that when you do surveys of the types of foods that people typically have the strongest cravings for and again we're not talking about hunger we're talking about food specific motivation cravings So that's more of that you know seductiveness the dopamine aic response um and also addiction like behaviors towards specific foods If we look at surveys that ask people which foods do you crave the most Which foods do you lose control around the most What you see is that the ones that rise to the top as most common are these combinations of fat and sugar things like chocolate That's the number one most craved food Chocolate also contains a habit forming drug that activates the same dopamine signaling pathway and um you know things like cookies and and pizza and um and many other foods But you know a lot of the foods that are common in our diet are you know we don't think of them as ultra processed foods or you know anything unusual but bread and butter and jam you know that has that's that's a pretty palatable combination and that's got the sugar that's got the fat it's got the starch got a fair amount of salt Um So it doesn't have to be necessarily an ultra processed food But I think it's the type of thing that you tend to find in ultra processed food because you know they're making it to be as rewarding as possible So they're gonna max out how much dopamine they're gonna try their best to max out the amount of dopamine that is secreted when you eat that food because that's the thing that gets you to come back and purchase it and and consume it again is there overlap here It sounds like there could be a couple of things going on Um I'm sure you're familiar with the sort of protein leverage hypothesis Uh I think David Robben Heimer and Steven Jay Simpson have put that forward Um And in fact I know they have and my understanding of that is that we you you just described it before but we have these kind of different appetites for different nutrients that are required and that their hypothesis is that the strongest

appetite is for protein and that in a a protein dilute environment So where you're adding a lot of these foods you're talking about that are rich in fats and carbohydrates but perhaps lower in protein that will will continue to have an urge to consume those foods even above our energy requirement in order to satisfy the protein requirement Um What's your kind of I guess view on on that hypothesis and how that may play into this Yeah they've got a lot of cool data on this and done some some really interesting experiments in all kinds of different species all kinds of bugs I think that you know it's clear that protein is very important It's the substrate for the physical structure of our bodies and you know the physiology of our bodies So obviously it's uh very important nutrient for you know physiology and for natural selection to act upon I think it's also really clear it seems quite clear to me that higher protein diets do reduce calorie intake So I think that so what I mean by that is if the proportion of protein in the diet increases total calorie intake will typically go down And I think that that is consistent with their protein leverage hypothesis Um where I'm not as convinced is on the lower end So I haven't seen really good evidence that reducing protein intake in the long run causes people to eat more and gain fat And in fact you know you look at demographics in the population who might typically have a lower p uh protein intake like people eating a vegan diet and they're usually leaner not heavier And so I don't know it doesn't mean it's wrong necessarily But I think I guess I would place less emphasis on that than they do um on in terms of how much of the variation in calorie intake and body fatness It explains I would place less emphasis on the kind of like not getting enough protein side of things The importance of that The other thing that is kind of perplexing is you know if you look at their experiments where they show this protein leverage effect they are creating a situation where animals cannot choose how much protein they're eating So to to kind of create to to observe these protein leverage effects They they'll offer an animal a food with a fixed amount of protein So they can't pick and choose they can't just add extra protein by eating a different food Uh you know depending on the experimental setup But you know that's the scenario where animals will overeat to get protein is when they have a food that has a fixed amount of protein that's all they have available And so they have to overeat to get that extremely valuable protein But you know living in the modern food environment there are tons of high protein foods available So what's puzzling to me is why people what I mean why would they increase their calorie intake to get enough protein when they could just you know eat more beans

or or eggs or whatever Um So it's kind of puzzling to me like why if this is how it works why the regulatory system would not take this extremely obvious you know way out of the problem quick One a lot of people ask me for tips on buying supplements and getting blood tests I've created zero cost guides for both of these which you can download from my website the proof dot com coming back to to fats and carbohydrates and hyper pail So if we think I guess uh ancestrally um I wonder if you've ever thought about do you think many meals had both fat and carbohydrates or do you think that our ancestors were sitting down and having a meal that was mostly fat And then later on they would sit down and or at another time and another season mostly carbohydrates And so and so they were separated So if someone's listening to this and just thinking about their meal construction how important do you think it is thinking about that combination Like if we get a lot of sweet potato and then put a a nice high fat sort of dressing over the top of that is that going to lead to excessive calorie consumption So I think we can decompose this into two separate questions Which one is e eating the effect of eating a food item that has carbohydrate and fat And the other one would be eating separate food items at the same meal that have carbohydrate and fat And I think um so you know there are probably other people who could answer this question better than me People with more you know experience living well I have no experience living with hunter gatherers I just know from reading books and speaking with anthropologists So you know I'm not like I don't have the deepest knowledge about you know the intricacies of hunter gatherer meals But from what I've read I think they often do have carbohydrate and fat at the same meal but they're not as often consuming them in in the same food item So there aren't a lot of foods in nature that already have fat and carbohydrate It's insignificant quantities Really The only one I can think of off the top of my head is nuts Nuts can have fat and carbohydrate But usually they're pretty heavily biased toward fat But yeah and you know you look at the hods that they ate honey but they didn't usually mix it with anything They usually just kind of ate it on the spot plain and they would bring it back and share it and eat it plain So you know I think when you're a hunter gatherer and you don't have a kitchen with a stove and countertops and uh you know all kinds of spices and oils and sugars and things you just keep it simple You just put food in your mouth and chew it And that is a much simpler experience than what we experienced You know most of these cultures don't even have salt So I think um having foods within a meal that combine carbohydrate and fat with in individual foods I think in

terms of the seductiveness of individual foods I think that is the main problem or that's a key problem I say problem depends on what your goals are Whether you're trying to you know lose or gain weight but in terms of overconsumption that's a key problem Having foods with different macro nutrients at a meal Probably that would I would think that your calorie intake would be higher if you had carbs and fat at a meal than if you just had carbs or just had fat Pretty sure it would be higher Yeah So I guess they're both impactful but it's harder for me to imagine someone like sustainably just eating fat or carbs at a meal It seems maybe harder to pull off and not as necessarily as ancestral consistent I guess the the Mediterranean diet I guess as defined in in the literature or whatever the kind of standard definition is it tends to be sort of moderate carb moderate fat would you say Yeah I think that's right Yeah And and that diet's not particularly associated with overweight or obesity I think it probably depends on what you compare it to I so I think that when you look at rodent studies and you look at human randomized controlled trials basically what you see is that the zone that is the most fattening is having abundant amounts of both fat and carbohydrate in the diet The zones that are the least fattening are on either extreme So either low carbohydrate higher fat or uh lower fat higher carbohydrate So the extremes you know whether we're talking about rodents or humans the extremes tend to promote leanness the middle tends to be more fattening That said you know macro nutrients are not the only determinant of food intake and body fat And so you know the Mediterranean diet tends to be a more unprocessed type of diet I think that's that's important too So you know I don't think the Mediterranean diet is a particularly fattening diet I think it probably is slimming relative to I think it certainly is slimming relative to you know let's say the average American diet But I also don't think that it's like really a weight loss diet I don't think if you if your main goal is to lose weight that's not a a just a typical Mediterranean diet is not what I would suggest I think that is more optimized for kind of cardio metabolic health than it is for weight Specifically I've had uh Christopher Gardner on the show a few times and we've explored the landscape of low fat versus low carb and he's kind of conveyed um the results from diet fits and and I guess the literature broadly where um on average there doesn't seem to be a sort of significant difference in terms of weight loss outcomes for low fat versus uh low carb The interesting um thing from diet fits and it's a question I haven't asked anyone So I'd be I'd be keen to hear your thoughts on it was that you know that trial was set up to test low carb versus low fat with a relatively

high diet quality There was emphasis on making sure these were um mostly sort of minimally processed or or whole foods and the subjects were working with dieticians to help them with that On average between the two groups there was no significant difference in weight loss but within in each group some people did well or seemed to do well with their weight loss and some not so well And I'm sort of left trying to work out how to interpret those results um short of having another study So is it that certain people are just um genetically or environmentally behaviorally um sort of set up to do better on a low fat or a low carb diet or do you think the people that did well in that study even if you put them into the other group they would have done well and and vice versa The answer is we really don't know Um you know to have a good answer to that we would have to cross those people over and you know have them do the other diet Um I would pretty strongly suspect that it's both that some people just have an easier time losing weight on any diet and then some people do much better on one diet versus the other and and I don't have any hard evidence um to uh to to support that with that's my intuition But it's based on the fact that those are both very plausible You know some people have tried a million diets and they can't lose weight and other people seem to lose weight more easily And uh and then we notice just anecdotally that some people will say oh you know I tried a low fat diet and it didn't do anything for me or I gained weight and then I tried a low carb diet and it was awesome or the reverse I actually you know I think what I just said is the one that I think people will hear most commonly But I get emails like semi regularly from people who are like man I'm so glad Thank you for uh you know your work uh critiquing the carb insulin hypothesis It allowed me to like try a low fat diet to like kind of open my mind to the possibility that carbs aren't so bad And I I actually was gaining weight on a low carb diet I switched to a low fat diet and now I'm losing now I've lost that excess weight and I'm getting back down to where I wanna be So I'm not saying that's typical but I am saying that that does happen Yeah So I would I would guess and again no hard evidence but I would guess that both of the things that you said are operating there And just to be clear you're you're not saying that a low fat diet is superior to low carb or low carb diets can't work You're saying you think that when a low carb diet works it's explained by the energy balance model not the carbohydrate insulin model Yes And I well ok so let me put it this way I feel more confident that in the statement that the carb insulin model is not the primary explanation for the development of obesity That's the statement that I feel more confident about and and note that I said

primary there So I think it's still very much on the table that it could be to contribute to some degree Like if that's accounting for 10% of variances in body fatness between individuals then I think that could be consistent with the evidence that we have I just don't think it's accounting for you know 70% or 100% Like some of its advocates seem to believe now in terms of the weight loss on a low carb diet I'm I'm less confident there about the role of insulin but I will say that you know it can't be all about carbs because if it was you wouldn't see weight loss on the other side of the macro nutrient spectrum So you need to have a hypothesis that explains weight loss on low carb diets and weight loss on high carb diets That hypothesis is not the carb insulin model Now could it you know if you if you compare weight loss on low carbon low fat diets if you squint at the data hard enough you might decide that there is an advantage for low carb diets And I think that's actually a reasonable interpretation that there is a modest advantage in terms of weight loss for low carb diets versus low fat diets I think that could be a reasonable interpretation of the literature And in fact you see that in diet fits if you look at the earlier time points there was actually a significant difference favoring the low carb diet for some of the earlier like 36 month time points and that trend was still there at 12 months It just wasn't statistically significant anymore And so if you want to argue like the insulin stuff is kind of giving it a little bit of an edge I think that's plausible at this point Um I just don't think this kind of like simple model of it's all about carbs it's all about insulin That is the determinant of body fatness I think that is just grossly incompatible with the evidence we have But could it be playing some role in some context I don't think we've ruled that out So if someone is listening to this and let's say they've they've tried a a low fat diet it's been unsuccessful in terms of helping them lose weight and keep it off What is your what would your advice be for that person to would it be to consider a low carbohydrate diet or are there other things that you would want them to kind of turn their attention to Yeah So you know I I don't work with clients so I'm just kind of like going by what I see in the scientific literature But to me my first instinct is to just try a basic stuff like a minimally processed diet trying not to eat snacks only eating at me meal times Um You could try higher protein that's often helpful Um Oh yeah and control your food environment Limit those food cues that can trigger our dopamine response and trigger our eating drive And so just kind of the basics like that I mean that's basically how our ancestors stayed lean or that's a lot of it And so I think you know some people are gonna need something more

intensive than that but I tend to think that's a good place to start and then if you need to escalate you could escalate And so you said specifically someone who's tried a low fat diet it didn't work for them I absolutely think low carb diet is a totally valid option I think if you're gonna do it you probably wanna tend more toward the unsaturated fat and you know have more whole plant foods in your diet just for in terms of the the other health impacts of it blood lipids and stuff My intuition would be to say start with those basic things If you need to escalate to macro nutrient restriction that's absolutely a valid option Are there any you know specific things in the research that have been shown or specific foods or components of foods that you would say uh are particularly good at helping someone feel fuller on less calories you know strategies with regards to like the order of having your your foods or um the distribution whether you're having more of your food earlier in the morning or late at night right before bed those kind of things I'm gonna start with food properties because that's the one that I know most about So we have this great study that I I always come back to from um Jenny Brand Miller's group Susannah Holt is the first author and it's called the paper is titled the Satiety Index of Common Foods And the cool thing about this paper is it's very naturalistic They're looking at they looked at 38 commonly consumed foods types of foods that many of us will eat on most days things like oatmeal bread um beans meat eggs uh candy uh pastries cereal wide variety of different common foods And they gave people calorie matched portions of those foods if I recall correctly 240 calories then they followed them up every 15 minutes for two hours and just asked how full are you on this semi quantitative scale What they found was that the amount of satiety that people experienced was strongly correlated with very basic very simple food properties So things like the calorie density of a food how many calories per gram And that is of course strongly correlated with the volume of a food So foods that have more volume per calorie are gonna fill you up more per calorie they're taking up more space in your digestive tract foods that are higher in fiber have more satiety per calorie foods that are higher in protein more satiety and foods that are lower in palatability So that you know eating pleasure how delicious it is the more pleasurable they are the less fullness you get per calorie It's like your brain takes the brakes off those simple food properties explained most of the variation in how full people felt And after after eating those those foods and interestingly they had a follow up paper where they tested the correlation of other things like blood glucose and insulin levels So how much people's blood sugar spiked and how much

their insulin spikes So there's this you know this idea connected to the carb insulin hypothesis that spikes and you know falling blood sugar and insulin makes you hungry So what they found was there was no correlation at all between the blood glucose response and satiety And if I'm recalling correctly the insulin response was inversely correlated to So satiety So the more insulin a food caused to be secreted the more filling it was you know the the carb the carbs and the insulin were not at all That hypothesis was not at all supported by that data Really What was supported is that these very simple physical and chemical properties of the food are the the main drivers of satiety So yeah if you're trying to control your calorie intake without feeling hungry it makes a lot of sense to select foods that have higher satiety value per calorie So these tend to be lower calorie density minimally refined and processed foods um that are more consistent with what our distant ancestors might have eaten I think that part there about the blood glucose blood sugar and cravings that might be news to some people because that seems to be quite a trend on on social media Um at the moment with a lot of people wearing CG MS and trying to avoid a kind of quote unquote spike and then um post meal low Um which as you said there there's um you know been certain people sort of putting forward that that would increase craving So that's thanks for clarifying that um the other thing that just came up for me there where you were talking about um insulin going up um makes me think about uh semi glut and um G LP one agony So um perhaps you could kind of explain what these drugs are why they're um sort of I guess picking up becoming more popular with regard with regard to treatment of obesity and and just how they're kind of working Yeah Sure So first of all let me start by saying that I have no conflicts of interest with the pharmaceutical industry So this is purely my opinion based on the evidence and my opinion is that these drugs are awesome So uh they just are much more effective than anything that came before them Uh more effective and more safe G LP one is a gut hormone It is a hormone that's produced by the primarily the small intestine primarily the distal small intestine and it travels through the bloodstream does a few different things But one of the things it does is it increases insulin secretion to help cover the glucose that you ate in your meal And it also signals to the brain to increase satiety or fullness And that insulin it uh secret or the insulin increasing function which is by the way glucose dependent And what that means that is that G LP one only increases glucose secretion or excuse me only increases insulin secretion in the presence of elevated glucose So it only ramps up insulin secretion when you need it the

most around a meal So that's it's kind of a beautiful thing It's that's called uh an incretin hormone because of that And there's another one G IP So yeah it's secreted by the gut And that was originally what got researchers interested in it is like Daniel Drucker they found that when you put this on pancreatic beta cells insulin secreting cells it makes them secrete more insulin So they said hey you know this is pretty interesting maybe this could be a treatment for diabetes because you know that's that's like beautiful if you're trying to increase someone's insulin secretion especially around meals which is when they need it the most That's exactly the kind of thing you want right And so they they uh patented this um for diabetes treatment and eventually in in 2004 um exenatide I think it's called exenatide um was released as the first anti diabetic medication made from G LP one And at the time you know these the initial drugs were not did not cause that much weight loss Pretty modest But what um you know some of these companies especially no vortis some of these pharma companies got their hands on it particularly no vortis started experimenting with it and started seeing that while some variants of this hormone cause a ton of weight loss And you know initially in rodent studies of course and uh and this relates back to the fact that G LP one is a satiety hormone that signals to the brain that that you know there's food in your digestive tract so slow down on your eating and basically through trial and error they were able to refine these uh these molecules to create molecules that were much more effective at causing weight loss And so the first one of these that the the first one of the latest generation of these G LP one receptor agonists which is what these drugs are called to be approved for treating obesity was some male And just to give you a sense of the magnitude of how what effect size this has and how important it is Typical prior to some male tide typical weight loss from intensive like best in class diet and lifestyle programs at one year was gonna be in the range of like 5 to 7% weight loss Medications were kind of like the better ones were kind of in that in that range So Magli Tide is causing in randomized controlled trials 15 to 18% loss of body weight so much larger effect size And if we use the benchmark of bariatric surgery which is the most effective weight loss method that we have that causes kind of like 25 to 30 something percent weight loss It's like getting up there to almost bariatric surgery levels weight loss surgery and then topi which is approved for diabetes not yet for obesity but probably will be that causes even more weight loss So that causes something like 20% loss of body weight So I mean these drugs are just a massive massive breakthrough and not only that

but they seem very safe Most in most people the long term side effects are minor There's some gastrointestinal stuff especially at first It can be actually it can be rough right at first Um but the long term side effects seem to be really minor and the biggest side effects are actually positive Like people get better blood glucose control they get less cardiovascular events Um people with type two diabetes have reduced all cause mortality And so these drugs are amazing and drug development is going at light speed right now in this space and it's just really cool to see And furthermore you know back to the kind of original topic that got us on this If you give someone some aletti or to initially their insulin levels go up and yet they're losing weight so they're losing weight their insulin levels are going up So this is kind of the opposite So of what the carb insulin model would predict So you have this compound that's these they act in the brain um to reduce food intake And that shows that this brain mechanism is dominating whatever insulin stuff is happening Um and the insulin comes back down over time as they lose weight So it's not like it's elevated forever But certainly initially there's an elevation of insulin while weight is being lost If I'm sort of understanding this correctly the jop one agonist is acting on the brain to essentially help normalize a deregulated appetite Would you say that's is that fair I think it is reducing eating drive And yeah I think you could maybe argue that it's normalizing But I think I'm kind of reluctant to use the word normalize because these drugs you know some some like pharma reps will say like you know you have low levels of this hormone and this is just replacing your hormone That's baloney these drugs are ramping up that signal way beyond physiological levels It's not just a replacement these drugs are going into the brain and activating G LP one receptors way beyond what a normal person would experience And so normalize maybe in a sense because you have someone with obesity who has you know deregulated eating habits maybe excessive eating drive and then bring that back down So it certainly can feel like a normalization But I think in terms of the physiology of it it's not really restoring you to normal physiology It's having a pharmacological effect that is outside of normal physiology And do you see that as AAA drug that someone would continue to take for for the rest of their life or would it kind of depend on what's affecting their hunger drive to eat And so some people who where it's driven you know predominantly or entirely by genetics they're going to have more difficulty coming off it Whereas others if they could work on sort of behavioral aspects at the same time they might have more success coming off We don't have hard evidence on this So you know to

some extent we'll have to wait and see But the expectation is that yes you will have to continue taking this drug You know that's certainly a limitation We would rather have a drug that you take one pill and the obesity goes away forever Um you know like you might take an antibiotic for you know a bacterial infection but that's not how these drugs work They're more akin to blood pressure drugs where you your blood pressure stays lower for as long as you take the drug or cholesterol lowering drugs you stop one of those drugs and your cholesterol goes back up Um And that's what we're seeing in the trials is that when people stop these drugs their weight goes back up Now whether you would see some lingering benefit if someone was on this drug for five years I don't know we don't have data on that You know would they 100% return to their original weight or would they stay a bit below There's some hints that maybe that people might be staying a little bit below even after they discontinue but we just really don't have answers to that But again the default expectation based on uh diet and lifestyle weight loss is that yes if you go off the drug you're probably going to regain And for people who perhaps are would not be I guess indicated for semi glut Let's say that they're they're not obese Um but they're still interested in G LP one And I'm assuming that through diet the the increase in G LP one post meal is nowhere near what it would be from taking semi glut for example But what are the the are there key components of food that result in this incredible hormone being released Yes So it is it can be altered by diet composition to some degree And unfortunately I don't have that on the tip of my tongue So I don't remember what um that is but I would say you know like don't chase the hormone just eat food that has been empirically shown to help control calorie intake and body weight and like don't worry about G LP one you spoke about exercise before and I made a note to come back to that So um clearly moving our body is uh a a process that requires energy we use energy to to move So it would um seem to be something that would impact this energy balance equation and and help promote weight loss or weight maintenance um or reduce our risk of becoming overweight But then there's this sort of constrained energy model from from Herman Ponce's work a lot of conversation about that So how do you think about exercise when it comes to the individual trying to maintain a healthy body Weight or get to a healthy body weight Yeah I think as a standalone weight loss method exercise is pretty mediocre It's not ineffective In my opinion it's just that you aren't generally gonna get as much weight loss via exercise as you are by modifying your diet Diet is really the main lever over body fatness In my

opinion That said um I do think that it probably is more effective at preventing fat gain than it is at causing fat loss And I also think it's probably more effective at maintaining fat loss than it is at causing initial fat loss The evidence that it prevents fat gain You know going back to the studies I was talking about with the the junk food diet that Anthony Scni did in rats Well it turns out in that initial paper in the 19 seventies one of the groups got a running wheel and so there were groups he was comparing that had that both had access to this uh you know buffet of human delicious calorie dense foods One of them had a running wheel and one of them didn't And the running wheel by the way you put that into a rodent's cage and they'll use it a lot They will exercise quite a bit each day on this running wheel voluntarily And what he found is that the rats with the running wheel did not get as fat as the rats without it They still got fat but not as fat So it attenuated the fat gain on that fattening diet And that's kind of how I think about it for humans too There's human data on this as well And you know it's not a home run like it most of it is observational But what it suggests overall is that regular physical activity can help keep your energy balance in a healthy range Part of that at least part of it is probably that it actually helps regulate your appetite Essentially people with low physical activity who are very sedentary In the observational studies they have paradoxically elevated food intake And you see this in rats too where where you can really control your variables So I think there's a decent case to be made that um physical inactivity causes people to overeat and higher levels of physical activity helps regulate appetite more effectively Why we would see greater energy intake in someone that's sedentary versus someone who is active moving their body And the logical outcome of that you would think would be an increase in energy intake for that person that's physically active So what you see in the rodents is that basically energy intake does go up So basically if you look at it if if we're looking at a graph where on the horizontal axis you have um physical activity level and then on the vertical axis we have calorie intake what you see is that at the lowest levels of physical activity calorie intake is kind of elevated and then once they start exercising goes down but then if they exercise more and more and more it goes kind of up again So at least in those particular studies there was a kind of matching between energy expenditure and intake but that seems to go out the window at the lowest levels of physical activity And I don't know why that happens I don't I'm not sure that anybody knows Um you know my just like really high level gut you know idea is just that we evolved for physical activity and if we don't get it

stuff just doesn't work Right One of the things that doesn't work right is our energy regulation systems So that's probably not very informative but that's my like simple way of thinking about it right now Yeah Well it's interesting we don't have to have all the answers today anyway Um I just want to change gears here as we get right to the to the end of this Um I'm interested with regards to the kind of seductive nature of foods and I guess how vulnerable we are to um a food environment where there's a lot of hyper palatable foods How important do you think mental health is to this Does being stressed or um having low mood or being sad Does that like play into being more vulnerable to these types of foods Uh I think it does and I think the direction it can go is very individual So if you look at survey data it suggests that people kind of fall into two categories Some people overeat when they're stressed and some people under eat And I think it it depends on you know so a person who overeats could also under eat under different circumstances So it's not necessarily that that's what they always do but that would be what they typically do And um and yeah so the people who overeat when they're stressed that is very much uh could be a contributor to to excess body fat mass And the other aspect of lifestyle that I've seen a few studies looking at sleep deprivation and looking at energy intake which I thought was really some some quite interesting um studies and at least in the short term from from these papers that I've looked at it seems that if you deprive someone of sleep you can increase their calorie consumption the following day And and some studies even went as far as looking at the sort of cravings for different foods And it seemed like people maybe have sort of a heightened um craving our appetite for the sort of less healthy foods How how important do you think sleep is for managing the body fat I don't think sleep is like necessarily an effective you know weight loss a standalone weight loss method uh for someone who are who is looking to lose weight who already has obesity But I think in terms of explaining why it develops I think it could be potentially significant So the studies you described yeah if you curtail people's sleep down to five or six hours a night they eat more and their brain activity suggests that their motivational drive toward calorie dense foods is increased And yeah you see activation of the reward regions and the the energy regulating regions that are kind of activated for this food And so um so that's as you said those are short term studies you can't do that to people for long But if you look at the observational studies they're very consistent with this idea as well They're the last time I looked which it's been a few years there was very very consistent and strong correlations between sleep duration and

uh weight gain over time So people who don't sleep enough basically are at increased risk of gaining weight over time So to me it adds up to a fairly convincing picture you know we don't have the like home run randomized controlled trial that lasts three years and randomizes people to five versus nine hours of sleep a night Uh and shows differences in body fatness So we don't have that you know home run trial and we probably never will But I think the evidence we have uh really is is pretty supportive I guess to kind of summarize some of those things that we've spoken about at AAA reasonable death but also um at a high level towards the end here it seems like if someone is wanting to um move towards a healthier body weight for them whatever their goal is that nutrition is the biggest lever um things like exercise and managing stress um and and sleep also important but perhaps not of the same magnitude Would you kind of agree with that Yeah in general with the caveat that I think that can depend on the person Is there anything else that you would add that we've kind of missed that would be important for someone to look at So I think the food environment is is really important um in in terms of controlling your exposure to food queues and how easy it is to access food in your environment I think that is uh an important variable that impacts your intake that you know a lot of times we we like to focus on the nutrients in food like what you know how much carbs you're eating how much fat how much fiber et cetera But the way in which we interact with food throughout the day I think is also very important in terms of how much we end up eating Stefan This has been incredibly interesting Thank you so much for your time I've taken up uh over two hours now so I'll uh land the plane here and let you go for those that want to learn more uh in addition to getting your a copy of your book Hungry Brain uh where where can they find you online Yeah So I would direct people to my Twitter That's where I'm most active My Twitter handle is at uh Sgnaguyenet I would say also check out red pen reviews We've got um we've got free expert reviews of popular nutrition books Simon's book by the way did quite well on on on our uh on our site And uh I also have a website sting DNA dot com I don't write there much anymore but there is material there that uh some people might be interested in There we go Friends Thank you for showing up and the effort you're making to take better control of your health I look forward to hanging out with you again next week for another episode