Danny Lennon: Hello everyone. And welcome to this special "Expert Ask Me Anything" session today. I'm going to be joined by Dr. Stephan Guyenet, who is a multiple time guest on the podcast. I believe possibly five appearances on the podcast, which I suspect puts you probably in the number one position of guests that have been reinvited onto the show.

I don't know whether that's a good or a bad thing on your end. But for me it's been a complete honor to be able to get to chat to you so often about some of these ideas. And of course, people that have sent in their questions today will have heard you on multiple of those in addition to the rest of your work that I think most of our followers are familiar with.

And so off the back of that, people have submitted questions that relate to many of your areas of interest. So we're going to put them to you. But before that, I want to say thank you for doing this and welcome to the podcast.

Stephan Guyenet: My pleasure, glad to be here.

Danny Lennon: Great. So with that, let's just dive straight in, I think is probably the best way to go and explore what we can do.

The first question I'm going to put to you comes in from James Kuhn, who asks, when someone undergoes liposuction or other surgery that removes adipose tissue. Is there a sudden reduction in leptin levels while this may

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reduce leptin resistance? Could the drop in leptin lead to increased hunger over time?

Stephan Guyenet: Yeah. So I did a little bit of digging on this question and empirically the impact on leptin looks like it's variable up to about six months. So it looks like studies are not very consistent on what the impact on leptin is, which is surprising because leptin typically is. In circulation in proportional to fat mass.

So I'm not sure what explains that discrepancy between study is why some found a decrease and some did not out to about six months. However, what is observed pretty consistently is that fat regain does occur. So there is a homeostatic reaction that happens to fat loss. In other words, whether it's leptin or some other mechanism, the brain gets the message that fat mass is lower than the set point and starts to reaccumulate fat back to the baseline level.

However, That doesn't necessarily mean that liposuction is useless or it doesn't accomplish the person's goal? The patient's goal, because it still causes a redistribution of fat mass. So if you have liposuction in the abdominal area, in the belly and by the way, I'm talking about subcutaneous fat.

So liposuction is on subcutaneous fat. So they're not going inside your visceral cavity underneath your underneath your abdominal muscles. They're just getting it from the subcutaneous fat, under your skin. However, if you are someone who aesthetically wants to have less fat on your belly and liposuction removes it from there, and then you regain it in other places that could still be, aesthetically a net gain for that patient.

So it's not to say that it's necessarily completely useless from the patient perspective. However, In terms of long term reduction of fat mass, it's not effective.

Danny Lennon: Brilliant. Thank you for clarifying that. But with that, maybe that builds on some of that. Let me put you the second question that comes in from Amy Allport.

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What is the current research around chronic energy restriction or following a crash diet affecting appetite hormones and or appetite regulation, long term? Is there a physiological mechanism influencing overeating attributable to appetite dysregulation caused by chronic dieting? Yeah,

Stephan Guyenet: I think a lot hinges on how we define the word dysfunction. Or appetite dysregulation, is the word that was used there. I think what I would argue is that the typical scenario that we see is not dysregulation it's regulation, appetite regulation. In other words, there's a regulatory system seated in the brain that is opposing. Fat loss. And so what is that because of this homeostatic system that regulates body fatness, when body fat starts to decline, it gets activated and it starts to increase eating drive and it can curtail energy expenditure as well.

And it tries to pack fat back into fat tissue. And that increase in eating drive can occur via a number of different ways. The hypothalamus has its tendrils throughout the brain. Basically when it wants you to gain fat back, it has many ways of nudging you to increase your calorie intake. So for example, just to give an extreme example, that folks might be interested in In the Minnesota starvation experiment that was run by Ancel Keys in the, I think forties or fifties, they had people on severe chronic calorie restriction and these people, they were like pretty skeletal by the end.

So this, this doesn't, it's not representative of a typical weight loss situation, but like these were people who started off not having overweight or obesity and got really lean, but they. Basically became obsessed with food and recipes. And they were like collecting recipes and cooking utensils.

And it was like this system just gripped their entire brain and put even their cognitive processes to work, trying to get them to eat food. So I think there are many the point I'm trying to make here that's relevant is I think there are many ways in which this can express itself. That could be more complex than just, oh, I feel hungrier. Or I have, lower satiety when I eat, which those are also manifestations that can occur that are perhaps more obvious. So I think, I don't think there's much scientific evidence that chronic energy restriction has a. Dysregulating impact on appetite in the long term, as in something that would persist after weight is regained, for example.

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So for example, if you look at long term follow up of weight loss trials, like for example, the diabetes prevention program trial, that trial, I think The main intervention went on for three and a half years, but they followed people out for a total of 10. And you can look at the weight curves of the diet and lifestyle, weight loss, intervention group, relative to the control group.

And they achieved maximum weight loss some time around I don't remember exactly like one to two years, and then they gradually regained, but they never exceeded the control group. Their weight never exceeded the control group on average. So they regained, but it's not like that chronic calorie restriction that they were under for years of this intervention caused some kind of dysregulation that made them eat more or gain more weight than they would have if they had never done this intervention.

If that makes sense. So weight wise, it leaves them worse off than if they hadn't done anything. So I think my view is that at least for the average person, there's not really evidence of like long term dysregulation that leaves you worse off. I think. Mostly, what we're seeing is just evidence of regulation, this normal regulatory process that pushes back against weight loss and can express itself in many different ways.

Danny Lennon: Yeah. I think that's a really crucial distinction again, to emphasize that you brought up that when we're talking about dysregulation and what someone may define that as versus what normal regulation that we would expect to see. On the basis of this homeostatic control of body mass regulation that you just outlined and that in these cases where you have someone that has gone through a period of time of a hypocaloric diet and lost a certain degree of body mass, that, that increase in appetite, someone then would experience is actually normal in the sense of that's what we would expect to happen.

It's a normal adaptive response. And so even though maybe some of the behaviors, people may experience. The atypical, the actual response is normal. And I, I think one example that came to mind as you were talking through that that anyone that has looked even from the outside, in, at something like competitive body building, where you see people getting down to something like four or 5% body fat for male competitors off the back of that, the degree of appetite that people have and the drive to consume food and vast quantities after a competition is obviously very large.

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But whether that's actually a dysfunction of the appetite system is probably not correct. It's actually that is normal, a regulatory process to gain weight back to that appropriate set point. And we could think of the same happening. In cases of, if someone has a higher body fat set point, then they see that same increased appetite just occur at higher levels of body fat. Yeah, that's a really nice way to paint it of this is actually normal appetite regulation,

Stephan Guyenet: Yeah. It may be unwanted, but it's not necessarily abnormal.

Danny Lennon: The next question comes in from Kristen Marshall. There's quite. Lengthy bit to this. I'll read through all of it. And then we can maybe just summarize then some of the key aspects to focus in on.

But Kristen asks, can you talk about the conditions of anorexia and morbid obesity and how they essentially defy the rules of metabolic compensation? In other words, I understand anorexia to be a mental health condition where the individual starves themselves with a purpose to control weight and morbid obesity being excessive consumption.

Over fatness, et cetera. If the body has these numerous mechanisms by which calorie restriction or calorie over consumption results in these compensatory processes, driving us to eat more or less, slow us down, speed us up more. Do these individuals not "hear" these signals or are they just adept at ignoring them? Or is it that their bodies have lost the ability to compensate for their under, over consumption?

Additionally, can anyone become anorexic or morbidly obese or is it merely genetics? So before even we get into those specific conditions and some of the aspects of that, I think this question really hits at the core of what maybe a lot of people hear when they first hear about the homeostatic control of body mass.

And they say they might say something to you. If there is this homeostatic control, how do we even end up with a situation like obesity? Off the base of Kristen's question what way would you tend to open up that conversation that you think might make sense to people?

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Stephan Guyenet: This is an important question. And I want to start off just by saying that I'm not an expert on anorexia. I think anorexia is a complex condition that involves some psychology that I'm not very knowledgeable about. But I will say that there is a genetic component to both obesity and anorexia, and there are mouse models of both, in fact.

So there are mouse models of anorexia in which they cause some of the genetic changes that. Observed or they changed some of the genes to be like, what is observed in some humans with anorexia. And that increases the mouse susceptibility to developing an anorexia like state. So there are definitely genetic factors involved in anorexia.

And certainly there is a very strong genetic influence on obesity. So the meta-analysis of twin studies, which are one of the best ways of measuring the genetic contribution to different traits. The one that I like to cite suggests that 75% of differences in body mass index between people is determined by genetics.

So genetics is the primary explanation. According to this research for why some people are fatter than others. So the genetics is very important. So the thing that's important to understand in this context, we have this regulatory system that regulates body fatness, and what appears to be the case is that people with obesity or people who are overweight, that system is not being overridden or malfunctioning.

It is actually regulating at a higher level. So it's if we use the thermostat analogy and we say that this regulatory system is like a thermostat that has a set point, and it's trying to maintain temperature within. , at that set point using heat and air conditioning, if we use that analogy it's like turning the thermostat up.

So you the brain is literally regulating around a higher level of body fatness and defending that against as far as we can tell both fat loss and fat gain, at least acutely. So obviously and I say at least acutely, because this comes from short term overfeeding studies and short term underfeeding studies.

And so we see that, people with obesity, you put them on a weight loss, diet, calorie restriction. You can cause people with obesity to lose weight, especially you use a very low calorie diet. You can make people lose a good

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amount of weight pretty quick. And, but what happens if then you stop the intervention that you were using to cause 'em to lose weight?

Do they just stay at that lower weight? That's what you would expect. If there was no regulation that they would just be able to cruise at that lower weight and maintain that easily. But that's not what we see a person who goes from having obesity to not having obesity via simple calorie restriction typically will regain weight at a fairly rapid rate, especially if they stop, if they completely go back to how they were eating and living before they will rapidly regain the weight that they had lost.

And if you have two people at the same weight, one of which. Was previously much heavier and is currently weight reduced. That person is going to gain weight a lot faster than the person who is not weight reduced. Those people are not the same physiologically. So we can, and there, there are other there's other evidence for that as well too, that I won't get into.

But basically what the literature suggests is that the set point for body fat regulation is elevated in people with obesity. And so it's not that the system isn't working, it's not that it's broken down or that it's being overridden. It's actually changed the way that it's regulating their body fatness.

That's what the evidence currently is suggesting. We don't know exactly how that happens, because this is of course the next question is, how does this system, how does the thermostat get turned up? because in most people it does right over the course of their lives. And we don't really know, is it just like you gain some fat because you, over consumed calories for whatever reason and your system's oh this is the new normal, or does the system itself drive the process?

So is there something like inflammation in the brain that causes that upward resetting and then your fat mass increases as a result of that? We don't really know and it could be both. I suspect the first explanation is at. Partly true, but we don't really know right now. So that's a key question.

Danny Lennon: Yeah. And it's something and I and others are at fault of presuming. Maybe we know more in that than we do. But speaking to that first hypothesis that you put there that you think at least partially explain some of this, would that be akin to saying, okay, if we take a situation before

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someone has established obesity, and if we look at the time course of that progression, that.

Whilst they do have these homeostatic controls of body mass for this or orchestra of various different hormones, that there's certain things about lifestyle and environment, that if we change those things that can then essentially for maybe a very simplistic term override the internal homeostatic control that person has, that then could allow obesity to develop.

Is that too simplistic? A way of phrasing what might be going on or how does that fit into the picture?

Stephan Guyenet: You've just described the two scenarios. The first one is basically that the regulatory system follows the calorie excess and the increase in fat mass. So just for whatever reason, you have too much food around or the food's tasty or calorie dense or whatever, you're over consuming the regulatory system, you gain, let's say, a pound of fat.

And then the regulatory system kind of adapts to that and that's the new normal. And then the second scenario would be that you let's say something about, for example, diet quality or your physical activity level. Let's say just theoretically that certain fatty acids in the diet, if your diet's high and certain fatty acids that creates inflammation in your hypothalamus, and then your thermostat gets turned up and then that leads to effects on appetite and energy expenditure that cause your fat mass to increase.

And I think the first scenario is. Probably at least partly correct. because we see in overfeeding studies, when you over feed people, usually they will lose most of the fat mass that they gain in a short term overfeeding study. But in some studies they don't lose all of it. So they'll lose like maybe three quarters of the excess fat that they gained and then they'll retain a quarter of it.

So I think probably what happens is that if you keep pushing on this homeostatic system, Over consuming calories relative to your needs. You just gradually ratchet it up. I think that's probably part of the explanation, but again, I think we're not totally sure yet,

Danny Lennon: Just as you said that one of the ways I've shown the people is one of the diagrams or the little graphics that's actually in one of your papers,

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I think a paper that you might have done with Mike Schwartz essentially shows what you've just described, that where you have this overfeeding situation, you have this adaptive process to bring body mass back down, but it doesn't do so perfectly in a lot of cases that there's this still residual net gain.

But then when you look at the opposite, when people have lost weight, you actually do see weight come back up at least to baseline typically. And so then if we can imagine that extrapolated out over time, that might give us an indication of what's going on.

Stephan Guyenet: Yeah. The system seems to be better at defending against fat loss, unfortunately and also I think it is very individual. When we talk about these graphs, we're talking about averages, but I think there are some people who, for, whatever reason, probably a lot related to genetics, they are better at losing excess fat. Like they're better at defending against fat gain. Than others. So probably in those studies, some people are retaining more of that fat mass than others.

Danny Lennon: There's so many avenues I could have explored there, but to get to the next question this comes in from someone, I don't have their full name, I have a username here of "Pstatev94" who asked, why do SDRIs so 'serotonin, dopamine re-uptake inhibitors' and serotonin precursors, reduce hunger and appetite? For example 5-HTP or Wellbutrin which is a brand name for the antidepressant Bupropion. So with relation to these SDRIs or serotonin precursors what do we actually know about hunger and appetite effects?

Stephan Guyenet: Yeah, so I poked around a little bit and bupropion is an atypical antidepressant. That it is a norepinephrine-dopamine reuptake inhibitor (NDRI), and a weak antagonist of the nicotinic receptor.

And the first point I'm going to make about that is that because it has these three different activities, it is potentially complex to determine exactly how it works. However, it does seem to activate POMC (pro-opiomelanocortin) neurons. POMC neurons are a key population of neurons in the hypothalamus that regulates appetite and body fatness.

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They're one of, two of the, really central neuronal populations and body fat regulation. The other one being Agrp neurons. So they've been shown to activate and POMC neurons, which suppresses food intake and body fatness, but there could be other mechanisms.

It didn't seem like this has been deeply studied. It also has impacts on reward and rodents. So that could be a mechanism. Now, bupropion is often paired with an naltrexone, which is a drug that affects the reward system. And that combination is called Contrave, which is FDA approved weight loss drug, and Contrave appears to also potentiate those effects on POMC neurons.

So it the combination has a larger impact on POMC neuron activity than either one alone. Now with regard to the serotonin effects specifically, the serotonin system can impact appetite. Although the effects are complex serotonin is a neurotransmitter that acts on many things throughout the brain.

And if you look into serotonin research, like there's still a lot, that's not known about it, or that seems confusing about it. There's not really a kind of like widely accepted unified model of what serotonin does. So that may be that we don't quite understand it yet, or it may be that it just does a bunch of different things and there's not, and there is no unified, function for it.

So some serotonin specific re-uptake inhibitors (SSRIs) , which are drugs that increase serotonin levels at the synapse. Some of them increase body weight. However, there are also serotonin targeting drugs that lower body weight. So for example, Lorcaserin activates the serotonin 5-HT2C receptor, and that is actually an FDA approved weight loss drug. And that seems to exert its effects also on, by activating POMC neurons. So I think the impact of serotonin really depend on what exactly parts of the serotonin system are being targeted.

Danny Lennon: Next, we have a question from one of our longtime listeners, James Valaitis, who often ask very interesting and thought-provoking questions. And he actually has one that is specifically about the ideal weight program. And I'll probably get you to give an explanation of that for other listeners, but he asks as an iOS developer, my instinct is to assume determinism and quantifiability of the entire universe. I believe this to be fundamentally true, but what is hypothetically possible differs from what we can realistically know.

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I worry that attempts like yours to quantify some seemingly qualitative measures are doomed. I have similar concerns about happiness research. How do you reassert reassure yourself that you can. Construct an algorithm that deciphers the ideal weight program for any given user. Do you rely on averages close quote?

So again, maybe just to start for maybe others, can you give it a very quick explanation of what the ideal weight program is, and that might kinda lay the basis then to dive into the nitty gritty of James' question?

Stephan Guyenet: Yeah. So the ideal weight program is a weight management program that I co-developed with Dan party it's on the human OS platform. It dovetails with my book, The Hungry Brain, and is based on similar principles. So it's essentially a collection of strategies and tools for managing what I believe are key influences on Energy balance and body fatness and creating sustainable habits that allow people to maintain those in the long run.

And yes, we absolutely do rely on averages. This program is based on evidence on that's been published on the factors that are most effective for impacting calorie intake and body fatness. Unfortunately, at this time averages are overwhelmingly how scientific research works. So if you want to generate statistically persuasive conclusions about factor X, so let's say like the impact of protein intake on appetite and body fatness.

You can't really do that at an individual level, in a way that's really practical right now to be able to do the types of statistics that are commonly used, you have to use groups of people, put them on different treatments and compare the outcomes. And so unfortunately what that generates is difference, the output is differences in average.

And there are efforts right now to get more precise about how we target individuals with weight loss interventions. And, the premise is if we had perfect knowledge for every individual of what, the optimal strategy for that individual is we could undoubtedly design a more effective intervention and what we can right now, but.

That's just not possible right now with the evidence that we have. And so no program of this nature is ever going to be, or I shouldn't say is ever going to

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be, but no program of this nature is currently optimally tailored to every individual. We don't understand all the things that cause inter individual variability and how people respond to things.

So we, just try to select the strategies that work the best on average and put those together to create the best outcomes that we possibly can. Another thing that I want to specify is I want to define what we mean by ideal weight. I don't want people to think that means that we promise that people will go from having severe, or I should say pronounced obesity to being ripped.

That's not the claim that we're making about this program. The concept of ideal weight is, and we try to set realistic and positive expectations at the beginning of this program. The concept of ideal weight is that you're finding the best balance for you between a lifestyle and diet that is effective and the level of body fatness that you're looking for.

You can, you could have an extreme intervention. That's more effective for reducing body fatness, but if that's not going to be sustainable in the long run, or if it makes you miserable, then what's the point. So we want people to find the balance where they are really optimizing their overall.

Life and their overall wellbeing as the best balance between the amount of effort that they're putting into the intervention and their body weight.

Danny Lennon: I'll move on to the next question that comes in from James Bruss, who asks: in 2018, a poster was presented at the annual meeting of the society for neuroscience titled "the human brain microbiome; there are bacteria in our brains" which showed that bacteria apparently penetrating and inhabiting the cells of healthy human brains while the work was preliminary. Have you heard of any further work in this area? What is your opinion on the possibility that if bacteria do indeed inhabit the brain, that they could play a part in appetite, regulation and or obesity, similar to how the gut microbiome can affect our health.

Stephan Guyenet: I'm not very familiar with this research, so I'm not sure what has been done since then. I know that there has been work on potential contributors to potential pathogens that contribute to obesity. There's one in particular virus actually that has a fair amount of research behind it that it's associated with obesity in humans.

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And if you infect, I think rodents with it it can cause them to gain fat. As far as bacteria, I'm not aware of much research suggesting a cause a link there, but I know that there is increasing research looking. The brain microbiome, which is like scary to even contemplate. And I know one area that there's been research on is Alzheimer's disease.

So they find elevated levels of certain types of pathogens in the brains of people with Alzheimer's disease. And I think a lot of these types of research. It's, you find correlations, but it's hard to determine cause and effect. But I'm not I don't know a whole lot about this, so I'm not sure how strong the evidence is in this particular case.

Danny Lennon: Yeah. And considering how much is published and at least discussed online about the gut microbiome. And even there, we still lack, I think a lot of evidence that is needed to make stronger conclusions, nevermind. Talking about the brain microbiome. Yeah. Interesting. But I think that's as much as we can cover there.

The next question comes from Gabrielle LaFontaine Chica. Who asks: it seems like there are significant differences in policies put forth between researchers from biomedical backgrounds and ones from public health policy backgrounds. Dr. David Allison touched on this during recent interviews, noting that there's very little evidence regarding the efficacy of upstream obesity prevention, interventions, such as community gardens, combating food deserts, nutrition, education, and cooking classes.

On the other hand, governments are increasingly turning to such interventions as well as policies such as front of pack labeling for example, Canada, 2022. Nutrition facts tables, calorie labeling on menus, as well as the aforementioned ones. Given your research on determinants of health and obesity, what are some of the most promising interventions to prevent non-communicable diseases, morbidity as well as Stone's unturned in public health policy. Would you agree with individuals such as David Allison, that in our current environment, the only efficacious interventions are drugs and bariatric surgery?

Stephan Guyenet: I want to start by saying that I'm not sure that's exactly what David thinks. I think I, I don't think that he would, I'm going to put words in his mouth here, so I apologize if I do so incorrectly, but I don't think

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he would say that drugs and surgery are definitely the only thing that works. But I think what he would say is that if you look at the scientific literature and. Let's say, you've, you have no preconceived notions. You're taking completely objective perspective and you're just looking at numbers and you're saying what actually causes weight loss or stops weight gain.

And you just look at the literature and say what's effective. Those, bariatric surgery and the new drug treatments are undoubtedly the most effective. There's nothing else that really compares. So I totally agree with him there. If we just take a complete evidence based numerical perspective, that is what it says.

And he's also absolutely right to call out that a lot of these public health strategies that have been tested don't really have much of an effect. You could say that the hypothesis is incorrect, or you could say that they're not targeting it in the right way, or it needs to be a longer term thing, or it's just part of the problem, only a small part of the problem.

But he's right. That the evidence that these things are effective is tends to be pretty slim for these public health interventions. So I think there's an attitude in public health of we have to do something. So let's, these things seem like they should work, so let's do them. But again if we're going to be scientific, then we have to respect the empirical evidence when it says that some of this stuff doesn't work or doesn't work as well as we would like it to public health interventions, aren't my specialty, but I'll give a few additional thoughts on what I think maybe a more effective path could be. I think the first thing that we should recognize, and I think this is part of the answer to the previous question that I was just addressing is that this is a big problem. So if you look at the estimated increase in calorie intake, that has gotten us from at least I'm speaking about the us here, but I think it's qualitatively similar in other countries the increase in average calorie intake.

That's gotten us from where we were in the seventies to where we are now, we're talking about over 200 calories per day in the average person. And not everyone has obesity now. So if we're talking specifically about people who are. Have obesity today who wouldn't have, if they were living in the seventies.

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If we're talking about that subset of the population and ignoring people who would be lean either way, those are the people who increased their calorie intake. So if we're just looking at those people, they might be eating like 400 calories more than they would have in the 1970s. And those are the people you have to target.

So this is a huge, we're talking about a huge effect. You'd have to reduce their calorie intake to, if we're talking about reversing this situation, you'd have to reduce their calorie intake by 20 or 30% on an ongoing basis. And you're not going to be doing that with, calorie labeling on packages or combating food deserts or community gardens, or, some of these other things you mentioned, those just are not potent enough to counteract the magnitude of the issue that we're facing. I think, the question is to me not, are there interventions that are potentially effective?

The question is, are there interventions that are effective and wouldn't be so heavy handed that we would be unwilling to tolerate them? I, if I was king of the United States, I could ban certain types of food. I could just blanket ban refined foods with a calorie density higher than X.

And that would probably be pretty helpful. I don't know that it would solve the problem, but probably help. And but that's never going to happen. People don't want the government to be acting with that level of they, they don't want the government to be controlling their diets to that degree.

So I, I think the question is what can we do that would be tolerable? And I think, there's some things that I think have fairly wide agreement are acceptable things to do, and that could have some impact, like you could target food marketing, especially to children. I support package labels. I don't know how big the effect size is going to be, it's just information. It's not going to hurt anybody. And then sugar sweetened beverages are, nobody thinks those are healthy. I think a lot of people are pretty open to taxes on those. I think the tax just needs to be high enough to actually substantially impact purchase decisions.

Most of the taxes that have been implemented are pretty wimpy, so they only have a modest impact on purchase decisions. We have a playbook for this that has worked in the past and it's tobacco. So in the United States, there were massive legal settlements with the tobacco industry as a result of them

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having lied to the public for so many years about the health impacts of cigarettes. And that money was used to pay for tobacco reduction campaigns, billions of dollars. And so how was that money used? They uh, in a variety of ways, so there was taxation of cigarettes that didn't necessarily require that money, but that was one of the strategies that was used heavy taxation on cigarettes.

When I was a kid, you could get a pack of cigarettes for 99 cents. And part of this is inflation, but today it's like $13. That's way more than inflation. It's, there's massive taxes on tobacco here. It's inconvenient. Now they've done a number of things to make it more difficult to smoke.

You can't smoke in a lot of places used to be able to smoke in bars, used to be able to smoke. When I was, when I first started doing scientific research, people would smoke in their own labs. That would be totally unthinkable today to smoke a cigarette like over your experiments that you're doing.

And then the last thing, this is one of the things that money was used for the most is counter marketing. So basically, if marketing is trying to get you to buy something, counter marketing is to get you not to buy it. And so there was this massive counter marketing campaign to paint basically cigarette smoking as disgusting and unhealthy and all that stuff put together really worked. Cigarette consumption in the us is dropped by more than 75% and prevailing opinion is that it's gross. Like my generation went from like most people smoking cigarettes, at least casually to like few people smoking and thinking it's gross.

And the culture really changed as a result of this intensive effort. Now, cigarettes, aren't a perfect analogy because you don't have to smoke cigarettes, whereas you have to eat. So it's, I think. Easier and more tolerable for the public, for the government to get more aggressive on something like cigarettes than food and with food, you have to parse out like, what is it you're going to regulate you can't just regulate all food.

So it's not a perfect analogy. But the point is, I think there are tools that could potentially if be at least somewhat effective. But it's really just a question of will the public tolerate it and will the government tolerate it?

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Danny Lennon: There's so much that, that we could unpack there. But I think you've discussed a lot of the big ideas that particularly that it's not a lost cause that no public policy would be beneficial. And indeed, I think there's probably things that would certainly be of benefit. But I think one of the big things is obviously that there's an opportunity cost depending on what you select. So if we are selecting some of these weaker kind of more passive policies that was mentioned in the question that we don't really see any benefit of when we look to any evidence that they don't really seem to do all that much, then continuing to put resources and time into those is not just leading that they're benign and don't do anything is actually taking away from time and energy that could be pumped into to other policies.

But that, yeah, it seems that there would need to be some degree of significant. Regulation that changes the role of the food industry in some way. But yeah, much to discuss for another time. So let's get to another question. This one is a second question from Kristen Marshall. And she has a question actually, based on the debate that you had with Gary Taubes on the Joe Rogan Experience, and she asks: would the insulinogenic effect of protein, specifically something like whe protein, which causes an insulin response, be something that should automatically refute Taubes' arguments about insulin's inherent role in increasing adiposity.

And second would overeating on any macro nutrient increase insulin, simply because you're eating more food. So if you're in a hyper caloric state, would that just mean that you're going to be increasing insulin overall? So I know there's two questions within that, but your thoughts on those.

Stephan Guyenet: Yeah. So just to unpack this a little bit, to make sure everybody's following. Different foods have differing impacts on insulin release. So typically what and it's more complicated than this, but typically at a high level what we say is that protein and carbohydrate release a lot of insulin fat does not release does not cause much insulin to be released. And it depends on the carbohydrate food quality as well.

So some carbohydrate foods cause a lot of insulin release some cause less and same with protein with whey protein causing a larger insulin release than most. And so the question is, and protein, of course, tends to constrain appetite. It tends to reduce body fatness. And so the question is, does the fact that protein, like whey protein increases insulin, does that refute the

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argument that insulin causes obesity and specifically this person said, does that automatically refute?

So is this, I take that to mean, is this a strong counter argument? So I think it's a counter argument. I don't think it's a strong counter argument. I think it's just a small piece of the overall argument, but yeah, if insulin is the dominant factor that determines body fatness, which is what Gary Taubes has argued, then why would increasing the proportion of an insulin secreting food, even at the expense of dietary fat, reduce appetite and body fatness. So I think it's a counter argument but not necessarily the strongest one. And to answer the second part of that question. So in the short term, macronutrient macronutrients have a large impact on insulin secretion, both in the post meal state, as well as the fasting state.

For example, if you take someone eating a typical diet and you put them on a very low carbohydrate diet, what you're going to see is that there is less insulin secretion after meals, and there is also less insulin secretion between meals. And when they first wake up in the morning, because there's just less glucose being trafficked around the body, not as much insulin as is required to metabolize that and help it get where it needs to go. So that's in the short term, in the long term, I think the impact of fat mass probably comes to predominate as a determinant of insulin secretion. I don't know. I'm not going to say that with a high level of confidence. I'm not sure that has been really definitively demonstrated, but there are a couple of reasons to believe that I'll expand on briefly.

So for example, John Speakman has a study where he put I think it was like five different strains of mice on 28 different diets that varied in the ratio of fat to carbohydrate. And so some massive mouse study to see how macronutrients impact body fatness among other things. And what they found is that essentially the higher you go with dietary fat, the more body fat, these mice ended up with up to a point.

And then when you get to very high fat and very low carbohydrate, they start dropping down in fat mass again, and this is consistent with the wider literature, but the follow up data that he showed was that their insulin secretion was actually correlated with their fat mass, not with which macronutrient they were eating.

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So in the long run, it was really determined by their fat mass. And then there's also the human genetics. where if you look at what the determinants of fasting insulin are, what you really see is a lot of genes that relate to adipose tissue and particularly adipose tissue capacity. So people who have adipose tissue, that's really good at just taking everything that's thrown at it. If you eat calorie excess, your adipose tissue is going to be really good... your fat tissue is going to be really good at taking that up and sparing all of your lean tissues from that excess energy. Those are the people who are going to remain more insulin sensitive and have lower insulin as they gain fat.

Whereas people who their fat tissue doesn't expand very effectively and their lean tissues get exposed to more energy. When they over consume, those are the people that are going to get insulin resistant and develop high insulin levels really quick. So I think the evidence we have currently points mostly to positive energy balance and fat gain, and also your own like ability to expand your fat tissues in determining insulin secretion. However, I think more research is required on that.

Danny Lennon: The next question comes in from Sylvia Hua and this question I suspect might require some degree of speculation, based on your best thoughts, but it essentially relates to fat loss and weight loss maintenance beyond that.

Sylvia asks: are there best practices for the maximum duration someone should spend in a fat loss phase or perhaps an optimal ratio of fat loss phase duration to maintenance phase duration, for example, should fat loss phases be a maximum of 12 weeks followed by a maintenance of at least equal duration before resuming another fat loss phase? Any thoughts around this?

Stephan Guyenet: Yeah, so I'm not aware of scientific evidence. That matters. So whether you are doing continuous weight loss, or you're breaking it up with maintenance phase or how it's broken up, I'm not aware of scientific evidence that. That matters. I'm not saying it doesn't matter, but off the top of my head, I can't think of any clear reason why it would matter.

Danny Lennon: Thank you. Yeah, it's probably, again, one of those things that might come down to if people can actually stay within the duration of their fat loss diet that they're planning without feeling the need for a break from it. So with that wheel round out on this question, I think from Shane Duqette

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who asks: I'm a naturally skinny guy who helps other naturally skinny guys bulk up. I think it largely comes down to a blunted pleasure response to food, smaller stomachs and or higher NEAT. A lot of us seem to be taller and more thinly built too. But why do you think things are so different for us? Why is it hard to gain weight and what can we do about it? So in this sense I'm presuming this is a gain of muscle mass over time and people are finding it difficult to actually consume more than they, they typically do. So any thoughts more even generally about people that tend to have almost the opposite of what many others respond of being able to have this either blunted response to food or higher NEAT levels, et cetera?

Stephan Guyenet: Yeah. This is a great question. And one that is very interesting to thescientific community. So some people have a hard time gaining fat and or muscle mass. Some people have just naturally very little fat mass and lower muscle mass. And if we can understand why some people are highly resistant to fat gain, it might become a basis for the next generation of obesity therapies.

So there's a lot of interest in this currently in the scientific community. And studies are ongoing on this and currently not a lot is known. I will say that there are potentially multiple paths to being very lean. So you could imagine you could imagine that a person just has a lower drive to eat. You could imagine that a person has lower capacity to store fat and adipose tissue. You could imagine that a person has. Differences in their body fat regulatory system, just like a naturally lower set point. So there are a number of potential ways that this could express itself.

But there are a few things that are currently known. So first of all, like obesity, leanness is partially genetic. So there's been studies showing that it, that state is partially heritable. So it's partially genetic. Second, there's been one genomewide association study on this, and this is a type of study where they look, they take a bunch of people and they look at their genome and they ask the question, what regions of the genome are correlated with whatever trait they're interested in.

So in this case leanness, so what differences between individuals in those. Genetic signatures throughout the genome are correlated with leanness and might explain their leanness. And what they found in this genome wide association study was substantial overlap with the genes that promote

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obesity. What that means is that basically, if you get the opposite version of the gene variants, that cause obesity, then you end up with leanness. So it seems that the mechanisms to a large extent are very similar. You're just getting the other side of the coin from obesity, genetically. However, the overlap is not complete. The genetic overlap is not complete suggesting that there may also be some unique mechanisms to leanness, but we don't really understand those well yet. I think that there are a number of levers, the brain and body can pull to determine body fatness, as I mentioned before. But the main lever that seems to be the most important just generally is calorie intake.

That, if you look at how the brain regulates body fatness in response to weight loss, for example, calorie intake is really the main way that the brain is making up the shortfall, the energy shortfall. And in turn, there are a number of factors that can determine calorie intake. And I think three big ones are hunger, satiety, so satiety, in other words, like satiety or satiation, when you eat, what, how long does it take you before you get to that point where you intuitively want to stop eating? That varies a lot between individuals and then there's the reward drive, which is what the question was alluding to. Which is people just don't aren't that into delicious calorie, dense food. So I suspect low calorie intake is probably the main factor involved in low fat mass in most people, but it may differ by individual and that also plays a role in lower lean mass too, which I think is probably more relevant to what Shane is asking about, because I'm sure that he's not trying to get his clients to bulk up on fat mass or at least I suspect he's not trying to get his clients to bulk up on fat mass, but rather primarily lean mass. And on that topic, I think it's worth noting that although overall calorie intake impacts both fat mass and lean mass, the mechanisms that determine fat mass and lean mass are mostly different.

So fat mass is centrally regulated. In other words, there's that regulatory system in the brain that we call the lipostat that regulates your fat mass, but lean mass does not appear to be centrally regulated. It appears to be, it is genetically regulated, but it's more locally regulated. So your muscles this is, I'm not an expert on this, but this is my understanding is. Your kind of local muscle tissue drive to grow is more a determining factor. And so that's why you can get these people or animals who lose function in the myostatin gene, which is a gene that regulates muscle tissue. And they end up super ripped. That's a gene that affects muscle tissue growth.

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So I think the kind of regulation of those two things is quite different. Although they're both to a degree, responsive to energy intake.

Danny Lennon: Yeah. And I think that is well born out when you look at and compare literature on overfeeding and impacts on fat mass versus some of the literature that looks specifically at muscle hypertrophy. And if you think of increasing caloric intake is almost like a, you can directly match it up with increasing fat mass. So in other words, if someone just were to consume purposely more and more calories in a linear fashion from 2000, three thousand four thousand five thousand, et cetera, calories per day and sustain that purposely over a period of time to higher that calorie intake goes, typically you're going to see a higher degree of fat mass accumulation, unfortunately, that doesn't work for muscle mass.

That it seems that the better way to think of it is simply being permissive that a certain. Slight surplus is supportive of gaining muscle, but doesn't actually drive it directly in the way it drives fat mass. And so that primary anabolic stimulus there is going to be resistance training and actual mechanical tension on the muscle.

And just the calories are supportive of that process. But don't actually directly drive muscle mass. Hence why we can't just. 10,000 calories a day and grow muscle faster than if we're consuming 3000. So I think that speaks exactly to the point you're saying of where they are that they're, those signals are driven from.

That brings us to the end of the questions we're cover. And we're just in on time as well. And as, as we do with these expert AMA sessions, we support a cause for each one of these. And today we are going to be supporting Red Pen Reviews. Stephen could you maybe tell people about red pen reviews if they're not familiar a bit about what's going on and anything else that if they might want to get involved either from consuming or supporting the work that you do there?

Stephan Guyenet: Yeah. Thank you. So Red Pen Reviews publishes the most informative, consistent and unbiased reviews of popular nutrition books available. We developed a unique semi quantitative method. Assigns numerical scores for scientific accuracy, reference accuracy and

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healthfulness. And we apply this method consistently to to the books that we review.

So I view it like taking nutrition book reviews into the 21st century and applying some scientific scientific methods to it. And so right now we have a library of 14 reviews and that's continually expanding. And yeah. Check out our website at redpenreviews.org. We are 501C3 nonprofit. We love to get donations to support our work. And also for anyone who has a master's or hire in nutrition or another relevant field we're always looking for new reviewers. So any yours, so anything you could do, check. Check out the work that we do. And if you like it, anything you can do to spread it, if you want to share it on social media or share it with your friends or family, we'd really appreciate that.

Danny Lennon: Fantastic. And of course, people can find that over on the website and in the show notes in the description box for where you're listening now as well. With that, Dr. Stephen Guyenet, thank you so much for giving up your time for answering all the questions from our subscribers and our audience who no doubt will have got a lot from this. It's very much appreciated and great to talk to you again.

Stephan Guyenet: All right. Thanks, Danny.

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