DANNY LENNON: Let's get into our topic for today, because there's quite a lot to work through. We're going to discuss the regulation of body mass, and we can distinguish maybe later between regulation of weight, we'll look at things that drive fat mass, but this regulation of body mass that is still, I would say, probably very much debated and controversial issue even within obesity research. And there's a number of different plausible models that may explain that, and that you will see differences of opinion on; and whilst there's probably many different variants of that, we're going to discuss three primary models of explanation that you can probably at least fit most explanations under one of these categories. So namely, we're going to talk about the set point model, the settling point model, and the dual intervention point model. So probably the set point model and settling point model are probably the two most well-known and probably most supported at this point with the dual intervention model being more recent, and then kind of proposed probably over the last decade most primarily as we'll likely discuss. There's a lot to dig through here. So before we get into each of those models, specifically, is there anything that you want to

kind of add that kind of sets the stage for much of what we're likely to discuss?

ALAN FLANAGAN: Yeah, I think, with each of these models, the one perhaps overarching theme that is fairly consistent through them, although possibly even more supported now than if you read papers from even 10 years ago, for example, the genetic, potential genetic underpinning of bodyweight and regulation was something that was starting to gather interest. But much of the focus back then was on monogenic genes, so single gene defects like leptin. And it's likely that we're looking at a combination of interactions between genetics, external factors, like the environment and other variables that influence both behaviors and the environment, and then, as it relates to physiology and genetics, as opposed to kind of distilling it down to any one single factor within that. So it's not entirely genetics that explains the phenomena that we have now in terms of population wide levels of adiposity. It's not entirely the environment, because obviously, not everyone becomes overweight or develops obesity, and it's not entirely down to behaviors at all. I think we've certainly exhausted a lot of that in relation to other similar or related subjects that we've covered, and it's not entirely biological, it can't be explained by insulin, for example, which we'll come back to.

So these theories have to be fairly encompassing of a number of different dynamics. And the more plausible ones will inherently account for a lot of those interactions, but it's because of the complexity of each of those potential variables that each model itself does have some flaws, so to speak, in the sense that it still will leave the total picture unexplained. So yeah, it's a complex area, but I think, thinking of it conceptually as an interrelationship between physiology, genetic predispositions, the environments and behaviors, that's kind of one umbrella, and then within which various models seek to provide an explanation by accounting for some

of these factors and the relationships between them.

DANNY LENNON: Yeah, and I think that's very important, given that there's a substantial overlap in some areas of these models, I think it's actually quite common to see, maybe people use one of these labels, when, in fact, they're actually referring to one of the other models or maybe something slightly different from what is actually originally proposed. So hopefully, this adds to getting clear on what we're talking about here. I think probably what's also worth noting is that really these are looking at a long term feedback control of energy intake and energy expenditure, because we know quite clearly, if we look at any single particular day, the inherent matching up of our energy intake and energy expenditure isn't actually super tight in that, on a certain day, we can eat far in excess of what we expend on that individual day, but most data would seem to support that for most people over a long enough timeframe, that matching up of intake and expenditure is actually pretty good in that the differences between those over a long time period are relatively small. But given that it's quite common for most adults in Western societies to gain weight over the course of many years, and over the life course, there is not an exact matching up going on here, and so we're trying to explore it, well, what are these factors that is leading to this change in bodyweight over this period of time. So that's worth something, maybe we can open a tab on and discuss at a later point.

With that, will we maybe get into the set point model to start – so as a kind of brief introduction for people, the set point model, sometimes also referred to as the lipostatic model, I think was first promoted by Kennedy back in the 50s. And this is one that you've probably most heard in relation to someone using that metaphor of a thermostat, right? If you go above or below your set point, then certain processes kick in to bring you back to

that set point. And so, it's an idea that is going to be based on this idea that we have a feedback system controlling bodyweight or body fatness, and it has this reference level or the set point that's going to come up and down to. And I guess, what's also inherently tied to the set point model is leptin, which was discovered early 90s, and this is what's commonly then suggested as this input signal that this system is based on, leptin get secreted by fat cells, and therefore, when leptin production increases with increasing fat mass, that gives a signal that the body can act on. And we can get into some of the details there, and obviously, that's a very simplistic baseline description. There's a lot more to get into, but I think that's a, from an overview, an easy way to conceptualize, when someone says set point model, it's usually in relation to that kind of thermostat idea, I guess.

ALAN FLANAGAN: Yeah, the idea of a feedback loop mechanism is, is what characterizes set point theory; and that feedback mechanism, as you said, going even back to the 1950s, work over that period, had identified the hypothalamus as a potential control center. Some of the work done in animal models at that time, I'm not sure whether you could do any more, but I remember reading about one study where the term used was surgically united rats, and like, does that mean they actually stitched rats together and created a Siamese twin rat. But essentially, surgically, unite animals and then knock out the hypothalamus of one of them, then the other one, with an intact hypothalamus still over consumed food and became obese. So this suggested that the factor that releases to feed back to the hypothalamus was in the circulation, and theories were proposed that that factor could be derived from fat tissue itself, and that would be released from fat tissue into the circulation and provides the signal to the hypothalamus that might regulate energy balance. But it wasn't until 1994 I think that the leptin gene was actually identified, and that was also done in an animal

model, and there is a kind of wave of enthusiasm for the potential implications where set point theory to be correct, then the discovery of leptin was welcomed as something that could potentially provide almost itself a potential solution to increasing adiposity, very high levels of adiposity and obesity.

But interestingly, the provision of exogenous leptin in the form of injections did not have any impact for the most part, with one exception of a very, very rare condition of congenital leptin deficiency. There was a study published, I believe in twins with this very rare condition in whom exogenous leptin – so with this congenital leptin deficiency, they essentially had uncontrollable appetites and overate from the moment they were on solid, so to speak, and became obese and the provision of exogamous leptin reversed that state. But as a general intervention then in people with otherwise normal or high levels of circulating leptin, that same effect wasn't noted, and that was certainly one flaw then in the model of set point theory, because the idea of this kind of "lipostat" it was termed this feedback loop mechanism, as the determinant of the set point would have posited then hypothetically that the actual, if the defect was in this signaling, then you would be expected to see an effect by providing kind of the signal, so to speak.

And interestingly, what this tended to shift in the literature wasn't necessarily a questioning of set point theory itself. Mostly the kind of failure of leptin treatment in humans seems to have kind of generated more of a focus of looking for other defects in this concept of the lipostatic control system. So one of the theories generated as a result of that failure was leptin resistance, similar to the way that there's insulin resistance in diabetes where cells become resistant to the signaling of insulin to uptake glucose, there is a theory posited that leptin resistance can occur, because in people with high levels of adiposity, they have high levels of leptin in the circulation, but clearly the

signal isn't getting through, so perhaps the hypothalamus develops a resistance to leptin. But that also has some flaws in the model and in the support of that model, and just as one example, bariatric surgery doesn't tend to restore leptin sensitivity in humans in the kind of limited evidence we have for that. So the emphasis on leptin alone within that model, is probably insufficient to explain the aspects of overall bodyweight regulation in humans, particularly with the failure of exogenous leptin itself, but also the fact that that there are factors that are independent of just a humoral mediated feedback mechanism to the brain that also influence appetite, energy intake, and, ultimately, energy homeostasis.

DANNY LENNON: Yeah, a couple of really important things that I want to touch back on that you've just brought up and reminded me of, there's also an acute response on any day to day basis, where if you decrease or increase caloric intake on that day, there's also a change in leptin level. So it's able to essentially give a signal back to the brain of energy stores both in acute and chronic sense. And so, that is where it plays in – one of the things that that you brought up, Alan was – two things actually, that I think tie in nicely here, one is on genetics, and then the other is on you brought up the hypothalamus, and its central role here. And so, with leptin resistance, for example, one of the things that gets tied into that is that there's inflammation going on at the hypothalamus, and this hypothalamic inflammation is some sort of injury that can tie into this leptin resistance. And one of the other things that we know from GWAS studies or genome-wide association studies, is that increasingly over time, it seems more and more that the genes of interest are indicating that it's the brain that is this main regulator here and not fat tissue as it would have been at least hypothesized previously before, and it seems more and more of the focus is now clearly on the brain is where the issue is at.

So I think it brings up a whole host of interesting questions from there. But like you note, one of the shortcomings, I guess, of this set point model, if it's looked in the strictest sense of this being a physiological feedback is that that's all that it accounts for, and therefore there are some potential areas that it doesn't address. And I know, for example, Dr. John Speakman, who we'll probably bring up later in relation to some of the other models, has kind of said, well, look, if this was explanatory, then how can we have this current prevalence of obesity, this can't be a complete explanation, because it's not accounting for those non-biological drives on people's body mass, I guess, such as lifestyle and behavior.

ALAN FLANAGAN: It also assumes that there is just, weather in response to kind of overfeeding or underfeeding, there would be this kind of set point that's fairly arbitrary at which there would be a settling, that this new kind of steady state would be achieved, and so, it's the hypothesis that okay, well, the environment and behaviors is what tips towards positive energy balance in a kind of acute sense. And then over time, you have this interaction then with genes and physiology that would create this new steady state, so to speak, at a higher weight, for example, or, that that would be in the opposite direction, resistant to weight loss, such that whatever point of departure in terms of bodyweight and composition an individual left offs and say loses 10 kilos, that there would be this fight to get back to where body left off. But I guess, some of the issues with that is well, why wouldn't it just keep continue going in one direction or the other, what would be the mechanisms that actually kick in to prevent that from happening.

So there's still some sort of regulatory process involved in the creation of some sort of new steady state and internal control or endogenous control of energy intake. It's not entirely mediated by just the level of the brain, for example. We know that factors like the

properties of food can influence satiety and gastrointestinal factors as well, in response to meal intake. So again, it's this combination of how do biological factors interaction with external factors to control food intake, why would there be a set point established at a certain level, and not a level beyond that, or why wouldn't an individual just continue to gain weight. So I think that the flaw within just set point theory alone is the idea that the feedback loop mechanism proposed is a proportional feedback loop mechanism that would constantly seek to have this level of regulation at a weight that say, for example, the body desire, so to speak. But we can see compensatory, the Minnesota Starvation Experiment where the rebound weight gain was actually correlated with an overshoot. So it wasn't a return to a previous set point, it was the establishment almost of a new set point beyond that.

So yeah, I think some of the idea of any feedback loop mechanism, if it relates to a homeostatic process in the body, is defined by kind of maintenance within a certain range. And that's not what we tend to see with weight loss in response to underfeeding, or, weight gain in response to overfeeding, because there are other physiological processes involved, like adaptive thermogenesis and compensation processes that happen in response to over or under feeding.

DANNY LENNON: Yeah, that's a really interesting point, because if someone is applying this model very strictly, and then they say, well, it's also possible due to behavioral or environmental factors that your set point can change, then at what point does that completely become meaningless in the context of having an actual set point model of saying there is this set point, or, if it can just change up and down in response to environmental and behavioral factors, then at certain point it no longer becomes we have a set point, right?

ALAN FLANAGAN: Predetermined, yeah.

DANNY LENNON: So it kind of, in of itself, is a way to maybe try and grasp onto it, as opposed to acknowledging that there may be something else could be explanatory here. I think one of the interesting things, at least, because one of the questions that often comes up, if there's a discussion, a set point is, well, if someone loses bodyweight, and then maintains that lower bodyweight for a certain period of time, can they kind of reset to this lower set point and at least of the studies that I've seen that have maybe shed light on this, that doesn't seem to be the case, that just simply keeping your bodyweight lower doesn't indicate that you've now reached some new set point, so to speak.

ALAN FLANAGAN: New set point, yeah, and there's continued responses, physiological responses to attempting to maintain a lower bodyweight that we know from the wider kind of weight loss literature and the well documented kind of lack of long term overall kind of average success in interventions, the relationship with behaviors, but even the relationship with the physiological adaptive responses. So set point theory holds that obviously, there's this kind of predetermined holding of the bodyweight that the body will fight to, that then only appears to be reset going upwards, which is a limitation on the kind of the theory of the model. It's basically saying that, yes, we can reestablish a new equilibrium at a set point that is a higher bodyweight. So we increase bodyweight, and then we have this new set point there, and then the body will guard this new higher set point. But there's little evidence that that can happen in the opposite direction. And if the set point theory was true that we will be able to establish a new set point, then it should hold true in the other direction, and if you lost weight, you could establish this new set point instead that increases in hunger, decreases in energy expenditure. And we know that phenomena like adaptive thermogenesis, where someone who reaches a new lower bodyweight, may have

to maintain their weight at a lower daily energy intake than an individual naturally at that bodyweight, for example. And so, these differences would tend to suggest that, although you could argue, well, that's evidence for a set point because the body is fighting back to its set point, but a big part of set point theory is the idea that, well, actually you can create a new set point at a higher bodyweight. But if this was a homeostatic kind of feedback loop mechanism, that should hold true within any range, and this is basically saying it only holds true in one direction.

DANNY LENNON: Before we move on, is there anything that you think is worth mentioning on set point model right now – We can obviously come back to it as a recap at the end, but for now, is there anything we should add before moving to settling point model?

ALAN FLANAGAN: Not that I can think of, I think there's things that might come up.

DANNY LENNON: Perfect. Yeah. I think that sets us up quite nicely, because I think most notably, what we've discussed so far is with the set point model, there's these proposed feedback mechanisms that will have an impact on energy intake and also energy expenditure. The settling point model then, as an alternative hypothesis, is interesting, because this seems to pretty much solely rely on adaptations in energy expenditure to explain this bodyweight regulation; rather than having a fixed point, here, there seems to be this adaptation or change in energy expenditure, that, in response to either decrease or increase in bodyweight and therefore energy intake, because of a change in energy expenditure, eventually, weight settles at a certain point. So, for example, maybe to kind of compare it with the set point model, because I think that's probably the easiest way to conceptualize it, if in both cases, from an energy balance perspective, we're talking at weight maintenance, we have an average of energy intake and energy

expenditure being roughly equal, in both the set point model and the settling point model, they both kind of propose that energy expenditure is a function of body mass.

So as weight increases, with increasing weight we get an increase in energy expenditure as a way to – as an adaptation to that; and the same, as you decrease bodyweight, you have this energy expenditure decrease as well. As we've just discussed with the set point model, that would propose that energy intake is also a function of bodyweight, but kind of works in an inverse sense. So as someone increases their bodyweight above their set point, these feedback mechanisms kick in to decrease their energy intake with the goal of bringing their bodyweight back down to that set point that has been set up. Similarly, if someone goes below that set point, feedback mechanisms kick in to get their calorie intake increasing with the goal of bringing weight back up. With the settling point model that proposes that energy intake is actually not a function of bodyweight, so it's independent of bodyweight; so, as weight, say, is increased, it doesn't have this same direct impact on energy intake, but rather it's energy expenditure that increases in response to the increased weight. And so eventually, it's going to increase to a level where it again matches energy intake, and therefore weight gain stops, and their weight settles at this point, hence, the kind of settling point idea. So I think that seems to be the major distinguishing factor between this that, as opposed to the set point model is actually no, we need to think of energy intake independently, and it's actually this adaptation of energy expenditure that will lead to someone's weight settling at this certain point when energy expenditure matches energy intake again, if that has hopefully been explained clearly.

ALAN FLANAGAN: Yeah, exactly. And that's why this model then also has its own potential flaws, even compared to set point model. So with this model, for

example, if you were dieting, the kind of increase in hunger and drive to eat and to overeat, that can occur with energy restriction, particularly over time, that would not be predicted to occur with a settling point. You would simply produce energy to X amount, and you would have this settling at this new level of the adaptation of energy expenditure to create this new level of energy balance. So you wouldn't be expected to necessarily experience some of the kind of negative consequences in terms of appetite and food seeking behavior that occur with diet, if it was only entirely a relationship between a resettling of energy expenditure and energy intake to match new a settled point of energy balance. And so that is a flaw with that model that would be something that points more to set point theory than settling point theory because that's where we see this defense of against weight loss, so to speak – I was going to say defense of a higher bodyweight, but that's not always entirely explained by set point theory either.

So just as a contrast between the two, as we highlighted with set point theory someone might lose weight, yes, they might have adaptive compensatory mechanisms in response to that that drive regain, but they may not regain all of the weight loss. They don't necessarily go back to the exact bodyweight they left off of, even in the opposite direction, if there's a total overshoot, they don't go entirely back. So there's something against set point alone within that, but with settling point, the fact that there are these compensatory mechanisms is itself kind of degree of evidence against the idea that that settling point entirely explains the changes in bodyweight that we are talking about. So you also, with this model, would not be expected to see compensatory changes in energy expenditure like adaptive thermogenesis, yet we do see that. So there are factors that would kind of speak against settling point theory, even though there are some aspects to settling point theory that do have kind of more merit than set point theory.

So they both have pros and cons in terms of trying to explain some of these phenomena.

DANNY LENNON: Yeah, and for people who are interested, there's actually a nice paper by Hall and Guo I think, I'm not sure if I'm getting the pronunciation correct, 2017 paper, I think it's like a meta-analysis of 30 something controlled feeding studies. And in that they tried to see, okay, is there actually one of these models that fits that data better, and at least there that would, again, seem to speak to that point, that of the two, the set point model is probably fitting the responses there better than the settling point model, at least, based on the data that they analyzed. So that is an interesting one to look over. I think the interesting or the way to maybe segue into the final model is that given these shortcomings of each of the two models we've discussed that you've just outlined, and we've clearly already mentioned that we're talking about this from within an energy balance framework, but that there's not only these physiological mechanisms that we have to account for, but there's also these like biopsychosocial factors that are going to have a role here too. And what has been proposed in a kind of what I find a quite compelling and really useful way, primarily by John Speakman, as we mentioned, is this dual intervention point model.

So this idea that there is what's called a lower intervention level and an upper intervention level, and this kind of zone of indifference between them that essentially, between that lower and upper intervention level, the main thing that's at play here is actually those environmental and behavioral factors, that then can drive someone to say, increase their bodyweight, and it will stay going up, until it hits the upper intervention point. And it's only once someone's bodyweight goes beyond the upper intervention point, that then these physiological inbuilt feedback mechanisms are strong enough to kick in and actually bring weight back down and stop that weight gain

happening. And so, that is a way to try and explain that you can see these changes within a certain range, but once bodyweight goes, say, beyond – above the upper intervention level or below the lower intervention level, then these physiological processes become more important. And yeah, I think that's my take on how it should be explained, if there's anything I'm missing though.

ALAN FLANAGAN: This idea relates to, and the development of it relates to something listeners may have heard of, if they're interested in this, which is the thrifty gene hypothesis. Thrifty gene hypothesis, was a kind of evolutionary theory that perhaps conditions like increasing adiposity, even the insulin resistance that occur with type 2 diabetes, because it's often stated that diabetes was recognized by the ancient Greeks by sweet urine, I'm not sure what diagnostics had to occur for that observation to enter the epidemiological lore, but this idea was that we would be almost predisposed to preferentially store fat, because during evolution, we would have been exposed to periods of foods and energy supply unavailability perhaps, entirely in the course of a famine, for example, or, even just seasonal food unpredictability in terms of access, and that this would have potentially selected for genes that were highly efficient and effective at gathering stored energy and storing it on the body to protect against any potential famine and make sure that we could survive a period of no or low food availability. There was a lot of initial attraction to that concept when it emerged, and it was positive then that those ancient wouldn't have necessarily always led to increasing adiposity or obesity at the time because you would have not had the level of food abundance that we do in the modern world, but when you dump this old evolutionary genetic makeup into the modern hyperpalatable western food environment, then you have this interaction between genes and environment that precipitates obesity.

But that itself has a number of its own flaws just in isolation. It's not clear necessarily that food supply failure, like a famine, although certainly common at periods, different periods over history, they wouldn't have occurred with the level of frequency and consistency that may have allowed for that kind of genetic adaptation, which does not just occur within a generation or two. The other part of it is that evidence from kind of more modern or recent famines doesn't suggest that people necessarily become obese in response to a period of food, kind of, restriction or lack of availability, although there is also some evidence to counter that that came from the Dutch famine cohort, 1944, there was a famine in Holland, and there's some evidence of genetic programming for obesity as a result of maternal malnutrition, it's a hypothesis, I should stress. But on the whole, there isn't really strong evidence, first and foremost, that again complete catastrophic foods supply failure would have happened with such frequency so as to cause genetic adaptations to that response. And second, like I said, there is some more modern evidence from such tragedies that would not even modern hunter gatherer populations don't necessarily show the kind of rapid onset of obesity in response to unpredictable food availability. The thrifty gene hypothesis had some potential flaws, and I think it was really from that that that Speakman seems to have developed the dual intervention model and the concept of a drifty gene hypothesis.

DANNY LENNON: Yeah, I think it was in maybe a lecture or a Q&A, I can't remember where exactly, that I remember listening to kind of discuss a really nice way of thinking through how robust of a hypothesis is the thrifty gene hypothesis. And so, he kind of references, well, there's this idea that it seems quite intuitive that those with more body fat will survive for longer during starvation, which gives this kind of evolutionary pressure that people refer to. And he says, indeed, if you were to look at trials where people are under medical supervision,

and they have obesity, and they are basically just forced to consume no food, you see these case studies published where people can go say beyond a year without consuming anything, and he kind of nicely contrasts that with data you would see on people who go on a hunger strike protest, who are not in an obese category, and you typically see people who will die within 40-50 days. But his point is that when you look at famines, that would have occurred over time, they are not really characterized by a complete absence of food, as in these people going a year plus with zero food. What actually happens is that there's a mass shortage, people move and go out then in search of acquiring resources. And his point is that what ends up happening is that there's not a difference in survival based on who is lean and who has obesity, but rather, it's disproportionately those who are not able to acquire those resources, so the very young, less than five, and then the elderly, And so, it's along those lines, and then given that the elderly are really not in the active part of passing on genes at this point, it even takes further away from this idea, that's an evolutionary genetic pressure that is causing it. So I think that's a – I've heard him kind of lay out that case, and that seems to be quite interesting.

ALAN FLANAGAN: Yeah, and so, with the jewel intervention point, like you said, there's this kind of upper and lower intervention, the lower intervention does relate to food unpredictability, and the risk of starvation, and that's a lower intervention against low adiposity. And so, there's a degree of protection against that, but it's not in his kind of concept, it's not necessarily food – the effect of food, unpredictability, as you say, but it's more the potential for like an infectious disease or something like that. So with the drifty gene hypothesis that he's come up with is that the kind of upper intervention point, sorry, so just to clarify, the upper intervention point, the lower intervention point is the protection against lower adiposity, the upper intervention

point is as against the risk of suffering from predation, so that humans would have been in an environment where predators were a daily part of life. The proverbial saber toothed tiger could have been a problem for navigating or hunting or anything like this, that risk would have served an evolutionary purpose to protect against high levels of adiposity. Right? And that if you had high levels of body fat, you're not going to be very effective against the said saber-toothed tiger in terms of running away, but because over the period of human evolution, establishment of communities, wider communities of hunter gatherers, and the evolution of human tools, in particular, hunting weapons, and particularly throwing projectile weapons that could then keep things at bay, that the risk of predation started to become lower and lower. And because the risk of predation started to become lower, then there was still the genetic imprint of a protection against kind of higher adiposity, but that those genes then would have kind of not been active for that time period, but they would have still been set in the genetic imprint, so to speak, and they would have drifted in time then. So this is the kind of the drifty gene hypothesis.

So in this, it's saying that, well, food unpredictability and starvation were probably insignificant factors for fat storage, the main force that would have driven up fat storage is risk of disease, and to survive periods of pathogen induced anorexia. So you know you get infected and you're vomiting or diarrhea and these kind of things, and that weight loss accompanying that infection was the primary threat to life, not necessarily food unpredictability. And so basically, it's saying that, well, we have these two independent intervention points, this upper and lower intervention points, the lower intervention point, protecting against too low adiposity is probably related to leptin signaling and some of the set point theories, but it doesn't explain it entirely. And so, for this upper protection against excess adiposity, that was likely

protection against accumulating too much body fat, because you needed to stay lighter to avoid predation. But that once that need was lost, that genetic imprint was still there, so that's selecting against too high adiposity at the other end. These two are then called the dual intervention point models.

DANNY LENNON: Yeah, and that that speaks to why it does a good job of tying a lot of these strands together. As you note there, I think Speakman outlines that at that lower intervention point, that leptin very much is a player, that when you drift below it, then it has this very strong signal, whereas it seems that leptin isn't really much of a player at the upper intervention point. And I think, again, as you've outlined well there for people thinking of this intraindividual variation we may see between people of where the upper intervention point is, can be based on this kind of genetic evolutionary pressure that Alan has outlined, where it has drifted higher over time independently of that lower intervention point, and for some people it may have, they may have a higher upper intervention point. And so, maybe like as an example of how this fits just in case people are unfamiliar to give some completely arbitrary and made up numbers, let's say, that I have a lower intervention point of 74 kilograms body mass, and an upper of 80 kilograms body mass, the movement between 74 and 80 is dictated by those environmental and behavioral factors, so things in relation to my lifestyle, activity, food choice, etc. may see, let's say, my bodyweight increase up and up without this feedback to bring it back down, up until it gets to around that 80 kilogram mark. And when it goes beyond that, then there's this very strong feedback pressure physiologically to impact my intake and/or expenditure to bring kind of bodyweight back in check, so to speak.

And so, it does a nice job of having both of those aspects, and I think one example that again Speakman himself may have mentioned, that kind of highlights how this kind of fits

anecdotally what we see is most commonly we can see people, let's say, put on a couple of kilograms in periods of time where we over-consume, let's say, the holiday season is most notably where you see a lot of data on that. And after gaining some of that weight, a lot of the time there's not a compensation physiologically to bring that back down, because it may be that for that individual, that couple of kilos weight gain is still within those parameters. It's still below the upper intervention point, where you see extreme examples, let's say, either a force overfeeding, or maybe a more clear example is, let's say, a bodybuilder doing a contest prep. After you finish a contest prep, someone has got so lean, and they are so far below their lower intervention level, that those physiological mechanisms are so incredibly strong, that that's what everyone will report, there's almost no way you cannot go and consume more food and put weight back on. So just hopefully that makes some degree of sense for people.

ALAN FLANAGAN: Yeah, I think that's actually really helpful, because, and then it allows us to tie back into the other models of settling and set point, because if you have the hypothetical scenario that you described, that you've got an individual with a kind of lower intervention point of 74, and an upper intervention point of 80 kilos, well, then what this can also argue for is that rather than a set point, even though there is some support for some of the aspects of the set points in terms of, like you mentioned, for the lower intervention point, leptin signaling and otherwise in the Hall and Guo meta-analysis of the feeding studies that, yeah, these compensatory changes will be more consistent with set point. But that's not at the expense of settling point, because what you would have within and between these dual intervention points, is various settling points, a number of different settling points. And so, there's potentially within jewel intervention theory, the opportunity to actually marry some aspects of both settling points and set points

versus set points or comparative set point versus settling point.

I've seen a paper by Manfred Mueller and Anja Bosy-Westphal, a couple of German researchers who I think are based in Kiel, in Germany; and they've produced a couple of nice reviews of set point theory, and one of their more recent ones – by recent, I mean, in the research center, within the last 10 years, was actually proposing that it's probably set and settling points. And they weren't addressing that in the context, necessarily of dual intervention theory, but I do think that the concept of an upper and lower intervention point does allow us to explain some of the aspects of both set and settling points theory for which there's at least some evidence in support off.

DANNY LENNON: To kind of wrap us up, and where that leaves us, or what kind of takeaways we get, given that we've kind of walked through those three models, and also noting that there is a lot of kind of nuance within each and there's certainly, I would say, not a complete consensus within obesity research of what exactly is most explanatory, where do you feel are the kind of, or, what do you feel are the key things that people should note to come away with, from what we've discussed, or, if there's anything additionally that we haven't brought up yet, that you think is worth tying in, you can add that too?

ALAN FLANAGAN: I think the first thing is that the kind of internal or endogenous control of energy intake in humans is still not entirely or fully characterized, but there are still aspects of neuronal regulation of appetite and energy intake, and even some of the more kind of the physical properties of foods, even with, say, Kevin Hall's metabolic ward study comparing the kind of low fat, higher carbohydrate versus high carb, low fat study, I mean, those are even factors that go into energy balance that are somewhat independent of some of these, they

are impacting certain of these processes, but they're often kind of not accounted for in these models, which focus very much on hormonal signaling, neuronal signaling, feedback mechanisms, energy expenditure, and less on actual kind of physical properties of food and the effect of gastric emptying, satiety, and all of these kind of related processes. So, I think the first caveat is there's probably a lot of digging still to do in this area of research overall, and I don't think anyone would – I don't think that's a controversial statement.

And then I think it's important to, you know, these are models attempting to explain a phenomenon, they have respective strengths and limitations, their strengths do have plausible support, but their limitations are often sufficient to counter the model itself in one way, but they do have aspects to them that can be supported by reference to the literature. And if we're talking about, for example, the effect of leptin on appetite, in the context of extreme dieting or low, going beyond that low set point, if it exists, that low intervention point, each of them have aspects that do provide some explanation, but they don't, in and of themselves, explain or fully characterize the phenomenon in entirety, and I think that's probably the best way to think about them is not as absolute theories, but as theories that provide a certain explanation for a certain contribution of some factors.

DANNY LENNON: Yeah, for sure. And, as you mentioned, appetite, I think, the whole human appetite system is just fascinating to think about, and I know, particularly some of the work that's come out of University of Leeds, Mark Hopkins and John Blundell's group has been really fascinating, and there's a lovely kind of paper they did in 2019, I think Nuno Casanova is the lead author on it, but they discuss, essentially, how it's a biopsychosocial phenomenon. And a lot of those points kind of fit into what we've discussed here, particularly towards the tail end of this conversation of appetite doesn't

really appear to be under very tight homeostatic control, but that an energy deficit and weight loss, those things can actually alter the strength of the homeostatic feedback. So again, that might give some credence to, depending on how far weight moves, that there may be a difference in how strongly these things are regulated, but that there is much more going on than just a simple physiological control of one these parameters.

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