DANNY LENNON: Mark, thank you so much for taking the time to join me on the podcast today.

MARK HOPKINS: You're more than welcome Danny, pleasure to speak to you.

DANNY LENNON: Yeah, a lot of things I would love to get into today and I think, as I may have mentioned to you over some of our email correspondence, your work has been something I've read for several years at this point, and some of the publications have been incredibly important, and I would love to dig into some of the details of those. But before that if we take a step back just to give people some context about your background, how would you describe the area of research you're focused on?

MARK HOPKINS: So I'm really interested in some of the responses that you see to diet and exercising and induced weight loss. So I'm kind of interested in some of the metabolic responses but also some of the behavioral responses around kind of appetite and food intake you see. And I suppose my main interest is really how the interaction between these two, so how does physiology influence behavior within a weight loss setting and potentially how does that influence weight loss success and weight loss maintenance, etc. And my original

background was in exercise physiology, so much of my kind of early work was around using exercise as a weight loss tool, but now moving more towards kind of dieting and some of the responses that we see there.

DANNY LENNON: Yeah, and I think there's many different routes we could go, but one, I think, may be to start us off, that might be useful is if we talk a bit about adaptive thermogenesis and kind of get into some of that interplay between energy intake and energy expenditure that you just mentioned. So how should we think about or define adaptive thermogenesis and how does this let us think about that relationship between energy intake and expenditure?

MARK HOPKINS: So when we talk about adaptive thermogenesis, what we're talking about here is a reduction in energy expenditure, typically resting metabolic rate that can't be explained by changes in body composition. So when we have a period of weight loss, clearly we lose fat mass and fat free mass, and we would expect resting metabolic rate to decline as a result because we're losing metabolically active tissue. But what researchers have also shown is that your resting metabolic rate drops to a level below which can be explained by the changes in body composition, so there seems to be an additional reduction in energy expenditure that can't be accounted for by changes in body composition, and that's thought to be a sort of auto regulator response that perhaps resists sustained periods of energy deficit.

DANNY LENNON: And so on the flip side of that, in an overfeeding situation, do we have that same degree of adaptation going on?

MARK HOPKINS: We do see responses to overfeed in both in energy expenditure and energy intake, but my view is that the responses are not as pronounced in terms of magnitude so when people do overfeed, you will see an increase in energy expenditure and changes in hunger and appetite, but I view energy balance as being

asymmetrical. So when people are in energy deficit, you see quite pronounced and potent responses to try and bring people back into energy balance. But when people overconsume and are in energy surfeit, you don't see that same magnitude of compensated response to try and bring people back down into energy balance.

DANNY LENNON: When we think about some of these metabolic adaptations that happen in response to say a hypocaloric diet as is usually discussed, one area I think that maybe you and your work can shed light on is do those metabolic adaptations happen in the same way if we induce hypochlorous via dietary restriction versus if we did that through increased exercises, are there differences that we see in those adaptive responses?

MARK HOPKINS: Yeah, that's a great question. There's actually not too much research on that area, there are some studies that have tried to create a matched energy deficit through diet and exercise, and what they tend to find is that the degree of compensation, when they use exercise to induce the energy deficit, is smaller than with dietary induced energy deficits. So you tend to see a smaller kind of compensatory drive with the exercise than diet. But as I said, that's not based on a large body of evidence, we're probably talking a handful of studies that have really kind of examined that. But there does seem to be some evidence that exercising isn't associated perhaps with the same level of compensation as diet at least in the short term.

DANNY LENNON: Is there any proposed mechanisms by which people are hypothesizing there could be a difference or that we would see some differences?

MARK HOPKINS: It's difficult to say. Some people have suggested it might be more kind of psychological around kind of feelings of restriction of energy with the diet, and I think there is some kind of evidence looking at differences in some of the hormonal

responses and appetite related peptides, and their responses may differ somewhat but it's difficult to say at the moment I think.

DANNY LENNON: One that some people at least have talked about or thought through is if we have a hypocaloric dieting situation and compare where there is exercise and a decent amount of exercise compared to none, where someone is just using calorie restriction to induce that deficit, that maybe if someone loses lean body mass over time that can play a role for a few different reasons, beyond that just being metabolically active tissue, is there anything that suggests that lean body mass loss could influence hunger or appetite, either of those hormones or behaviorally?

MARK HOPKINS: Yeah, so this is a research question that we've been examining now for the last four or five years. Initially, we looked at data in people in energy balance and weight stability and what we're showing is that fat free mass and resting metabolic rates seem to be important drivers of hunger and energy intake, so they are contributing to this kind of excited drive or motivation to consume food, and that works alongside some of the kind of inhibitory factors that we see from the gastrointestinal tract. In terms of what happens during periods of weight loss when we're getting these kind of dynamic changes in fat free mass is a little bit harder to say. There are a couple of studies and one in particular is the kind of Ancel Keys semi-starvation study that have linked losses in fat free mass to changes in appetite; and there's some evidence that suggests that greater losses in fat free mass during weight loss may promote increases of hunger in response, but we're kind of dealing with a handful of studies; and actually when you look at the degree of weight loss, it's very severe weight loss and it's probably not reflective of the typical kind of diets that you see in real world situations.

DANNY LENNON: Yeah. One of those areas that I know that your group has published on is looking at some of

these weight loss responses to different exercise interventions, and one of the key observations that we have is this massive inter-individual variation between different people in terms of their response to that intervention in terms of weight loss. One thing that I think probably people would logically jump to first was, oh, maybe that's just because people are sticking to exercise programs differently, but it seems that your work has suggested it's not just down to adherence to certain interventions, there's something else going on with that variation. Can you maybe just expand a bit on that?

MARK HOPKINS: Yeah, certainly. So clearly any adherence to an exercise intervention is going to influence the responses in body composition that you see. But what we try to look at in studies going back 10 years or so now is what happens if you clamp adherence. So we take a group of individuals and we get them to exercise under supervised conditions and we get them to perform the same volume and intensity of exercise and we have objective measures of that, and even under those kind of highly standardized conditions where we can objectively say people are expending the same amount of energy, we see a large variation in a number of physiological and behavioral kind of outcomes and body weight is one of those responses that we see. So it's pretty well-established now that people respond very differently to a whole range of different interventions and certainly you see a market variation in body weight responses to exercise interventions.

DANNY LENNON: And that kind of leads me into one of the areas that has been most interesting to look at with some of the work coming from your lab, looking at compensator eating or how certain exercise sessions may influence feeding afterwards. First of all, how should, again, people think of or define this idea of compensator eating?

MARK HOPKINS: So when we're talking about compensator eating, we're looking at changes in energy intake above, I suppose, habitual levels as a result of a single bout of exercise or a more prolonged period of exercise. And, I suppose, the first thing to think about when we talk about this research is important to make the distinction about research that looks at the responses to a single bout of exercise, so they might get someone on a treadmill or a bike for 45 minutes and look at the intake and appetite responses over their following 12 or 24 hours. But compare that to research that looks at long term changes in appetite and energy intake. So if we get people to exercise regularly for three months, six months, what are the responses in appetite and energy intake? Because I think that's a really important distinction to make because the key exercise bouts are great from a mechanistic standpoint, you can control the study well and you can create a nice environment where you can look at changes in hunger and food intake and perhaps some of the gastrointestinal peptides. But unfortunately, I don't think that necessarily represents the responses you see to long term exercise, and if we're looking at this in relation to weight management, well, that's the type of exercise that you will prescribe to someone if they're looking to lose weight; and getting someone to exercise regularly for 12 weeks, I think, it imparts a much greater physiological stress or demand on the body, so I think we have to be a little bit careful in drawing conclusions from acute based exercise studies to those that look at more longer-term interventions.

DANNY LENNON: For sure. So potentially, either there could be transient changes that happen acutely that don't persist or there could be adaptations over the longer term that don't show up early on.

MARK HOPKINS: Yeah, certainly. As I said, I think what we find is within the literature, someone does a single bout of exercise, evidence indicates that there's no automatic increase in hunger or food intake

to compensate for the energy expenditure in the exercise bar. But then when you contrast that to more long-term studies, that's when we start to see some evidence of compensation energy intake. And when people start to exercise on a regular basis for three to six months, we tend to see that energy intake increases and seems to track energy expenditure, and it's important to say that that increase in energy intake is partial and doesn't fully offset the energy expenditure exercise and people are still a negative efficiency deficit. But there's certainly evidence indicating that over the longer term, energy intake does begin to track increases in energy expenditure that we can induce through exercise.

DANNY LENNON: So one of the interesting things about that, and I remember seeing this a while back in one of the papers you published which had a kind of wonderful graph plotting activity levels versus caloric intake, and like you say, from levels of maybe light activity and going upwards for someone being more and more generally active, you tend to see this increased caloric intake which makes some kind of sense, right, that we have this linear increase because someone is expending more energy. But it also showed from going from light levels activity down to completely sedentary, if I remember it correctly, you kind of see a tick back upwards in caloric intake, suggesting that at sedentary levels of activity, there's an inability to be able to regulate caloric intake in the same way. Again, you can correct me if I'm not explaining any of that correctly, but this idea that there's a zone that becomes unregulated or we don't have the same ability to regulate chloric intake to match up to our expenditure once activity drops below a certain level, do I have that in some way correct and can you maybe explain a bit more what's going on?

MARK HOPKINS: Yeah, I think you've done a great job on explaining it. So this is kind of work that I suppose my mentor John Blundell has been developing over the last 10 years or so and a

post-doctorate fellow is now really developing in it, and it looks what we have turned a J-shaped relationship between physical activity and energy intake. So going back to some kind of work in the 1950s by John Mayer and Benjy in mill workers, what they showed is those individuals with high occupational physical activity had elevated levels of energy intake and there seemed to be a kind of tight relationship between the energy that they expended and the energy they were consuming. But at the other end of the spectrum in those individuals that were kind of doing office based jobs which were for all intents and purposes sedentary, they also showed elevated levels of energy intake, but at a period where they had very low levels of energy expenditure. And John Blundell sort of took that research and tried to develop a theoretical framework around that and came up with this idea that appetite has regulated and nonregulated zones, and what we have proposed is that those with higher levels of physical activity exist in this regulated appetite zone. By that we mean that there's this tight coupling between their energy they expend and the amount of, or the energy that they consume and that kind of tight coupling helps to maintain a healthy bodyweight if you like. But at the other end of the spectrum we have this nonregulated appetite zone reach, I suppose, dysregulated appetite control. So those who are habitually inactive or centered, we tend to find that energy intake far exceeds their energy needs or their energy expenditure. So these individuals are overconsuming relative to their energy needs, so we have this kind of J-shaped relationship between intake and expenditure where we have elevated levels of intake at both ends of the spectrum, but I think that the mechanisms and reasons why that elevated intake exists is different depending on whether you're a sedentary individual or an active individual.

DANNY LENNON: Yeah, that's really fascinating because it kind of gives us an insight into, number one, we see that trying to have someone at, let's say, energy

balance is not necessarily equal in all circumstances if we have someone that does no physical activity and therefore has a relatively low energy expenditure than trying to match up an energy intake pragmatically might be more difficult compared to someone else who eats a lot more food, but is a lot more active because of it, and I think the work you just mentioned at least gives us some insight to what might be going in on that particular case, and it's this idea of more energy flux going on maybe allow us to be better able to regulate that seems like an interesting and quite logical hypothesis as well.

MARK HOPKINS: Yeah, I sort of view it when the physical active individuals of having kind of improved appetite control or sensitivity, and they seem to be able to respond better to internal physiological cues in response to meal consumption, and better able for some reason to kind of balance their intake relative to their expenditure. We're not 100% sure on the mechanisms behind that at the moment, and that's what the research is looking at, at the moment. But there is evidence to suggest that when you take sedentary individuals and put them through a training program, there are changes in some of the appetite related hormones that may promote increased association after a meal, so there are a number of physiological responses that we see to exercise training that seem to map onto this kind of J-shaped curve that we look at.

DANNY LENNON: Yeah, and I guess it would or we could presume that there's probably many of these things going on at the same time, it's probably unlikely I would guess, and I could be wrong, that it comes down to one specific hormone or mechanism, but it could be changes in all various different types of appetite hormones, maybe it's sensitivity we see to these different hormones, and then like you mentioned earlier Mark, we should probably not only just look at this physiological impact but also behavioral impacts of this; and of course when we

presume having regular physical activity might do to someone's behaviors outside of that, that probably could account for some component, I guess.

MARK HOPKINS: Yeah, that's a great point. I think when we talk about food intake and energy intake, it's important to remember that ultimately it's a behavior, so there clearly are some underlying physiological cues that perhaps promote sensations of hunger and fullness and food intake. But the food that you consume and put in your mouth is ultimately a behavioral act, so there are clearly cognitive and environmental issues as well; and personally, I think, one of the kind of limitations of the air is that as scientists we tend to stick to our own little domain, so as a physiologist, I might look at the responses in peptides but I don't then also look at some of these psychological kind of responses. So we tend to sort of operate in a kind of silo type environment. And I think when we're looking at appetite and food intake and what determines those it's really important to try and look at the kind of interrelationships between the physiology and behavior because I think that's really key to understanding what people eat and why they're consuming those particular foods.

DANNY LENNON: Yeah, and I guess the difficulty is actually going and doing that because it sounds maybe simple to some people listening of, well, we take both these physiological and behavioral aspects into account, but doing that through research and accounting for both of those things and this kind of big overview model is incredibly complex and difficult, I don't even know how you'd start going about doing that. What ways do you think there are going forward for groups of researchers to start piecing this together and move away from being stuck within those silos that you just mentioned?

MARK HOPKINS: I think initially it's important to come up with, I suppose, a hypothetical framework that you're working in and think about what are the

potential mechanisms, whether they're biological or psychological that are going to influence the outcome that you're looking at. And we know with energy balance, which is what I'm particularly interested in that there are both physiological and behavioral responses, so we can start to, I suppose, identify the key methods around them, so in terms of energy expenditure, we can use metabolic carts for the resting metabolic rate and we can use things like doubly labelled water or accelerometers to look at the free-living total daily energy expenditure, and we can kind of tally that up with measures of body composition; and then we're fortunate here at Leeds with a very strong appetite focus to be able to also map in a range of behavioral kind of measures and psychological measures around the food intake. So we often use test meal type designs where we get people to consume foods within a lab and we look at some of the psychological appetite responses to those and sometimes some of the appetite related hormone responses to those foods. And we can try and integrate that into a larger kind of framework around long term exercise.

DANNY LENNON: One thing I did want to pull back on in relation to the compensatory eating was a recent publication I think from earlier this year where you would discuss the potential for hepatic glycogen availability to potentially play some role in compensatory eating after exercise. Can you maybe explain some of that hypothesis that you had mentioned in that paper?

MARK HOPKINS: It goes back to some work from the early 90s looking at what was known as the glucostatic theory that really kind of postulated that because the amount of glycogen stored in the body is relatively limited, and particularly in comparison to the amount of fat stored, when we see depletion of glycogen whether that be in the muscle or within the liver, that produces some form of compensated response to try and restore those glycogen stores, so now we know glycogen is on pretty tight regulation. And

much of that kind of early work was by J.P. Flatt set in the early 90s, and that was predominately done in animal based models, and people started to explore that within human based studies and they actually found pretty equivocal kind of findings. So strong evidence in animals but in terms of humans there wasn't huge amount of evidence for that. And I kind of started to look at that and to see whether changes in glycogen or glucose metabolism were a driver of post exercise compensatory eating and there's a little bit of evidence to suggest so and there's a recent paper, a really good paper by Javier Gonzalez at Bath showing the changes in the hepatic glycogen metabolism were related to some of the post exercise compensatory eating. But I think it's pretty early days, there's not a huge amount of evidence to support a strong role; and if it is playing a role, it's going to be one of multiple other factors that are influencing post exercise compensatory eating.

DANNY LENNON: For sure, yeah, it's super interesting to think about and see where that goes. Over the next, let's say, five years, what are the next couple of big research questions you'd like to tackle within your field that you think are important ones to look at or that are most interesting to you right now?

MARK HOPKINS: I think one of the big issues comes back to this conversation we had around individual variability and it's pretty well-established now that people respond differently to exercise. What we're not very good at is predicting how someone will respond before we initiate an intervention, and there's a lot of discussion now around the best, in both statistical ways of identifying individual variability, but I think there's going to be a lot of focus on trying to come up with predictors how people respond. At the moment, we are clearly not there, we are not able to predict how someone responds to an exercise intervention or a diet, I think that is the focus of the research in this area moving forward. From a personal standpoint, a lot of

my recent work is looking at fat free mass and food intake and we've shown functional associations between body composition and food intake; and what we'd like to try now explore is those at an organ tissue level to start looking at whether changes in particular organ volume or mass influence food intake, but also what are the underlying molecular signals that link fat free mass to food intake. And I think those personally are the two things that I'm looking to pursue over the coming years.

DANNY LENNON: Before I let you go, if we maybe were to boil down to a short or pragmatic bullet point list if someone stopped you on the street and said, kind of based on your work over the years looking at these impacts of diet and exercise on energy balance homeostasis, what would be a couple of the key takeaway things you would like people to take most from what we currently know in this area?

MARK HOPKINS: I suppose my first one is not rocket science, exercise is good for you and you should be doing it. When we do get individuals to exercise, they will respond differently and I think it's important to try and understand why people respond differently to the same exercise stimuli. In terms of exercise and food intake, it's likely that some individuals will show increased levels of energy intake in response to long term exercise training. However, that also is a reflection of their increased energy expenditure and isn't overconsumption. So I think, being physically active over a prolonged period creates a physiological environment that's more conducive for maintaining a healthy body weight over the longer term.

DANNY LENNON: Excellent. And before I get to my very final question Mark, for anyone that's trying to track down you or more of your work online, is there any good place for them to go whether that's ResearchGate, Twitter, anything like that, where should they try and find more about your work?

MARK HOPKINS: You can find me on ResearchGate, hopefully. I am not sure of my username if I'm honest. I think it's just Mark Hopkins at Leeds University, but the university has a website as well where you can find me on. I work in the school of food science and nutrition at the University of Leeds and you get on my personal webpage from there and there's links to the wider research group that I work in, and also my ResearchGate link as well.

DANNY LENNON: And with that Mark, it brings me to the final question that I always end the podcast on, and this can be completely divorced from anything we've discussed in the rest of this episode, but the first thing that comes to your mind if I were to ask you: if you could advise people to do one thing each day that would have a positive impact on any area of their life, what would that one thing be?

MARK HOPKINS: Do something that they enjoy.

DANNY LENNON: And with that Mark let me reiterate, as I said at the outset, that your work has been incredibly useful and interesting to me to be able to read over the kind of past few years, so it's been amazing to be able to talk to you about it today, and thank you for giving up your time to come and do this, I really appreciate it.

MARK HOPKINS: You're more than welcome. It's been a great opportunity to speak with you.