DANNY LENNON: John, thank you so much for taking the time to do this first of all.

JOHN HAWLEY: You're welcome.

DANNY LENNON: There's obviously so many areas we could get into, but as someone who has an interest in circadian biology, I've noticed that over the past few years your group has been involved in this area of circadian metabolomics and has been doing some really novel work, particularly in human trials. Can you maybe just give an update on where you are right now with those projects? What stage you're at, what you have done and what's in the pipeline maybe?

JOHN HAWLEY: Well, it's a really hot topic. You know, the Nobel Prize was awarded a couple of years ago for work in circadian biology and since then the area's just really taken off and exploded. Having said that, most of the early work is not in humans. So, as you correctly pointed out, we've sort of filled that gap as it were. And we started looking at how nutrition for the first instance and secondly, exercise, can perhaps modify or rescue circadian biology. And let me explain what I mean by that. At the moment, you know, we've got a 24-hour lifestyle. We can eat, drink, party around the clock. The problem is we disrupt our circadian biology. So, what we're

looking at now is to see if exercise and appropriate nutrition can somehow bring that circadian clock back to what it should be and reset the thermostat, so to speak.

DANNY LENNON: How is it best to think of words like the human metabolome and then even how the circadian biology, so that relates to what you've been doing?

JOHN HAWLEY: Okay. Well, the circadian clock, again, without getting too technical, is basically the input of all the signals that were received from both the brain and also external. So, let me just give you an example. You're flying to Australia. You probably would jet lag when you get here. The first thing you should do is actually get into normal eating patterns as soon as you can. The second thing you should do is make sure you're exposed to some daylight because that's a very big, what we call Zeitgeber, a time giver. And the third thing is if you can get out and be active. So, that sets the scene or there are some of the cues for circadian biology. Now, when we start measuring this stuff, it's very, very complicated. Do you measure metabolomics? There's a whole lot of omics technology out there at the moment. And without getting too involved for your listeners, we can measure a whole host of metabolites that are circulating in the blood and the muscle, for that matter. The point I want to make here is that they're disrupted when you disrupt this circadian clock. So, what we're really looking at is if we disrupt the circadian clock, what is the impact on all these circulating metabolites and perhaps the muscle, perhaps even athletic performance? Although we're looking at in the context of metabolic disease. And then, how can we rescue that clock back by giving appropriate exercise and nutritional stimulus?

DANNY LENNON: Right. So, maybe, if we talk about some of the papers that your group has published so far on it, and then we can get into some of the work that's in the pipeline. I've seen a couple of papers. I think Evelyn Power was lead author on

some of those. From an overview level, what was the question you were trying to answer with some of those specific studies?

JOHN HAWLEY: Well, the first one is that we were interested in giving subjects a high fat diet. So, we wanted to see if the circadian biology could be disrupted by a high fat diet. And one of the first things that the early animal studies showed for sure and we can replicate in humans, that is a high fat diet disrupts the circadian clock. Now, secondly, and following that up, we were very interested in a very new concept called time restricted eating or time restricted feeding. So, there's a view at the moment with circadian biology that time restricted feeding or time restricted eating may be a very positive cue to recalibrate the circadian clock. So, let me just explain what circadian clocks are and also what time restricted feeding is. Circadian biology works on a 24-hour cycle. Normally we can have access to food 24 hours a day around the clock. And what the studies in animals have shown quite clearly is that if we restrict the time of feeding, in other words, close that window of feeding to about eight to ten hours a day between your first and last meal, this is associated with better metabolic health and certainly weight loss. So, in the early study that we did with Evelyn, we were interested in looking at if time restricted feeding could ... if you like reintrained some of the circadian rhythms that are normally present but are lost with high fat feeding.

DANNY LENNON: Super interesting. So, there was a couple of aspects of that paper that I found fascinating. One that you, I think, alluded to a moment ago is that some of these metabolites we can look at, you can not only look at serum but also in muscle and your route was doing muscle biopsies, particularly in this area where it's pretty challenging to probably get participants to do it for human trials. So, I thought that was amazing you were able to do that. Can you maybe touch on why it was you looked at both serum and muscle biopsies and why that was an important feature?

JOHN HAWLEY: Yeah. That's a really good question because as you've alluded to, it's pretty hard to get human subjects into the lab for muscle biopsies. And in a minute, I'll tell you about another heroic study that Dr. Power has pulled off. So, what we are interested in this study is to see if the serum could act as a surrogate for what was going on in the muscle. In other words, if it could, we then didn't presumably in our next studies have to take muscle biopsies because it's a very invasive process and again, it's quite aversive for the subjects. So, at the moment, I'll tell you about an ongoing study, which we're actually analyzing and shortly, hopefully, due to submit for publication, if you think that study was heroic, this one's absolutely crazy because in this study we had the subjects in the laboratory for 24 hours and we took circadian biopsies. We took biopsies and serum from subjects every four hours. So, even during the night the doctor literally crept in. We tried to disrupt the subjects as little as possible, bearing in mind that any external cues could probably upset circadian biology. So, it was a dark room. The doctor literally had a mining helmet on with a lamp. We took biopsies every four hours. It was an amazing study. We're analyzing that at the moment to see once again how the diet in this case particularly effects and disrupts the circadian biology. So, you know, watch out for that one soon. It's very interesting. We're still analyzing it and not really in a position to give you any more simply because we're not at that stage yet.

DANNY LENNON: Sure. So, in some of those early trials, were you seeing differences in those kind of diurnal patterns between serum and muscle?

JOHN HAWLEY: Absolutely. Yeah. And for the non-technical and technically minded, what we see is phase shifts. You push the clock out. So, in some occasions, it sort of freewheels and goes longer and in other occasions, shorter. Now, that's not a good thing because the whole of the internal clock machinery is basically tied to a roughly 24-hour

rhythm. So, once you disrupt that, and again, this is something that is now quite well established from epidemiological data. For example, shift workers we know live less. Their longevity is less than people in normal jobs. Why? Well, you only have to look at their sleep patterns, number one, their activity or inactivity patterns and perhaps the inappropriate time that they exercise. But more importantly, their feeding schedules. And that's a very good example of how external stimuli completely disrupt the internal clock machinery. And you end up with, you know, high rates of obesity, metabolic diseases, hypertension. So, we now know that shift workers and their associated abnormalities, if you like, in 24-hour normal daily activities, causes massive disruptions to the clock.

DANNY LENNON: Yeah. And you're ... I think, some of the groups in the U.K. have started to look -

JOHN HAWLEY: Yes.

DANNY LENNON: - at meals given during the night versus during the day the metabolism ends up being completely different.

JOHN HAWLEY: It is. And the question is ... and then we haven't really got the answer, you know. If you are a shift worker and you're working nights, should you maintain your normal daily schedule of 18? Or should you eat at appropriate time? Should you eat to hunger? And again, it depends on the duration of the shift. It depends on how long you're on that shift rotation. But the bottom line is, if you're a shift worker, try not to be.

DANNY LENNON: Absolutely. You've obviously been taking muscle biopsies. So, we're looking at skeletal muscle and changes there. Are you of the opinion right now, at least, that we're probably seeing differences depending on the tissue or organ that we'd look at rather than everything being a kind of having the same global pattern?

JOHN HAWLEY: That's again, a really good question. And as you're probably aware, we ... a few years ago, we coined the concept of crosstalk. So, organs actually talking to each other. We used to think, you know, the muscle did its own thing and the heart did its own thing and the liver did its own thing. That's completely inaccurate. We now know that there's a massive amount of crosstalk. In other words, if you disrupt something in the muscle or if it does something in the adipose tissue, then there is far reaching effects in lots of the other tissues in the body. So, we've gone away from looking at, if you like, the single organ approach, and getting back to your early question, if we can somehow get surrogate measures that are in the serum that give us a good reflection of what's going on with the whole body, then so much better because we don't have to take the samples. Now, having said that, it looks like we probably can't because there's so much into organ crosstalk. So, one thing talks to another and really, you've got to try and measure everything, which of course is impossible in human models.

DANNY LENNON: Sure. One thing that was ... we've already touched on was in one of those studies you compare that high fat feeding versus high carbohydrate feeding at least for a period of five days, I believe. Comparing both of those conditions to people's baseline circadian rhythms, what was the impact of some of that feeding?

JOHN HAWLEY: Well, it's a good question. And the problem these days is that when we get subjects in, if you look at their habitual diets and then you give them what we call a moderately high fat diet, it wasn't a super high fat diet, which is actually what they do in the animal studies. So, we sort of, if you like, draw it back a little bit to make it more realistic. But of course, then you run the risk of doing a study, which you're really studying people in their habitual daily living situation because most people eat a moderately high fat diet. Look, as far as the circulating metabolites were concerned, as you well know,

you know, you take carbohydrates out. You put carbohydrate in. You affect things to do with glycemia. You put fat in, or you take fat out. You know, most of the fatty acid transporters and the metabolism of fatties change. So, your circulating metabolome, if you like, is really a function of your daily eating patterns accumulated over time. The muscles a little bit different. The muscle takes a little bit longer to sort of react as it were. And you know, your listeners will know from physiology or listening to your podcast that it takes a while, for example, to get carbohydrate into the muscle for it to be stored as glycogen. So, these things take longer and, therefore, when we take the plasma, it's an instantaneous snapshot of what's going on. When we take the muscle, it's a little bit of a delayed response.

DANNY LENNON: Really interesting. So, from those couple of studies that have been done, what were the main research questions that came from that of, "Okay, this is what we want to go and investigate next"? And then, what does that look like now for your group in terms of what you've been doing?

JOHN HAWLEY: Okay. Well, we've got a really good and exciting study going on at the moment because one of the problems with ... and we'll just touch on a health aspect ... is diabetics. Type two diabetics have high circulating blood glucose. So, we think that time restricted feeding and bringing their meal times into a very tight window is going to have a very good and profound effect on their blood glucose. Now, I was at a seminar the other day and someone said, "Well, isn't time restricted feeding just prolonged fasting?" And it may be. It's the flip side of the same coin type thing. But there is now evidence to show that if you do time restrict feed and certainly in subjects and individuals who have poor control of their blood glucose, that you can actually bong the glucoses down, bring them back to normal glycemic levels, but certainly have a whole host of other health benefits which are again very good for health prognosis and longevity.

DANNY LENNON: Yeah. And I think the interesting conversation there is comparing it to just a prolonged fast. There's now this conversation about when that time restriction comes in.

JOHN HAWLEY: Yes.

DANNY LENNON: So, there's early time restriction. So, eating more earlier in the day versus that restriction later. From your impression of the data so far, where do you come in on that?

JOHN HAWLEY: Yep. Great question. And again, there are a couple of studies. There's one being done in animals, but we'll forget that for the time being because most of your listeners are human, presumably. The study which really, I guess, caused a lot of controversy was published last year from a group in the states and they did what we call early time restricted feeding. Now, it's great science, number one. Don't get me wrong. But the practical message is kind of, well, so what? Because their early time restricted feeding was from ten o'clock till two o'clock. Now, you know, it's nine o'clock as we have this interview in the morning in Australia. Can you imagine just having a small window of eating opportunities? Socially, that's unacceptable.

DANNY LENNON: Right.

JOHN HAWLEY: Now, having said that, I just want to make the point that that study was incredibly well controlled, an incredibly hard study to do and the results were very, very convincing that if you time restricted or early time restricted feeding, you could lose weight in that trial and that was only a five week study and again it was very extreme. To get back to your question, I think practically two things, if people want to enforce this in their daily lifestyle: Just push your breakfast out to a little bit later and bring your early evening meal in. The first thing you've got to do though is establish if you are already time restricted feeding. So, as far as your listeners as concerned, here's the quiz that you have to take.

What time do you normally have breakfast or your first eating occasion of the day? What time is your last eating occasion? If it's twelve hours or over, and certainly if it's over 14 hours, you're what we call unrestricted feeding. And you might want to think about bringing those meal times closer. If you're already only eight to ten hours in between meals, you're probably okay. So, the danger zone is probably the twelve-hour cutoff.

DANNY LENNON: Right. And it's interesting, most of the time when you get people to think that through, it actually ends up being longer than they would have presumed. Right?

JOHN HAWLEY: You're absolutely right. And it generally ends up to be about, you know, twelve hours. People have breakfast seven or eight o'clock and they're still eating at eight o'clock at night. I think the simple take home message is the grazing in the evening is the problem because anything taken later in the day, generally people are sitting around on the sofa; they're watching a movie. They're not doing any activity. So, when you get that normal meal induced rise in blood glucose, you then go to bed. So, the problem there is you're hyperglycemic throughout periods of the night. And we now know that that's been linked to a whole lot of endothelial function cardiovascular disease. So, again, later morning meal, earlier evening meal. Eight to ten hours, probably in good shape.

DANNY LENNON: Right. And then for the timing itself, is it simply restricting that window like you say? Or is it a biasing towards more of earlier in the day for circadian rhythm reasons? So, if people talk about insulin sensitivity, the muscle or ability to metabolize glucose or fatty acids late at night is impaired and things like that.

JOHN HAWLEY: Yes.

DANNY LENNON: Do we have any evidence in humans that that's what's playing out?

JOHN HAWLEY: Very little. We have some animal studies which perhaps hint that the fact that the earlier feedings are probably more beneficial. But again, you've got to take the animal studies with a grain of salt. Rats and mice are nocturnal. They eat at night and they do all their activity at night. We're completely the opposite. So, I have a huge problem, really, when we look at the translational value of some of the animal studies to human. I don't think they have much translational value. But again, in direct answer to your question, if I had to take a punt on it, I would say the earlier feeding with the earlier cutoff at night is probably where you want to go. And you know, it begs the question, what if you started at twelve o'clock and finished at eight o'clock at night? Is that just as good as an earlier eight hours? We haven't got that study done yet, but I'll take a hunch and say it's the earlier time course.

DANNY LENNON: So, what aspect of this area of research are you most excited by that you think shows the most promise for potentially answering big questions?

JOHN HAWLEY: Again, that's a really good question and excitement is the right word because I think here with the time restricted feeding, we've got a practical strategy which people can take home. And it's a simple message. Let me explain just really what I mean by that. At the moment, if you're going to see a dietician, they'll say, "Well, maybe, you should cut out this. Maybe, you should restrict this. Maybe you should do that." Time restricted feeding doesn't actually do any of those. It just says eat what you normally eat, but just do it between this window. Now, that's a simple message for people. We're not saying to you, you know, you have to be a nutritionist and cut out certain macronutrients and only get so many kilocalories from this, that and the other. And, in fact, I think those diets are doomed to failure when you say to people, "Don't do that." I don't like those sorts of diets. We're saying just eat what you normally eat, but just think about the timing. So, we're saying look basically at the

clock, not at the scales and not at what you're putting in your mouth.

DANNY LENNON: It's a really good point because when we think about large scale interventions, particularly if we're talking about diabetics or these folks that are coming to a doctor's office where we don't have that time to educate them about nutrition, this is something that's a simple thing everyone can understand and implement without any real prior education which everything else takes.

JOHN HAWLEY: Well, I'll pick you up on two points there. I mean, firstly, you've got to remember that the medics are very time poor, as you said. For them to write an exercise prescription, which they're not trying to do, of course, or to give dietary advice, which they're really not trained to do either, it's not likely to happen. So, here's a message which you can give very simply: Just eat your normal food, just pay attention to the time. And so, I think, yes, you're right. I think it's a simple message which should be out there in the public right now.

DANNY LENNON: And probably even on a pragmatic level outside of the physiology, it probably has these other secondary benefits ... because I think you already mentioned that for a lot of people, at least, that danger time is consistent snacking in the evening. It might even be small snacks, but three or four of them add up to several hundred calories without really much thought.

JOHN HAWLEY: Exactly. And we've found the interesting thing in our studies that we've done and also the others, the data that's out there published at the moment, is that once you've trained your body into this new pattern of eating, you'd think: Well, I'm going to be hungry later in the evening. I'm going to be, you know, have these hunger pains. No, that's not necessarily true. The data on the subjective ratings of stomach fullness, hunger and this, that and the other are actually lower. So, the time restricted feeding is almost having an appetite suppressant effect later in

the evening. So, all those things are very positive if you like secondary outcomes.

DANNY LENNON: Right. On a kind of related note, but a bit separate, if we're talking about athletes, one of the things we've talked about in relation to meal timing and circadian biology is the potential to rescue changes in some of these circadian rhythms that may happen, for example, with travel. If we're thinking about athletes that travel internationally. Obviously, light/dark exposure may be a big one there and sleep timing, but from a nutritional perspective, as well, where do you see some of the literature?

JOHN HAWLEY: It's a good question. I mean, time restricted feeding for athletes isn't really something that they have to worry about. For the most part, at least athletes who burn a lot of energy and a lot of calories a day, it's about getting food back as quickly as possible. So, I don't think I'd be advocating time restricted feeding for an athlete, per se. But in the context of travel, most certainly. And I'll give you an example. You know, I'm in a plane every month overseas. One of the first things I do as soon as I get to the airport, not even on the plane, is adjust my watch to the time zone I'm going to be living in for the next week or wherever it happens to be. So, when people come around, you know, with a meal at two o'clock in the morning, my body time ... I'm not going to eat it. There is no point. So, if you like, one of the first things I do and I'd certainly recommend to people who are trying to change time zones, whether it's athletes or non-athletes, is don't eat all the meals that they give you on the plane. Adjust to the new time zone as soon as you can. Even try a period of, if you like, prolonged fasting. I mean, you may not be used to it, but it's certainly not going to hurt. And again, sleep patterns are very important. So, as far as the athlete time restricted feeding, we haven't done those studies yet, but certainly if an athlete was trying to make weight then certainly time restricted feeding maybe, you know, an option that they could consider.

DANNY LENNON: Amazing. There's so much stuff we could get into here. But as you said, there's a lot of questions still to be answered.

JOHN HAWLEY: Absolutely.

DANNY LENNON: Hopefully, your group is one of the leading groups doing some of this. So, I'm excited to see how that's published. Before I wrap up, I did want to mention quickly about another review that you and Louise Work had published last year in Science, which for the field of sports nutrition is absolutely phenomenal. Can you maybe just give people an overview of why you wanted to write that paper specifically and maybe some of the key insights from it yet?

JOHN HAWLEY: Well, firstly, you're right because generally, you know, to get an article in Science is considered, you know, almost unobtainable by the likes of people who do exercise physiology and nutrition. So, we were really excited about that special issue. Again, it's free access. If you really just wanted access to that, I'm sure you could put a link on somewhere. But there's a series of papers to do with, again, one on high fat diets, one on the gut microbiome, which we haven't touched on. But that's another thing that the circadian clock changes, but we haven't got time to go there at the moment. I guess the point of the Science review was to actually say, look, sports nutrition is a science, number one. And you know, a lot of people sort of dismiss exercise physiology or nutrition as being, you know, a poor cousin to some of the stronger sciences. That's not true. It's based on very solid foundations. It's based on a lot of literature. It's based on a lot of excellent studies that are, you know, for the most part, probably better control and a lot of the epidemiological work that goes on in medicine. So, it was a nice opportunity for us to showcase sports nutrition and perhaps pick out some of the, you know, major strategies which are commonly used by athletes but have massive scientific credibility and scientific evidence that actually they're effective.

DANNY LENNON: Right. And I think that's important, especially this day and age when there's so much nonsense about, that finally there's something to refer back to, like this is what we actually know.

JOHN HAWLEY: And again, you've touched on that as far as the article in Science goes, but that's the same for nutrition and just general messages out there. You know, if I had a dollar for every book that's published by a celebrity, you know, the latest one is the Tom Brady thing. There's a lot of Twittersphere talk about his book that's just been published about his diet and what he does. And it's got very little science, if any science at all. But the problem is the general public reads that stuff. It's much easier to get a sexy message from a celebrity or a sports star than actually get to the science, have access to it and actually interpret it. So, I mean, programs like this are very good because you're disseminating hopefully science-based logic and information and evidence rather than just, you know, what some particular superstar says.

DANNY LENNON: Yeah, absolutely. And so yeah, I just wanted to congratulate you on that publication because that was phenomenal for the whole field.

JOHN HAWLEY: Yeah, that's nice. Thank you.

DANNY LENNON: Amazing to do that. And before I wrap up with a very final question for people who are looking to hear more about the work you're doing, your group, you on social media, where are the best places on the Internet to go and find you?

JOHN HAWLEY: Well, generally, you know, we're the Mary MacKillop Institute of Health Research and all our topics and what we do research wise are on there. Both Louise Burke, who happens to be my wife, who co-authored the Science paper and I have a Twitter presence. And although social media is not really the way I like to disseminate science, every time we put out a paper, we generally do put it on there, so it reaches a wider audience and perhaps a lay audience. And again,

you know, a lot of the literature that we publish is now freely available to download. So, if you go to any site and you know, put my name in or whoever your favorite scientist happens to be, you can generally get a lot of information just for free, which is actually very, very good.

DANNY LENNON: Yeah, absolutely. And for people listening, I will link up to everything we've mentioned today, so far, and I encourage you to check that out. So, John, that brings me to the final question that I always round the show out on, and it can be to do with anything completely outside of what we've discussed today. If there's one thing you could advise people to do each day that would have a positive impact on any area of their life, what would that one thing be?

JOHN HAWLEY: I'm a very big advocate for both exercise and nutrition and I'm not going to ... I'm not going to answer your question. I'm going to give you two things. I think exercise and nutrition are the cornerstones of a healthy lifestyle. And I'd be the first to admit that exercise on its own probably doesn't give you all the health benefits. Nutrition on its own doesn't. So, I prefer to think of exercise and nutrition as, if you like, bedfellows. If you're doing one, you're doing the other. So, for a healthy lifestyle ... you know, and again, it's a boring old message. You need to have exercise daily in your life and if you like, you need to take care of your nutrition and perhaps, you know, in a year's time we'll have enough documentation to show that time restricted feeding is the way to go for everyone.

DANNY LENNON: Amazing. John, with that, I just want to say thank you, number one, for your time. Two, for everything you've contributed to the field. It's been a pleasure and thanks for doing this.

JOHN HAWLEY: No problem. And enjoy your time in a rather warm Australia.

DANNY LENNON: Yes, I will try my best.

JOHN HAWLEY: Thanks very much.

