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

LEONIE HEILBRONN: Thanks for having me.

DANNY LENNON: This is a real pleasure and honor for me as someone who has read several of her publications over several years now at this point, and I think you've been one of the researchers that's been looking at some of the different interventions we will talk about today, so various fasting protocols, caloric restriction and related fields for what, probably 15 years of guessing, because there's at least papers in the mid to late 2000s of yours that I've definitely read. So how long have you been looking at some of this stuff and what areas have you been involved in?

LEONIE HEILBRONN: Yeah, so I reckon it's maybe 18 years or so since I got my PhD, so awhile now, and most of that time has been really interested in calorie restriction, intermittent fasting, and now moving on to more of the time restricted feeding, and both in terms of healthy aging, but also in obesity and obesity prevention.

DANNY LENNON: So maybe if we start with the kind of parallels between different interventions and particularly when you look at some of the area

of longevity and how caloric restriction has been typically a model of interest, from animal models and also in humans, and then kind of after that it seems that fasting has been something that's been looked at in longevity circles as well, what is it about caloric restriction and fasting that have parallels that they end up being looked at for longevity?

LEONIE HEILBRONN: Yes, so I guess, I mean, all of the initial work was caloric restriction. And so that is moderate reduction in calorie intake without malnutrition, so that kind of 30 to 40% reduction in calories per day; and all of these studies, it's been known for many, many years that they increase not only health span, so the amount of time that you're healthy for, but also can increase longevity. And I guess, around 2005, although there are a few earlier studies on fasting every day, each 24 hours, really began to be of interest. And I think more recently a number of studies where they're looking at when mice are eating when they are calorie restricted are actually – a lot of those studies, they've discovered, have actually been studies of intermittent fasting because these mice tend to gobble all their food down in a couple of hours, and so they're fasting for really long periods during calorie restriction.

DANNY LENNON: And so I think that kind of leads to one of the interesting concepts around fasting and this definitely applies to time restricted feeding which we'll get to later. Is there something uniquely beneficial beyond just restricting calories that happens when we have extended periods of essentially not eating or not being in this constant postprandial state, I guess, and so, how do we start trying to piece those things apart because it becomes quite difficult at the surface level, I'm guessing?

LEONIE HEILBRONN: Yeah, and I'm not really sure those studies have actually clearly been done yet, but I think that is inborn, so often they get mixed up a lot of the time. So when you're fasting, you are on calorie restriction; or when you are on calorie

restriction, you're fasting. And so, absolutely separating that out is difficult. The only place that's really worked is in the mice that when you put mice also in day fasting, at least if they're not obese, they are just normal body weight, they tend to eat as much food, so when they have a fasting day, they make up entirely for that fasting day and really don't have a big difference in body weight. So these mice have a lot of, I guess, health benefits too that you know occur with calorie restriction but they actually don't lose weight, so that's really what's telling us that fasting is, it can work without calorie restriction. In people we seem to see that whenever we calorie restrict, we are fasting as well. And the one study that we've tried to do where we tried to stop people from losing weight on intermittent fasting, we actually didn't show you the same health benefits. So maybe people aren't mice or maybe we just looked at a particular group. But the people that did intermittent fasting without losing weight didn't have the health benefits.

DANNY LENNON: At this point, we should probably talk about some of the different models of fasting that your work has looked at. So for example, I know you've done a lot with alternate day fasting, but then there's been obviously some of the other models that you've looked at. So can you maybe just give us an overview of those different types of fasting interventions and how they differ?

LEONIE HEILBRONN: Yeah, okay, so alternate day fasting is probably the original fasting protocol, so that's fasting every other day without breaking at all. So you'll have, Monday, you'll be Monday-Wednesday-Friday fasting and the next time you'll be Tuesday-Thursday-Saturday. So every three days a week one week, four days a week the next week. They're more of the original studies, and then we quickly kind of morphed in human studies to 5:2 diet where it was two days a week of fasting, and those fasting you are allowed to eat calories during the fasting day, and that probably hasn't been clearly

defined of when you should be eating your calories during your fasting day. And also, I guess, intermittent fasting which is two or three days a week which includes the 5:2 diet, which is the most popular in the community at any rate, not so many studies done on that. And then we've got the time restricted feeding which is probably more of the emerging style of fasting where it's fasting every day, but for really just prolonging that overnight fast so that you are eating maybe for about eight or nine hours a day and fasting for 15 or 16 hours every day.

DANNY LENNON: Perfect, and I definitely have questions about all of those if I can get to them. So I think from that it shows us just how difficult it is to try and come up with what a "optimal fasting protocol" might be, because there's so many variables.

LEONIE HEILBRONN: Yeah. Well, we haven't really tried to compare and put them against each other, so I mean, that would be great to do. but yeah, no one's tried to really sit down and compare how long do we fast for, how many days per week do we need to fast, and when can we eat during our fast, because it'd then negate all of the effects of fasting and macronutrient compositions really haven't been touched much at all, so it doesn't matter what we're eating during the fasting day.

DANNY LENNON: Yeah, there's so many moving parts that's going to be intriguing to see how some of this plays out. With alternate day fasting, if I can turn to that first, in general, and you can correct me if I'm wrong in any of this, it seems that there's generally pretty consistent impact on weight loss and in turn then health biomarkers that tend to get influenced by weight loss as well. One of the concerns some people propose with alternate day fasting is they worry because of that fasting on every second day, is there concern about a greater loss of lean body mass with something like alternate day fasting versus a different type of eating strategy, in that, on those days you can consume more

protein readily, what's the kind of, do we know from this?

LEONIE HEILBRONN: So, I think, there has been a bit of a concern, there's two, I guess, two kind of thoughts. So maybe you're not fasting, you're overeating on the other day, and maybe you've got time to put some lean mass back on, but where the fasting really is because you're requiring all those amino acids for gluconeogenesis. So you need to be making a lot more glucose yourself when you're fasting and that happens from amino acids. But the evidence really hasn't come down that we're seeing any protective or beneficial effects from alternate day fasting, so it's doing similar calorie restriction, it is reducing fat free mass a little bit but not to any greater extent than what happens when you do calorie restriction, at least from the studies so far, but there's no – it's not very many big studies, I guess, to have a look at that in a lot of...

DANNY LENNON: One of the areas that I'm most fascinated by is time restricted feeding purely because I think, at least compared to some other fasting protocols or even in the general population, people that use fasting, it's usually just as a means to either eat at a certain caloric intake and they find it easier to set up that way, but it's all kind of based around that they're getting health benefits from some degree of type of fasting, whereas time restricted feeding has these kind of deep roots within kind of circadian biology and is looking at it from the perspective at least originally I think from this kind of circadian perspective. Can you maybe explain some of that now interplay we're seeing between feeding and circadian rhythms and how some of this might play a role in that?

LEONIE HEILBRONN: Yeah, so, I think it is fascinating, and it's something that's really only been known for kind of the last 10 years is that, not only do we have circadian rhythm in our heads that is controlled by the light-dark cycle and the sleep-wake cycle, but all of our tissues have clocks in them, and so all of our tissues have the same

circadian patterns going on, and they are controlled to some extent by your brain's clock, the suprachiasmatic nucleus, but they also are very sensitive to the feeding-fasting cycle. So if you are eating late at night, you are telling your liver to have a completely different clock from the clock in your head, and so you're uncoupling those clocks. So now your liver is getting a different signal from the brain than the signal that it's generating itself. And so that's kind of, I guess, the basis behind time restricted feeding as really trying to recouple the signals that you're getting from the Sun and from your sleep-wake clock to your clock that your – the food causes you have with changes in food intake.

DANNY LENNON: Yes, and with that, and that's why I think one of the papers to come from your lab that was only published this year is one of the very few that has not only just looked at time restricted feeding but compared where does that timing take place. So an early time restricted feeding model compared to one later in the day, and so both of nine hours, just separated differently, can you maybe talk people through the methodology behind that paper and how you set that up?

LEONIE HEILBRONN: Yeah, so I love the concept of time restricted feeding but I am… I can't not eat at night a bit, so I guess that's where it came from, I'm one of those people who is more likely to skip breakfast than to skip dinner. And also our participants, so we were talking to them as well, and the first time we tried, it's like "eating from eight to five is all well and good, but I don't get home until five, six, I don't get home till six o'clock at night, so it doesn't really work for me." So we didn't have a lot of funding, so it's a small trial and these trials really need to be repeated and we have funding to try and do bigger studies in these spaces. So it's only 15 men and we asked them to eat from eight to five every day or from 12 to nine every day. So that was basically trying to either skip breakfast, or not skip breakfast, but just to eat

for nine hours a day. And we saw in this – it was only going for one week long, so again, it's a small trial, in a short time-frame, but we saw that if you did time restricted feeding, you had quite big improvements in glucose tolerance under both conditions. So if you chose to eat the 12 to 9 kind of pattern, you had just as good an effect on glucose tolerance, is if you chose to go earlier in the day. We actually didn't hypothesize that, we thought it wouldn't be as good, and so, I think more studies are required, but yeah, we really saw that it didn't matter.

DANNY LENNON: And like you said, there's probably many people that would find that as good news if they do prefer to eat later on, but one of the interesting things, as you just outlined, is that it kind of does go against some of the mechanistic rationale from a circadian perspective, I guess, of that we could at least make a hypothesis that eating early in a day or biasing calories early in a day might be beneficial for some of those reasons. What is your overall sense of the limited literature we do have in this area looking at how important, not only total calories for the day but where they're distributed may make a difference on health via impacts on circadian biology?

LEONIE HEILBRONN: Yeah, I think, if we were going to choose a timeframe, potentially, going a little bit earlier than that again would probably be the most optimal to kind of sitting between 10 and 7 or something like that. But there is some sense to skipping, so the rise that you get in cortisol tends to happen kind of seven – eight o'clock in the morning, so if you kind of delay just a little bit past that, it actually does make sense for glucose tolerance, but yeah, it’s kind of dependent upon what the real drivers are that are syncing those clocks; but also maybe once you get into a pattern, even if it's not quite in sync with the day/night cycle, the fact that you're following a pattern all the time and your body is always expecting, these changes do happen at these times that you can adapt to that.

DANNY LENNON: Yeah, and I think that actually brings up another interesting component to this is rather than a specific best time of the day to eat is it more about day to day consistency of whatever those times are, rather than erratic eating patterns.

LEONIE HEILBRONN: Yes, I think that could be something to it as well, so yeah. I mean, as I said to you, we were expecting to see the most optimal effects from the morning ones. But just based on circadian biology, but yeah, I think there could be something to that absolutely, that we are – as long as we are not chucking our body a curveball over time, then it can kind of adapt and do the right thing at the right time.

DANNY LENNON: In terms of some of the changes that we reliably see with different fasting interventions, again, a lot of time markers like glycemic response, changes in serum lipids, these types of things are looked at, and we do often see changes. One question people might have is, are those transient changes that happen when someone has this particular type of feeding regimen and maybe they're losing some weight, or, do those kind of persist over time if that makes sense?

LEONIE HEILBRONN: Yes, so again, I mean, calorie restriction, we've got lots of long term studies that at least in terms of diabetes prevention, if you calorie restrict for a year, then if you can have long lasting effects to prevent diabetes for quite a long time, so 10 years, the DPP studies, Diabetes Prevention Program studies showed that one year of active weight-loss intervention was better than going on metformin for preventing diabetes and the effects lasted, they could see effects for 10 years. So we don't know that with any of the fasting trials, they're all quite short-term at this stage, and how sustainable are they and do they – is it the weight loss that comes with them that maybe does have those longevity effects or is it the fasting.

DANNY LENNON: One area of fasting that I've seen a few people hypothesize could have some benefit, and there's again various different protocols people suggest is in relation to dealing with jet lag or, at least, prophylactically ahead of time, people who are going to travel across multiple time zones, people using some type of fasting during that time essentially to mitigate some of the impacts of jet lag, do you have any kind of thoughts on that area?

LEONIE HEILBRONN: Really, only from what Satchin Panda says about it. So I've talked to him before, and he'd always try to eat exactly in the time zone frame that he is – as soon as he leaves the country, he's always trying to eat within breakfast at breakfast time, lunch at lunch time, because it helps resync your body as well. So food does have cues and so if you stay to your old eating patterns, it's going to take you longer to transfer to the new time zone. But yeah, this is from him and not from what I know, sorry.

DANNY LENNON: No, that's perfect. If I can throw you another pretty tough one that we probably don't have an answer to and is one of the most I think complex areas to try and help people with on both a nutrition and just general health and lifestyle perspective, is people doing shift work and why this might come up here is obviously because of impacts on circadian biology. In terms of those that are doing shift work, we know that there's going to be changes in metabolism at the times that they're likely to be eating. Is there anything we know that may be good practices for those that are, let's say, doing night shifts or changing shifts or so on? Is there anything that may mitigate some of those downsides?

LEONIE HEILBRONN: Yeah, I think that's the hardest thing with shift work is that they're always changing from night to day and afternoon and very rarely they don't stay on their night shift schedule, and probably if they were always on a night shift, they could adapt to those things, but they're always

changing back to days schedules. And so, we've done some acute studies looking at simulated night shift work and if you, I guess, are eating or not eating those big meals in the middle of the night, there was better effects in terms of health, and that's just acutely in people who had never been exposed to shift work before, but going into the lab for five days and either eating their meals at midnight like shift workers tend to do, they tend to change their meals to night patterns, or, just preventing them from eating over those phases, they had better outcomes. We've just recently completed a study where we're trying to see the difference with snacking as well, so trying to have maybe just a high-protein little snack in the middle of the night, is that detrimental for health, and those results were hopefully be coming out soon.

DANNY LENNON: Very cool. And so, on that, what kind of projects are you working on or maybe others that you know that you're most excited about, what areas or research questions are being looked at right now?

LEONIE HEILBRONN: I know some of the groups as well are trying to do the delayed early versus delayed time restricted feeding studies. I know there's a lot of studies going on in people with diabetes as well trying to see with time restricted eating, with some shift working studies going on, I know there are some colleagues in Melbourne and Adelaide who are doing fasting studies in shift workers with kind of a time restricted feeding focus as well. So it's a bit of both at the same time, and that will be really interesting, so we are actually doing those studies in people who have done shift work for years rather than simulating that, so that will be very interesting, . We're doing a big study of intermittent fasting at the moment, trying to have a look at up to 18 months, so doing quite a long trial in people who are at risk of diabetes, so that's going to be a long time coming in that trial though, because we are recruiting 260 people and it's an 18-month study. But in four years' time, we

are going to have results on that one, so it's going to take a while.

DANNY LENNON: With reference to, if we look at that population of those with either type 2 diabetes or even maybe prediabetes and where there's insulin resistance going on, that seems to one of the big target areas where there could be a benefit from these various different protocols, one that seems logical but I don't know what kind of data we have is rather than just looking at that distribution of calories across the day that we mentioned earlier, is there where we place carbohydrates, how much that matters? Because again, intuitively, if we were to look at this from a mechanistic perspective, you would probably hypothesize earlier in the day might be better than later due to changes in insulin sensitivity, but does that actually play out for end outcomes in any way?

LEONIE HEILBRONN: That's a tough question, so I'd say that it would. I mean, if I was going to tell people if they wanted to have their carbohydrates, they should definitely have them for breakfast, so you should have your ice cream in the morning, rather than after dessert if it is in the evening, that's what you were going to do, because you could definitely handle that better. And interestingly, we just tried to do a time restricted feeding study where we locked up people for 24 hours and we did shift that ice cream from 9 p.m. to 11 a.m. and they had a much smaller glucose curve to that same ice cream. But yeah, I don't know whether that is going to play out and – I think it probably depends on how well you handle carbohydrates as well. So if you are someone who's fit and healthy and exercise, most likely you can handle that carbohydrate at any time of day. But if you have that higher risk of diabetes and already a bit of an impaired carbohydrate handling, then definitely, I think, time of day has a bigger effect.

DANNY LENNON: There's one question I forgot to ask whilst we were on the early versus late time restricted

feeding. Would you suspect or hypothesize, there could be a difference depending on if those meals were weighted differently – so in the first meal of the day, if we put 60% of the calories, and the final meal being very light – does that kind of change some of the outcomes as opposed to just the length of the feeding window for the day, if that makes sense?

LEONIE HEILBRONN: I'm just thinking of the Jakubowicz studies. So she has done some, she has done, yeah, definitely with the small breakfast same size lunch, large dinners. I think they are acute, so maybe they are only just one day long, but definitely they see that you have a better glucose profile if you have the big breakfast, same sized lunch and smaller dinner. And for weight, there's some weight studies, long term weight studies trying to keep that profile as well, and if you followed that profile, you would lose more weight than if you had the reverse going on. So I think there is some evidence for that, yeah.

DANNY LENNON: Yeah. You exactly nailed that; the Jakubowicz paper was the one that had sparked off me to think with would that play around, and I've talked to a friend of mine, Alan, who kind of thought about the same thing in relation to some of the TRF papers. So yeah, like I said, one we probably can't answer right now, but it's interesting to think about.

LEONIE HEILBRONN: Yeah, it is, and yeah, so that's something, but we don't think about TRF as well, how many meals are you doing, all of that kind of things as well. I think that doing a lot of meals used to be a thing for dieticians all the time and how they would tell people to manage diabetes is to have lots of small meals, and maybe six small meals a day. So you are always postprandial and that was management practice and still is in some practices, and so the problem with that is that people tend to then just overeat at each one. And so if you're eating six times a day, it's actually quite hard to manage your total calorie intakes.

DANNY LENNON: One thing that we've mentioned in the podcast before in relation to time restricted eating that I find one of the most interesting and kind of exciting things from a practical perspective is the ease at which this could be given to someone as a recommendation. If we do find that this is beneficial, there's at least a couple of pilot trials where they've essentially had to not really educate people about nutrition at all apart from say can you just eat your normal diet within these hours and you still see some potential benefits which then, on a broad scale, kind of gives some degree of optimism about how this could be rolled out at a larger population or public health level because it doesn't have that barrier in the way.

LEONIE HEILBRONN: I think that's why there's a lot of excitement around it, yeah, absolutely, it's difficult to change what you're eating... what they are doing is difficult. But at the same time I think time restricted feeding could be changing their diets a little bit, just because people don't tend to take those snacks at night or take the alcohol and have that at 10 o'clock in the morning. So they are actually probably changing their diet quality a little bit anyway, because it tends to be the poor quality foods that we tend to snack on in the evening. So yeah, it could have an unintended improvement in diet quality without really telling people what to do.

DANNY LENNON: That's a really, really good point. So for some of the questions that are still yet to be answered in this area, what do you think are the next couple that are most important for us to get some more data on that would really help move the field forward?

LEONIE HEILBRONN: So I think looking at what people are doing with macronutrients a little bit on non-fasting days with feeding, so we are not always seeing good things, they are sometimes really changing what they're doing on those days, so we just, do we need to control macronutrients at all or can we just forget about it. I think to

know how long we need to fast is always a question that people always ask me is, do I have to fast for 24 hours, can I fast for 20 hours, can I fast for 16 hours, so we don't know what's the optimum time to do and how little, how many days do we need to do. So do we need to do this as you said earlier to me, do we need to – can we do this a number of times per month, something like that or do we have to keep going forever and what's the longevity effects.

DANNY LENNON: Yeah, that's the thing, there's so many variables when you consider, like you said, the length of the fasting window, how often we should do that; and then, I suppose, the other thing is what is the extent of that restriction as well, whether it's, if on, say an alternate day fasting model, do we allow 500 calories without no calories, without – whatever it is, all these variables can give us a myriad of different protocols.

LEONIE HEILBRONN: Yeah, and I really think we jump there pretty quickly, so we jump from going, alternate day fasting which had all the evidence in mice to allowing these calories on fasting days and we don't really know if that's doing or blocking some of the effects, but maybe it's fine to. So yeah, but maybe spiking your insulin at 12 o'clock by having a big carbohydrate meal in the middle of the first day is undoing some of those benefits which could otherwise be useful.

DANNY LENNON: Super interesting. Before we get to the very final question, Leonie, for people who are interested in keeping up-to-date with the work that you've got going on, that the lab is putting out, or to find more of your papers, is there anywhere online that you can direct them?

LEONIE HEILBRONN: No, I can't. I mean, I just – I don't have a Twitter handle or anything. I should actually get one of those things one day. But yeah, no, sorry.

DANNY LENNON: No, I would advise against doing it. I think one of the reasons probably why you're so productive is you stay away from the hellhole it is, Twitter. So yeah, that's a good call. So yeah, for anyone listening, I'll link up to any of the papers we've, of course, referenced today and you can check those out through PubMed or ResearchGate. With that, Leonie, I'll get to the very final question that I always end the podcast on, and this can be completely outside of anything we've discussed today, and it's a broad generic question, so forgive me. 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?

LEONIE HEILBRONN: See my immediate thought was to say, a bit of exercise every day is great, but, of course, that's probably, you know, that's why I probably should say, don't eat after 8 p.m. or something. But my immediate thought was exercise. But yeah, exercise and maybe don't eat after 8 p.m. How's that for two of them?

DANNY LENNON: I don't think we could get any better, so a great way to round this off and, Leonie, let me again just reiterate, thank you so much for not only coming and talking to me today, but just for the work you've done in general, it's been incredibly informative and has been definitely helpful to me, and has contributed well to the field. So thank you so much for your work and the time.

LEONIE HEILBRONN: It's great, and it was nice to have questions that were so well informed, absolutely.

Watch Danny's Chrononutrition lecture here: https://youtu.be/fA2zjGz0VaA