DANNY LENNON: Alan thank you for coming back on the podcast.

ALAN FLANGAN: Thank you for having me back.

DANNY LENNON: First, to give people some context, let them know what area of research you're involved in right now, may be an overview of the type of project, your specific role within that, and where you guys are at with that.

ALAN FLANGAN: So right now, I'm currently a PhD at the University of Surrey and in the chrono-nutrition realm. We have a study underway right now which the final phase is actually coming up where it's in conjunction with the University of Aberdeen, they're doing an intervention looking at temporal distribution of energy intake earlier versus later in the day in the context of a weight loss intervention, and we're looking at the underlying circadian mechanisms that may or may not be able to explain the potential for earlier distribution of energy to be more beneficial and one of the hypotheses and issues to be teased out in the literature still is this idea of whether the benefit to temporal distribution of energy more relates to behavioral factors or whether there is a kind of inherent internal circadian control of these metabolic factors that that actually is the primary driver of that benefit. So it's

interesting to build on kind of the body of work that's there already in an area where there's some really interesting findings particularly in the last, I think, five or so years or five to 10 years certainly, where previous issues that we thought had been completely teased out in nutrition, such as timing of food intake and distribution of energy and "whether a calorie is a calorie" have kind of somewhat come back up and resurfaced. And, in a way, I think it challenges the establishment of a certain dogma in relation to those issues and no one's suggesting that energy balance isn't fundamental, but what, there's certainty is suggestive of now in the literature is factors that influence energy balance over the course of the day and what those factors are and whether they are inherently circadian or behavioral or again the influence of a combination of both, and certainly from the circadian perspective with some genetic influences on that.

DANNY LENNON: Maybe a way to start working our way through this, I'll let you know how I've tried to conceptualize this, and I got to speak about this recently in Melbourne and tomorrow you'll actually get to see my amateurish presentation, I am butchering this area of research. But in terms of ways to start thinking through the different facets of chrono-nutrition, there's kind of four areas we can maybe explore. One would be the timing of nutrients and how that might affect say postprandial metabolism. From there we can look at the calorie distribution that you just mentioned. We could look at consistency of meal timings or frequencies from day to day. And then maybe finally fasting and feeding windows or cycles between those and it's because of different categories. So if we think of that first one of time of day and when we eat a meal, what do we know from a circadian perspective right now or where's the starting point that we can maybe think of in this discussion.

ALAN FLANGAN: I think the starting point is probably where we're at in terms of understanding that there

are diurnal variations in metabolism, probably the most well-established is the diurnal variation in glucose tolerance which we know is amplified earlier in the day and is decreased later in the day. We know that there are circadian and peaks in circulating free fatty acids and triglycerides that occur during the biological night in the fasted state that may be one of the reasons why the cardiometabolic effects of eating at night in the context of shift work are quite deleterious, one reason. And we seem to have this emerging body of research that does suggest that there is a benefit to earlier distribution of energy intake in terms of metabolism, and in terms of thermic effect of feeding, and potentially again kind of mediated by factors like increased physical activity that occur from an earlier distribution of energy intake. We have generally a predominance of my studies in terms of understanding mammalian and circadian architecture and also the impact of nutrition. But the emerging human research in terms of factors like the aforementioned glucose tolerance do accord today with that hypothesis that there is a strong diurnal i.e., daily distribution in glucose tolerance, of course, across the day, and that that may be one of the reasons why there is enhanced capacity to digest, utilize, absorb the nutrients that we do eat earlier in the day.

DANNY LENNON: So with some of those trends that we're seeing either with timing of different meals or distribution, what are some of those kind of key patterns we see – I know you've mentioned some already, and then what does that or how does that relate back to practically what that might mean going forward or what questions we need to answer?

ALAN FLANGAN: Yeah, I think we're at a point where it's probably more useful to focus on the human research, because the translational models in mice are very interesting and generate a lot of fascinating hypotheses, particularly, in terms of the protective effect of time restricted feeding. But they also are prone to the fact that over the

metabolism of a rodent is much more responsive to over or under feeding. And so, while there has been some really interesting research in those animal models, they've often BEEN the subject of probably some overstating of some of the factors that are discussed in terms of chrono-nutrition. But we do have an emerging body of trials in humans that have generated some interesting findings, a number of them that have, for example, looked at the difference between distributing a higher calorie breakfast and a lower calorie dinner with a fixed calorie lunch versus the opposite with this lower, say, 200 calorie breakfast and then the 700 calorie dinner or vice versa that have suggested a greater weight loss in the group consuming the majority of breakfasts of energy of breakfast. We have other studies conducted kind of with more control over global energy expenditure assessment and energy intake, the Bath Breakfast Project being one of them suggesting that one of the benefits potentially accruing from greater distribution of energy earlier in the day – and by earlier, in that study, kind of before 11 o'clock in the morning, results in increased physical activity. So there's also a very interesting intervention in Spain that looked at the effects of timing of lunch, and so with a fixed breakfast at 8:00 a.m. and dinner at 8:00 p.m. altering the lunch meal between 1:30 and 4:30 p.m., with the later timing group of course, what this meant was that 75% of daily energy was being consumed between 4:30 and 8:00 p.m., and some kind of deleterious cardiometabolic effects and trends towards impaired glucose tolerance lower fat oxidation and factors like that, yes, in the context of short-term studies, it's difficult to extrapolate out what that would mean over the long term. But if we added up in relation to the epidemiology in the area where we see some significant associations with temporal distribution of energy, we can start to perhaps glean some mechanistic insights into why later timing of energy intake over the long term may not be conducive to cardiometabolic health.

So again there are, with all of these trials that have looked at temporal distribution of energy intake between earlier or later in the day, or some of them in particular that have found greater weight loss in the context of nominally similar diets although a lot of them use self-reporting, it is suggestive of some degree of benefit that the whys and wherefores of the benefit of course still to be teased out of it, but does suggest a benefit to an earlier distribution of a greater proportion of daily energy, whether that's because of the resulting impact on behaviors like physical activity or whether it's to do with an inherent circadian benefit is again kind of what certainly works with our research trying to tease out, but again where those kind of questions and nuances in the field still lie to be teased out. And I think in that context it is important to highlight that some studies, and two in particular, so this is still rather nascent, have found a strong genetic heritability to breakfast timing in particular. So a study that compared monozygotic, so identical twins to dizygotic twins to be able to tease out that the heritability of meal timing as it relates to kind of environmental factors as well, that actually breakfast was the strongest genetic heritability in terms of meal timing. And over the course of the day, interestingly, there was a progressive decrease in the strength of the heritability for lunch and dinner. And so, when we get into these kind of arguments that have been common about like is breakfast or is breakfast not the most important meal of the day, it very well may be for some people that have a strong genetic heritability for breakfast timing, and those people tend to be earlier chronotypes than their preference there, genetic heritability for breakfast tends to tie to their sleep and wake timing, but what it does suggest importantly is that certainly lunch uncertainty dinner are more behavioral in their preference as opposed to influenced strongly by genetic heritability, and it therefore means that there are probably meals that are more modifiable in their timing and the behavior. And so, when we consider

that in the context of, certainly, in the UK, average daily energy intake in the evening being sometimes up to 46, 47, 48% of total daily energy, that later distribution, that temporal eating pattern may not be conducive to metabolic health, but unlike breakfast, it may be that actually that's a more behaviorally driven factor and perhaps more modifiable kind of for general population health recommendations but certainly also individual recommendations.

DANNY LENNON: You mentioned chronotypes and that this morning type may be more associated in this case with a heritability for breakfast, on that, when we're talking about meal distribution in terms of the timing of where the bulk of those calories come across the day, do you have any idea yet over if there's a difference between talking about clock time versus someone's chronotype, so the relatively where we place them across the day?

ALAN FLANGAN: Yeah, that is the really interesting thing right now to tease out, there's the recent Muniz paper which we kind of talked about offline where this paper that looked at – so the first thing to probably highlight if people don't know is the concept of a chronotype is that people will individually have a degree of variance in their internal circadian timing. So you may have people that are more prone to be early risers, perhaps breakfast consumers based on this genetic research recently, and broadly speaking, morning larks is the kind of colloquial term; and then you have people that again with the colloquial term may be known as night owls and have this later chronotype where they are prone to perhaps not be great in the morning. And so, this is quite interesting because all internal circadian rhythms run on internal once they're synchronized to external environmental factors to the 24-hour daily period, but the actual phase of that internal rhythm may be different in some people. And so, one of the suggestions is that temporal eating patterns if we, for example, distribute

more energy later in the day is problematic because it's out of phase with when someone may be more optimal and enhanced in their metabolic capacity. But what would be the effects? And so, you may have much more profoundly, over the long-term, negative effects in someone who's a morning chronotype consuming a lot of energy late in the day.

And a recent paper looked at the distribution of someone's energy of their intervention diets relative to someone's chronotype. So people that were early chronotypes using a questionnaire evaluation for that's common in the area, who were early chronotypes, consumed their energy according to that chronotype where they consumed more kind of energy earlier in the day, and the evening chronotypes has somewhat of the reverse in terms of their caloric distribution; and interestingly, found pretty much identical weight loss in the context of a weight loss intervention. I think the issue with that study is there is no objective measure of circadian phase and also there is actually no – from what I can see in the paper – there's no description of the clock time either that it was consumed at. So they give the caloric breakdown of how energy was temporarily distributed, but we can't reconcile it against either clock time or circadian phase. So it's been a very, very interesting publication. But I think it's probably left us with a few more answers. From other work in the field, it does suggest that actually when you correct for someone's internal rhythms, their chronotype, and you adjust food intake or nutrient intake relative to circadian phase, you do see an alignment between their kind of – you don't see those negative effects if you take into account internal phase, if that internal phase is aligned to meal timing. And that is a very, I think, subtle variation that does warrant further exploration, because a lot of the experimental models in the area use quite extreme discordance between circadian phase and food intake; and a lot of that stems from the fact

that shift work has been a primary focus of trying to understand more because we know that there are deleterious effects to working night shifts over the long term, food intake at night maybe one of those reasons why. And so a lot of the studies looking at more extreme circadian perturbations are feeding at times that are irrespective of someone's circadian preference for morning or evening are still discordant with their internal biology. So whether you're a morning or evening type food intake a 3 a.m. is never going to be in sync with an internal kind of metabolic regulation under circadian control. But generally, I think this idea that perhaps accounting for circadian internal phase with food intake could be a factor that influences cardiometabolic health over the long term in an individual, is definitely interesting and I think that paper was certainly suggestive of that type of alignment. But again, we can't really say anything because we've nothing objective to quantify the actual timing of intake when the meals came, and when that would have been relative to circadian phase.

DANNY LENNON: Let me throw something at you that could be completely “off the reservation” and you and other chronobiologists were probably saying, you dummy, why are you even asking such a stupid thing; but here's a thought that I had when it comes to chronotypes and I understand that there's a genetic kind of distribution between that and that's kind of some of that is genetically mediated, but if we know at least to some degree a chronotype seems to be trainable and it can alter over time, and we know that people can change their exposure to light and dark when they choose to eat meals, so eating more earlier in the day and later, so if we're looking at something that has a preference, say they're classified as an evening type, and they do better eating later in the evening, could that just be that they've just trained themselves to be more of that chronotype and really very few people are really actually a very late chronotype? Does it make sense?

ALAN FLANGAN: Yeah. Well, I think even if you look at the kind of research looking at chronotype per se, the kind of, the wild extremes are the exception not the rule. Most people don't fall into an extreme of morningness or eveningness. And certainly with a lot of the questionnaire based research, don't fall into the extremes of morningness us or eveningness. The other variable to consider there is to synchronize our internal rhythms to the external temporal world we require external environmental inputs that, like you said, have to do with light exposure primarily; but then, secondary, meal timing is emerging as quite an important factor in that; and then also things like body temperature and these variables. And so, there obviously is a big conversation now about the discord between our environmental inputs and our internal circadian architecture in terms of artificial light exposure at night, altered meal timings. We know, and most people have probably experienced jetlag, and so, we know that there is an adaptability to the circadian system; we know that there will be a capacity if someone was to alter all of their exposures by say 12 hours, that there will be an adoptive response and ultimately those internal rhythms will eventually synchronize with the new environmental exposures.

So the degree to which there is a trainability is certainly evident from those lines of inquiry. It's more a question of, I think, whether something like an extreme temporal distribution of energy intake could be adoptable, and I think that once an individual or a population, if we're thinking about it that way, when you're in an environment where largely you're aligned to that temporal world and that clock time of the day, even if there is an internal variability in someone's phase, there's still going to be, and one of the characteristics of circadian rhythms is that they will run if we remove all of these external cues, they just won't run to the 24-hour day, in humans they'll run slightly longer than that. So

the fact is that even if we remove all of these environmental exposures, you'll still have a diurnal variation in glucose tolerance, you'll still have a diurnal variation in triglyceride peaks and circulation free fatty acids.

So I think when we consider it in that way, the idea that there could be an adaptive response to late-night eating, for example, I don't think would actually have much support right now. And the other variable is that we know that that later distribution of energy intake, it certainly would have a phase delay impact, but really all its contribution to is this kind of less extreme than jetlag but more a long-term desynchrony between someone's internal rhythms and their external environmental time cues. And that's what I think the focus of the field very much is on now while, like we said, with the shift work example, a lot of the research looking at extreme, in terms of jetlag and shift work, but the interest now is variables like social jetlag. And so, ultimately, although there is a degree of trainability, I don't think that will extend to someone kind of training themselves to be able to have better metabolic responses to say the largest meal of the day at 9:30 p.m. versus 9:30 a.m., and that's because your internal rhythms remain in that context. And so, what that eating pattern is likely contributing to is actually just a more long-term desynchrony. You're altering the internal input or the external inputs that help synchronize the system.

DANNY LENNON: Right. That's kind of what my question was trying to get to, almost the opposite of trying to train yourself to eat later. I wonder, is it more a case that probably nearly all of us wouldn't do well at; that time that we've almost, through behaviors, some people have trained themselves to believe they're more of an evening type than they could actually be with a few behavior modifications.

ALAN FLANGAN: Yeah. And so, one thing that I think is important to separate out from this

conversation is that a lot of the, shall we say, anecdotal support for, well, I can eat X amount late at night and I'm fine and it doesn't impact my ability to lose weight comes from kind of physique oriented intermittent fasting regimes without involved practices like macronutrient tracking, calorie cycling, and a more controlled nutrition approach for physique enhancement, body composition goals. So I think comparing those kind of dietary approaches to the kind of conversation we're having about population, health, and individual health is they're completely distinct, because it's very easy to say in nutrition that nothing matters once you're controlling for energy balance and these factors. But of course that's not applicable to the population as a whole, and we're talking about a minority subset. So separating that kind of often used critique of the idea that timing of food intake matters, that's the equation, I do think that largely it seems that when you look at some of the kind of behavioral correlates, the secular trends to later distribution of energy intake would certainly appear to be environmentally driven, whether that has to do with factors like artificial light exposure at night simply means that people have a propensity to be up later, there's a greater propensity for eating, there's greater opportunity to eat later into the biological night, it may be to do with people's, again, their working hours or after work activity. And so there are a lot of factors that are influencing the behaviors that appear to correlate to, like I said, a secular trend over the last 40 years, towards greater distribution of energy intake. But if we again come back to the genetic heritability studies, it definitely suggests that dinner is or the later meals in the day are more behavioral correlates and have less genetic heritability than breakfast. And it, by implication, suggests that actually they're behavior driven and more behaviorally modifiable than someone's preference for a breakfast intake, for example.

DANNY LENNON: Yeah, there's a few things there that I want to open a tab and hopefully you'll come back to – one is on the idea of this can be a way almost the Trojan horse in to get people to think more critically about some ideas, like, as long as you match macros that all that matters, all right. And then the other thing was the human trials that you brought up; I want to definitely get back into. But I want to take a step back just to kind of clarify, for people listening, a really important point that was kind of embedded within there, is that when we talk about food intake and meal timing in the context of circadian rhythms, that kind of works both way around. By that I mean, we've seen some examples you've given so far of things like variation in insulin sensitivity across today, people's postprandial metabolism of those meals across today. So these inbuilt circadian rhythms can influence what we do at meals but also it works back the other way that you just mentioned that we can have meals that will set circadian rhythms or entrain circadian rhythms in those peripheral clocks. So I think it's probably worth laying that out for people, first, with like central circadian clock, peripheral clocks, and then what food actually does to those and then that will kind of bring us into the concept of actually what we mean by misalignment or alignment...

ALAN FLANGAN: Alignment, yeah. So in terms of human circadian architecture, the primary in-training signal in human – and by in-train we mean external signal that allows our internal rhythms to synchronize to the time of day outside the external environment – is in a region of the hypothalamus known as the suprachiasmatic nucleus. So the SCN receives input from our eyes, relayed through specific channels to that brain region which then incorporates the signal based on light that it is daytime or it is nighttime. And that primary signal detector is known as the master clock and does feed down and communicate with other brain regions and the rest of the body to synchronize our internal rhythms. But over the years, it has become

more evident that there are other environmental inputs that influence synchronization, and although we have this master clock that synchronizes the circadian system in individual peripheral tissues, so the part or the pancreas or the kidneys or the liver or the digestive system, each of these organ tissue systems has its own clocks that self-oscillate based on other inputs. And so, they do synchronize with the SCN, but they can act and be phase-shifted based on altered inputs. So for example, we know that glucose rhythms in the liver and in the pancreas can be shifted by late meal timing independent of whether the central clock has been shifted by, for example, a change in light environment.

So for quite some time, there was a concept of what was known as food-entrainable oscillator that was a mechanism by which food intake was a signal to help these peripheral tissues to synchronize. But it was quite elusive in the literature. And then a few years ago, a Japanese group published a paper, I can't remember the name of the lead author, looking at the role of insulin and that's been recently followed up by the University of Manchester chrono group who looked at the capacity of insulin to drive through circadian proteins, the kind of amplitude of circadian rhythms. And so what it suggests is actually there is a molecular mechanism by which food intake potentially via insulin secretion acts as a signal to peripheral tissues to synchronize. And so when we have alignment between the external environmental light inputs to the central clock and accordance and synchrony between that and the meal timing that synchronizes peripheral tissues we are perhaps looking at a state of circadian alignment, in the context of, as humans, the day time is our active phase and our feeding phase. So these are all phases that go together. And so, what you're looking at then is a scenario where, in the context of appropriate light exposure in individuals, meal timing is tied to their waking and active phase which is the day phase in humans; and the

night time is the corresponding diametrically opposed version of that, so the night time is resting, fasting, sleeping; and those contrasting signals are really important to overall circadian integrity in terms of preservation of circadian rhythms, and it's that disconnects that is potentially one of the factors that is influencing certainly in the extreme circumstances, like, shift work, health over the long term; but the question I think that is of interest to the field now is, what are the long-term implications of more minor but chronic disturbances between someone's light exposure which they may not be – if they're in closed buildings during the day, they're simply not getting the level of natural outdoor light exposure that would have quite a high effect on synchronizing internal circadian rhythms; and then if the meal timing is later or distribution towards the evening or even quite erratic in its consistency. These may be factors that then add up with the lack of consistent light exposure to perhaps influencing what we call misalignment or desynchrony. And again, the question is to what degree does that more chronic misalignment influence health over the long term.

DANNY LENNON: Right, and that really is the question, to what degree does some of these changes like food intake make a difference. What we know for sure already is that circadian misalignment just screws everything up.

ALAN FLANGAN: Right.

DANNY LENNON: So that’s not something you need to still dwell on, but to something like food timing, what degree is that having an impact on this.

ALAN FLANGAN: Yeah. I mean, we've well enough established links between shift work like other variables, we know that there's a negative consequence to sleep curtailment per se, we know that that influences food behaviors, food seeking behaviors, caloric intake. But if we take those factors out of the equation and we look more at

these and potential mediating factors like meal timing, the question then becomes independent of sleep curtailment, independent of shift work in jetlag in the extreme examples what if – and I think from a circadian, from a chronobiological perspective, I think it is a long-term cumulative thing because I don't think you can necessarily take the meal timing issue itself if that is a negative delay or distribution of energy intake without also factoring in the light exposure issue, because [inaudible 00:39:48] and light is the primary time cue for the circadian system. So I think this may be a global environment fact in terms of the way that we are currently living. An artificial light exposure at night may be one factor. People still may be getting adequate sleep time but the question is, is the sleep quality still the same; and then following on from that then, the subsequent day for example, if particularly in regions of the world where over certain periods of the year there's going to be quite a fluctuation and in light and dark exposure, there's a seasonal study being conducted at Surrey now which is going to be really interesting when the results come out in the same people looking at rhythms across the seasons. So that's something we don't really know, particularly in these parts of the world where we don't have a consistent kind of 12-hour light-dark cycle, we do have shifts in the year. And so there are going to be periods of the year where people probably commute to work in the dark, go into an enclosed office lighting environment where we know the intensity of light and the spectral composition of light is not sufficient to give them circadian entrainment; and then go home in the evening to a light environment that perhaps, in terms of, like proximity of screens to the retina and size of screens and all these variables that might actually completely change the spectral composition of the light they're exposed to, then we factor into that the meal timing issue. And so the question then is what degree of metabolic dysregulation over the long term will come from that disconnect.

I think when we look at the epidemiology there's pretty, although breakfast intake in observational research is kind of inconsistent in terms of health outcomes, the one thing that is fairly consistently shown in terms of temporal distribution of energy intake is that there is strong correlates between BMI and cardiometabolic outcomes and later timing, certainly, if we're putting a figure on that 8:00 p.m. or after, later timing of energy intake. So that factor is there, those observations are there. When we tie that into, again, what we know about underlying circadian rhythms and the variability in metabolic capacity over the course of a day, there is mechanistic plausibility as to why we would see those observations. So I do think that a disconnect between nutrient timing, internal peripheral clock synchrony, and these are all really important organs for cardiovascular and metabolic health, so I do think that in terms of where we're at now, if we view the research globally as a totality, mechanistically, observations what human intervention trials are there, there is a suggestive body of evidence that would say that yes desynchronizing your meal timing from your natural circadian phase of wakefulness activity and daytime does seem to appear to add up over time to adverse health outcomes.

DANNY LENNON: Yeah, I'm glad you mentioned the point about how we can't really divorce it from the light-dark conversation. And if anything, that is even clearer and stronger evidence that has a bigger magnitude of effect. One thing I wonder about that lack of exposure to bright light during the day, because, as you mentioned, even indoor bright lights are maybe a tenth to a hundredth of what it could be outside depending on how bright the day is, with that, I wonder does that play a role in the degree of the problems we see with exposure to blue light at night in that, is that when you get exposed to blue light looking at a screen at night, is it just the absolute degree of that blue light you're getting or is that

relative to what you've had over the course of the day?

ALAN FLANGAN: Yeah, so light history does appear to be an important factor in someone, in an individual's response, and there was that recent Philips and Colleagues' paper on light exposure that we discussed offline as well and what's been really interesting about that is it was a really, really elegant study, and not only did it look at obviously just brightness, generally, as a measure of looks, it also controlled for irradiance levels as well at those different looks intensities. But what may have had an influence and what the study found was quite a wide inter-individual variability into what light exposure led to melatonin suppression. There is a conversation in the field about the adequacy of using Lux as a measurement but I don't think – that's a rabbit hole that's kind of we don't need to go down, but it is a measure of brightness and ultimately there can be this right suppressing effect on melatonin as a result of brightness. But certain individuals in the study, certain participants, had melatonin suppression at quite low levels of brightness, certain individuals had, you know, it took quite a much higher exposure to elicit any melatonin suppression; but it doesn't appear that light history was factored in, and if it wasn't, there is this suggestion that, and there is supporting research that an individual's light history will have an influence on their sensitivity. So we know that, for example, that the same intensity of natural light exposure has a greater entraining effect than the same nominal intensity but from artificial sources, not maybe to do with a multiplicity of factors like the actual global perception of the light coming from different angles and the irradiance factor, different contributions of different cells in the retina, rods, cones, and melanopsin, but in an individual who's exposed to really low amplitude lighting during the day, if you were exposed to only natural light, you would get a really high variance in the intensity of the light you're exposed to during the day; and then you

would get a really sharp contrast with the dark period once the sun went down. So you remove shortwave blue light once the sun goes down and then you have this quite extreme contrast. And it seems that the strength of the contrast is quite an important factor for circadian entrainment. So if someone is exposed to a relatively constant but low intensity of light during the day, they're not getting that high contrast and certainly then it may mean that you get a greater degree of melatonin suppression with things like artificial blue, shortwave blue light exposure or monochromatic light exposure in the evening.

And again the question marks over that are, like, what are the long-term health implications of kind of chronic melatonin, relative melatonin suppression, you will still get a rhythm in melatonin but you don't get that high peak, the robustness, and there has been, there's been a couple of studies that have looked at the effects of blue light blocking glasses, there's quite a significant – I think one of the studies in teenagers the difference in melatonin kind of amplitude was like 58%,. So quite significant differences, but again, those kind of experiments are really interesting and certainly support the light exposure ideas, but to what degree can you get people to do that i n the general population? probably not.

DANNY LENNON: Yeah. purity anecdotally for myself and a few people that have kind of asked for recommendations around sleep, everyone is, at this point, I think, to some degree, familiar with, yeah, avoid white blue light at night, put on your blue light filter on your phone, things like that, but for people who don't usually get out during the day, getting some early daylight exposure seems to, again, like I said, just anecdotally, seem to have a massive payoff even for their sleep, onset of sleep, things like that.

ALAN FLANGAN: And that's because if you get that high kind of intensity of natural light exposure, you are

getting the full spectrum of light exposure externally, you're getting the wavelength, you're getting the intensity, you're getting the kind of global reaching of light to the retina, and that will have a phase entraining effect, but generally have the effect of phase kind of advancing someone or aligning someone. So a lot of the behaviors we have now delay someone's internal circadian rhythms whereas those kind of behaviors may ultimately have a payoff later in the day to your sleep timing by having that greater exposure. So you are influencing your entrainment but influencing it in such a way that would lead potentially, again, chronotype and stuff factored in, but lead to an earlier onset of sleep and an earlier self-selected sleep time.

DANNY LENNON: Yeah, that's one of the reasons why I wonder about people who just subjectively turn themselves an evening type without any kind of testing is that, well, maybe you're one of those individuals who doesn't get outside and is going indoors all day long, and maybe that's what's, you have that phase advance so you would get.

ALAN FLANGAN: And I think that one of the big difficulties with a subject of questionnaires in our current environment is the fact that it may be very difficult for someone to actually have a real handle on where they stand on those questions in terms of preference for wake time, self-selected preference for wake time, preference for different activities during the day. So I think certainly from a research perspective, objective quantifications of phase are quite important in that sense. But it is, I think, quite arguable from the kind of the wider research looking at certainly light and the kind of preferences that are articulated for later may very well be more behavioral than purely circadian driven. So yes, there are later chronotypes but a lot of what we discussed earlier in terms of people's work environment, their light exposure, the fact that the evening may be the only time to have kind of downtime

basically, and an entertainment time, and the preference to then put on that extra Netflix series, and reach for more food at 9:30 – these are all behavioral factors that probably have a certain amount to do with chronotype, but I think in a lot of people are certainly behavioral and obviously modifiable as a result.

DANNY LENNON: There's a couple of things in terms of, if we're trying to put some of this stuff into some general heuristics for a practical application. One that I'm not sure we have a direct answer for, but is one of the things I try and think through is if we're going on the premise that there's this rhythm to instant sensitivity or glucose tolerance across the day, it may stand to reason that having more of your carbohydrate intake bias towards earlier in the day and certainly not a large amount of carbohydrate at night. And so, I wonder, how does something like exercise particularly for people who do resistance training or hard exercise influence or mitigate some of that potential negative having carbohydrate later in the day based on the rationale that we know something like resistance training that muscle contraction leads to this Glut4 translocation, we're no longer relying on insulin to move glucose into the cell. Does that allow us to escape from some of that or do we – is there anything that you think along…?

ALAN FLANGAN: Well, that's the thing. I think certainly if we kind of factor in sports nutrition, literature to the Chrono stuff, then arguably, yes. I mean, the insulin independence, glucose uptake that you would get from resistance training or glycogen depleting training, ultimately is going to, we know, lead to a preferential glucose uptake to replace depleted glycogen. And we also have some insights into the potential for circadian rhythms in body temperature to correlate to performance, typically tied to kind of the afternoon it seems, kind of on clock time say 4:00 to 7:00 p.m. So I do think that there are certain factors that, as intermediaries, do change the general status quo because you're

altering metabolic homeostasis with something like a sprint session or a resistance training session or something that is glycogen dependent. And so, I definitely think that in that context the preference, advice wise would be to stick with what we know in terms of sports nutrition, and it would not be to forgo carbohydrate intake in the evening because of diurnal variability in glucose tolerance when we've just engaged in an activity that actually completely, you know, we relatively concretely know increases glucose tolerance and insulin independent glucose disposal. So I think the advice would be to stick with what we know is good sports nutrition principles in that respect.

DANNY LENNON: Sure. The other thing that we had mentioned before we started recording today was on potentially some pushback that some people may have when they hear about this area of research of trying to incorporate that into what they typically promote with their clients or for themselves or just kind of publicly, and one of those is, well, if we're not sure how much of a difference this makes and we know the kind of core fundamental things like overall energy intake and protein intake and we know that these things matter quite a bit, general food sources that we're going to include, then does trying to get people to take on board some of these things make it more difficult for them to stick to, will it impact the adherence, is it worth me even factoring in some of this stuff into my decision making?

ALAN FLANGAN: I've heard that argument a number of times that this is just an extra layer of complication on simple stuff that we know; and I do think that on a cursory overview, it's a valid criticism. But I think that the obverse of the coin is true, I actually think that the focus on, for example, distributing a greater proportion of energy earlier in the day or delaying breakfast by one hour and bringing forward dinner by one hour which is an intervention that you've seen in some of the time restricted feeding, the kind of real world's field studies, their behaviors, they

move us out of this realm of micromanaging diet at the level of macronutrients and calories, they largely remove the focus of the kind of food based emphasis that everyone tries to place on when it comes to weight loss or improving metabolic health; and I actually think that this approach allows people to have access to behaviors they can engage with, that can actually make a difference, and the free living interventions are quite encouraging, they are not [inaudible 00:57:10] emerging but they are encouraging that simple behavior modifications in the context of considering a chrono-nutrition approach may actually be more accessible for people and may allow for less focus on those variables and more focus on these behavioral factors that can ultimately lead to an improvement in their cardiometabolic risk factors and health over the short term, and then potentially over the long term because it is behavior based.

DANNY LENNON: Yeah, I think, to me at least, one of the things about time restricted feeding that makes it such a potentially attractive intervention is because it seems to have much more scale than things that require us to educate people about calories, energy balance, macronutrients, being able to track those things, in that it takes zero education almost; it's like, here's this timing feeding window and now you can roll out a larger scale quicker rather than relying on individual education.

ALAN FLANGAN: Exactly, and it’s applicable across the board, it could certainly be a population wide recommendation, obviously not for like six or seven hours, eight hours, but something like 10 hours or 11 hours could be an accessible population wide recommendation that doesn't have to have a large degree of knowledge or all these other variables to engage with, and that's often a barrier to public health dissemination. And the other thing that is perhaps quite beneficial in terms of its accessibility is the flexibility in it, because there is still the capacity to allow people to self-select for how

that would look for them based on their habitual breakfast-time or based on their habitual dinnertime. So if someone's habitual breakfast time is at 7:00, the concept of them delaying breakfast by an hour is different from someone who's habitual breakfast time is 8:30 in the morning. And so there's an adaptability and a flexibility and an applicability of this concept that I think is a lot broader than people think when they look at some of the interventions that are very tightly controlled, very narrow eating windows, matched for energy. It's like those studies are interesting because they're teasing out mechanisms. But actually, if you take the strictures off their design and look at the actual principles at play, those principles I think are much more accessible and applicable and flexible.

DANNY LENNON: Yeah, I find this whole area interesting for many reasons, but one that I mentioned to someone recently is that because it's kind of, for anyone that's interested in nutrition, it's kind of very exciting and you can almost use it as like a gateway drug for getting people to care about light exposure, because that's difficult at first.

ALAN FLANGAN: Right, yeah, it is difficult.

DANNY LENNON: Whereas if you mention chrono-nutrition, all this stuff, that's really cool. Like, yeah, but it won't mean much if you're not taking care of that.

ALAN FLANGAN: Right. Yeah, if you're like sitting up in front of a 70-inch plasma at midnight, there's maybe less point in worrying about how much energy you distribute to breakfast.

DANNY LENNON: Right, yeah. It’s a great way to introduce at least some of that into a conversation. So with maybe your own work and then maybe you can talk about the field more broadly if you wish, but what is the kind of next steps with where you're at with the study, when do you hope to

be able to get some of that stuff out, is there any timeline?

ALAN FLANGAN: No timeline really as it stands. The final actual cohort phase is coming up on the 31st of July, finish on the 8th of August, and then we will have our completed participants. So it's really just a question of then thinking about how we want to look at the data and starting that process of looking at – I think the most interesting thing or the thing that I'm certainly most interested in to see is thermic effect of feeding, because most studies to date that have looked at this have looked at it in the rather short term; whereas we have thermic effect of feeding, we have RMR measures over the course of the entire test day which adds up to kind of six hours of total measures. So from their baseline measure, from the days in which they're aligned to the three test days that occur when they're misaligned, it's going to be quite interesting to see the more longer-term picture of the influence of alignment and misalignment, and obviously the meal timing on thermic effect of feeding; and the way that the protocol is set up as a five-hour delay means that after the misalignment the breakfast and lunch meals coincide in timing in each participant with when they would have had lunch and dinner during the alignment. So it'll be really interesting to see because those meals come at the same clock time relative to the phase shift than what the effect on thermic effect of feeding is going to be and to what degree is that under circadian control. And so where this fits into the wider field, I think, there's a couple of nuances that are there now that are going to be really interesting for the field to tease. One is the relationship between actual chronotype and circadian phase to distribution of energy intake – is that something that is more aligned with an individual's chronotype then, is the implication of that that a lot of the observations we see because people are much more discordant in their behaviors with their chronotype even if they're an evening type, like I said, there's only

a certain point at which being an evening type will still coincide with eating at a time that's in sync with internal biological rhythms, like, later distribution of energy intake at some point gets to a stage where your internal rhythms are moving toward the biological night. I think that the potential for distribution of energy intake to influence energy balance is still quite interesting because the studies that are there today are really suggestive whether it's increased physical activity like the bath breakfast project found or whether it's other variables like enhanced postprandial metabolism, then those are areas that I think are interesting to continue to tease out because some of the studies have lacked more objective assessments of dietary intake or not incorporation and assessment of energy expenditure.

And the other thing that I think is quite interesting is there's this, in the kind of wider nutrition fields, there's been a lot of focus on postprandial dysmetabolism and postprandial lipemia, postprandial hyperglycemia, and these factors are potentially the real drivers of things like liver fat accumulation or atherosclerosis in terms of the duration that people spend in a postprandial state and we know that people on average are spending 15 to 16 hours in a postprandial state. The other element of the field that I'm interested to see where it goes is, is there, because one of the things that was debated nutrition for years was whether there's any advantage to meal frequency and timing, but that was again like a lot of things in nutrition clouded by the fact that it was always looked at through the lens of body composition and weight loss. There are other markers of health improvement, and I am interested to see whether the temporal distribution benefits results and whether there is a benefit to a certain type of or a certain temporal distribution of timing or spacing as well, because there is some suggestive research that erratic meal patterns or inconsistent meal patterns may impair glucose tolerance and

insulin action, and again that may be because there's then a disconnect between the synchronization of these internal clocks from meal timing if there's constantly meals being consumed as erratic times of the day or night with no pattern. The circadian system by nature relies on very constant timing of its environmental cues and meal timing may be one of them.

DANNY LENNON: I wonder on that, because it's something I've thought about with meal frequency that could there be at least make a hypothesis that a reduced meal frequency is beneficial due to having more periods of say a true fasting physiology kicked in, right, which is potentially one of the reasons why we see benefits with prolonged fasting or time restricted feeding, in that we're actually giving people time where they're in a non-postprandial state.

ALAN FLANGAN: Right, exactly.

DANNY LENNON: And I wonder if people are constantly snacking throughout the day, is that where you are never really getting out of a postprandial state perhaps depending on how you set up of course.

ALAN FLANGAN: You're always having postprandial incursions of blood lipids and of blood glucose, and I do think – I think that area of research is really fascinating, I think it would be interesting to see what the effect of different combinations of a degree of restricted feeding, in terms of time and meal pattern might have particularly for conditions like non-alcoholic fatty liver disease or the progression on the spectrum of diabetes risk where visceral fat accumulation is compounding, decreased glucose tolerance and beta cell function over time. So I think there is some insight with that Sutton and colleagues, early time restricted feeding study which was very interesting, very, very tightly controlled in everything used at an early window where participants ate between 7:00 1:00 p.m., it's a six-hour window. But some really interesting

elements of their findings were things like massively reduced blood pressure, like the blood pressure reduction in that study was quite striking. And so the question is it just the time restricted feeding time or is it to do with the temporal distribution, and I don't think that's being teased out yet; and from a postprandial perspective, they were fasting 18 hours with the majority of their energy intake coming at a time where we believe circadian regulation of metabolism to enhance metabolic capacity. So a really interesting nuance there is what is the relationship between feeding time and duration and the structure of meal timing as it may relate to improved cardiovascular and metabolic markers.

DANNY LENNON: That's a really good point because I think the Sutton paper, may be that group, I think, Jamshed was the lead author the following year; and maybe similar with like the Hutchinson paper, you see a lot of them that are most highly controlled seem to go with those three kind of square meals which again would we see any different whether it's different meal frequency.

ALAN FLANGAN: Yeah.

DANNY LENNON: And the other thing, when you mentioned the degree of or the magnitude of the differences we see with that, that was compared to like the control was like a 12-hour window, right?

ALAN FLANGAN: Right.

DANNY LENNON: So when you consider most people are like at 15-16 hours, that's even more impressive.

ALAN FLANGAN: It's even more, yeah. And I think within that then the question is what would be the effect of a slightly longer window but maybe not that early in the day, like, would there be and what would potentially the benefits be or the difference be between say consuming between 10:00 and 6:00 or somewhat expanded from that. And I think it may be semantics, but I do

think that the relationship between the distribution, not just of total energy, but of meal timing across the day, could be interesting, and it could be a novel means of approaching nutrition interventions to enhance certainly kind of reductions in visceral fat and certain of those risk factors thus may be compounded by extended postprandial metabolism over the course of the day. So to what degree can you modify meal timing or meal spacing to kind of optimize those interventions I think is something that is going to be interesting to tease out. And then how does that then relate to time restricted feeding or, for example, is there an added benefit too, because in that study, like you were saying, that the control was 12 hours, but is there the distribution was equal across the meals. So the question could be, in the absence of any real restriction of eating time per se, let's say, you just go with the normal say 12 hours, in that context, does the greater distribution of energy intake earlier in the day lead to the same benefit as equal distribution but in a time restricted context? So is it the temporal distribution of energy or is it the restriction on total feeding time? So I think that's an interesting thing to tease out.

DANNY LENNON: Yeah, there are so many great questions in this, so you won't be sure on to investigate in the future.

ALAN FLANGAN: I think we're generating more research questions in giving people answers.

DANNY LENNON: Right, yeah, you are like, okay, we are good for the moment, yeah.

ALAN FLANGAN: Yeah.

DANNY LENNON: Yeah, so with that, maybe if we just bring this to kind of close and summarize some of the key ideas you said, if someone were to walk up to you and they said, Alan, I've got 30 seconds, here's a napkin, can you jot down four-five

bullet points of kind of general heuristics of what this may mean for things I can try with my diet that you at least have some leaning, may have some benefit, how would you kind of summarize where you're most confident in right now?

ALAN FLANGAN: Yeah I think overall, I think, number one would be, there does appear, certainly, in the kind of the real world, so to speak, there does appear to be a benefit in free living conditions to a greater distribution of one's total daily energy earlier in the day; and by earlier, I mean, within the first two meals of the day; so it doesn't all have to be at 7:00 a.m. And do bear in mind, the heritability of breakfast, if one isn't a breakfast person per se, breakfast is largely a social-behavioral timed meal in many respects, so, by breakfast, I simply mean one's first meal of the day, whether that's at like 9:30 or 7:30, it's possibly irrelevant. And I think when we factor in the total body of evidence, total distribution or the greater distribution earlier in the day – by earlier in the day, possibly means before 3:00 or 2:00 p.m., so first two meals, like, breakfast and lunch in that timeframe, I think, there's enough evidence to support saying that right now, although there are caveats in terms of where it's going, whether it's that relevant, I don't know.

The second one would be a certain degree of time restricted feeding, not extreme. The reason I say this is less to do with, oh, like, there's a benefit to an intermittent fasting TRF approach, and it's more to do with what we talked about earlier in terms of circadian alignment. So giving the body distinct cycles of feed and fast that correspond to our cycles of wakefulness and activity and daylight and corresponds accordingly to our cycles of dark rest and sleep. And so, earlier distribution of energy in the day, a degree of thinking cyclically about intake tying to the day phase, I think in terms of the later timing of food intake, even if we consider what we've said about the earlier distribution of energy,

avoiding eating late into the biological night I think is relatively supported from the totality of research that we have to date; and by late, certainly, past 9:00 p.m., irrespective of chronotype would not appear to be beneficial over the long term. So I would also try and factor in an earlier timing of dinner where possible and if someone does habitually have a 9:30 dinner certainly trying to even just bring that forward by an hour at the start, and again factoring in again the suggestion that evening intake is more behavioral in nature and therefore more modifiable; and then having a degree, where possible, of outdoor light exposure early in the day to help this whole process of internal synchrony, and trying to have some activity in the day phase as well. So it's funny that even though we're talking about chrono-nutrition, some of these ideas that you end up giving to people have actually kind of little to do with nutrition and more to do with the overall circadian system. So if I had to boil it down to five things, I think, yeah, that earlier distribution of total daily energy to the early part of the day, a degree of distinct feeding fast cycles that correspond with being awake or being asleep, an earlier timing of dinner/avoiding large intakes of energy late at night, trying to get natural light exposure earlier in the day, and also trying to get activity earlier in the day, both of which are – or not necessarily earlier in the day but during the day, both of which are behaviors that will help kind of the whole process of synchrony and circadian alignment.

DANNY LENNON: Perfect. And with that, for people who want to find you on social media, on the internet, where can they track you down?

ALAN FLANGAN: Yeah, so right now, on Instagram @thenutritional_advocate, it's the only social media channel that I use. I do have a website coming out which I had been planning and then parked for a few months while I basically got sunk into the PhD process – deal with one thing at a time basically. So that's going to be

out in a couple of weeks which I'm looking forward to which is very much research focused nutrition science. And yeah, that'll be a nice project to get stuck into for the next couple of years.

DANNY LENNON: Nice. I'll link up to that in the show notes for people listening and, Alan, thanks for talking to me.

ALAN FLANGAN: Thank you for having me back.

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