DANNY LENNON: Hello and welcome to Sigma Nutrition Radio. My name is Danny Lennon, I am here with Alan Flanagan and Niamh Aspell, and today we're going to be talking all about fasting and longevity, a lot to unpack within this. And for those of you who follow our content regularly, you will have seen a Sigma statement appear on the website in relation to this issue, but there's a lot to unpick in some of the things that are raised, so hopefully, we're going to dive through some of that today. With this topic of longevity, and particularly, any nutritional intervention that is aimed at, I suppose, the origins of this typically have been in the form of things like caloric restriction and looking at that impact on lifespan, or at least that was the initial emerging idea around the longevity/anti-aging community of looking at some of this data that originated in yeast, and maybe in some other places that we'll talk about of increasing lifespan. But, of course, now in other areas, and particularly more recently, some of the focus has become on, well, we also have this other element of the health span to look at, in other words, for the period of time that someone is going to be alive, how can we have as much of that as possible free of loss of function in relation to mobility, and then also chronic disease risk. So this ties in other areas around preventative interventions for some of those chronic diseases. So a lot to move through within this, so as we typically do with these types of discussions, probably best to start with some

degree of definitions, I might ask you to lead us off on this Niamh, seeing as you were the lead author on our recent Sigma statement on this topic. And I suppose, we'll start maybe first on the side of thinking about longevity, because I think before we get to any intervention, understanding what exactly we mean by that, what we mean by any areas that look at aging or anti-aging, and then these specific concepts of lifespan, health span, and anything else you think might be useful, what are some of the primary terms you think we should get people up to speed on?

NIAMH ASPELL: Yeah, I think when we talk about longevity, most people just consider it, as you said, in terms of extending the years that we are likely to live. When we talk about aging and longevity, essentially, we do just mean preserving our life for longer, so it's living in good health for a longer period of time. And over the last, we've always kind of really focused on this and nutrition, if you think about nutrition research, it's about living in a healthy state for as long as possible. Health span is just the period of your life where you're in generally good health, so this would be with kind of a lack of any sort of cognitive or physical disability, and then longevity is more so the capability to survive past the average age of death. So this obviously varies between countries, and it's been increasing pretty consistently since like the 1960s. In Ireland, I think the current lifespan for the average age of death, I suppose, determined is at 82 years, so it's been increasing, it was around 70 years in 1960, so it's been increasing on average about like two years. When we're talking about, there's a lot of studies, there's a lot of research on kind of exceptional longevity, and this would be people who live past the age or survive and live independently past the age of 95, and this is typically seen in populations where there's kind of a, or in sub populations with a strong genetic backing there, so it's usually you'll see it, there's like a generational type thing, so there's a strong familial association with this extreme kind of or long periods of life. And then you see it in other kind of smaller communities as well, which have been kind of extensively researched around their behaviors and diet, and it's one thing that's kind of important to know around kind of living longer, and living longer but in better health, which is kind of what most of us

want. I don't think most people want to live to 100 plus, if they're in poor health from 20 or 30 years beforehand. But it's still a little bit unclear in the research if we're experiencing a reduction of morbidity, so the rate of disease, even though the age of the onset of disease is kind of not really significantly changing, we're living for longer. So some of the reductions in the prevalence of disability and dementias have been reported, but most large longitudinal studies, there's a good longitudinal study, The Berlin aging study, and they showed that greater longevity resulted in fewer, not more years of disability, but then other studies have shown at the Global Burden of Disease study demonstrated that the prevalence of diseases is actually increased. But that's largely due to the fact that we have more treatments or better treatments, so people are still getting these illnesses as they get older, but they're being able to sustain their health with these illnesses for longer, because there's better interventions or better treatments to keep people relatively healthy even with these particular diseases. So a lot of this extension of lifespan is around better access to healthcare, and I think, even though our life expectancy is kind of increasing, we're starting to see more increases in sub populations with a history of disease, so people who are more likely to have, say, diabetes or other age related, sorry, and age related diseases, they're starting to increase their lifespan as well, compared to the general population who are kind of healthy. So it's a little bit complex, there's lots of reasons why things are kind of changing, but it's unlikely that life expectancy at older age will continue to increase much more beyond levels that we would expect somebody to live to from birth. So we still expect that these diseases will be there, but there's no strong real evidence that we can delay the aging process so far looking at the data that we have.

DANNY LENNON: Yeah, I suppose that really gets us to one of the, I suppose, the crux of this issue, or where much of the debate is of what we're actually trying to do, and, I suppose, one of the things you raised there is that now on the positive side, we have much better treatments, healthcare, access to healthcare, etc., which means that people who do develop certain disease states that may be earlier would have been more likely to end life

sooner, can now sustain life and be actually relatively healthy despite this burden of disease for a longer period of time. However, then, on an individual level, on the flip side, we also then could have this issue where in cases where people have a longer life, or at least we're getting to this point of, let's say, a long life expectancy, if much of those years are spent in a state of disease, or, let's say, significant disease that leads to severe impairment on quality of life, etc., then that can be problematic. And so, from an intervention standpoint, then we need to be clear on what are we actually asking are we trying to do, are we just simply looking at extending lifespan, or actually looking at interventions that can allow currently where our life expectancy is, how can we get more people in the population to have a longer period of time before there's that real impairment of quality of life through disease. And, I suppose, teasing out that distinction is an important starting point before we're asking about outcomes related to, quote-unquote, longevity. I don't know if anyone's thoughts around framing of the question.

ALAN FLANAGAN: I think this is where, certainly from a nutrition perspective, and certainly from perhaps the kind of invitation to quackery that this question seems to generate in certain communities, is the lack of operational definitions that are really kind of refined as far as like outcome goes. I mean, if we're talking about a lot of the hyperbole over various interventions, and obviously, we're going to focus on, say, fasting today, or various kinds of forms of caloric restriction or otherwise, when people talk about then longevity, if we're using that term, in the manner that Niamh has defined it as, which is correct, is we would expect the outcome is going to be that a particular intervention leads to someone having an extension past the median average age mortality in their given population. And, of course, then, if you define it at that granular level, you suddenly run into the absence of evidence rather than potentially evidence of absence, we don't know, but I think that this is a question that because of the nature of the outcomes, we're likely never really to have any sort of evidence directly answering that, and I think most of where we're at now with nutrition research is related more to the effect of interventions on reducing other metrics

like disability adjusted life years, for example, reducing the burden of disease, so to speak, in a given or the years that someone spends living with a disease and trying to attenuate that risk of developing the disease in the first place and/or having an event or resulting mortality from that particular disease. And they're actually very, I mean, they may be related, obviously, of course, if someone dies before whatever the median average death age is in their population, but they're fundamentally very different questions from does this type of diet make you live longer than that median.

DANNY LENNON: Yeah, so maybe let's start getting into that, because on this side of potential nutritional or dietary strategies to look at aging or longevity, again, we have to get very specific on what question we're actually asking, but even on, I suppose, the history of where this even emerges, there's these different classes that we can maybe put these different interventions in, and I think Niamh, you've outlined this, so you can have kind of the origins of like lifespan extension in caloric restriction, and then caloric restriction more generally in other areas, and we could look at specific types of nutrient restriction in different ways, and then, we can look at maybe some other interventions where you have something like fasting where we might not have, say, caloric restriction or the restriction of a specific nutrient, but more a kind of time based one. So I suppose, in that sense, you could have complete nutrient restriction for a period of time, but how should we distinguish the maybe different groups of interventions, and is there any kind of maybe useful history that might be used in framing of where did we start looking at longevity related ideas in terms of these nutritional interventions.

NIAMH ASPELL: Yeah, there's lots of things that spring into mind. I think the first thing I was thinking there just on the end of that conversation around aging and longevity, and what we're trying to test and what the outcomes are, I think one big, I suppose, gray point in all of this research is that the FDA or the regulatory bodies don't recognize aging as a disease, but a lot of these research groups are trying to cure aging. So when they test any of these interventions, they're not being strictly controlled by the FDA, because they're not

technically saying that they're developing something therapeutic, because they're not actually working with a disease state. So you'll find with a lot of the – there's a lot of, we could maybe talk about the random kind of different supplements or different interventions that are currently available by certain researchers who are referring to them as rejuvenators of health, and they have different animal models where the mice have been rejuvenated, because by the FDA, you can say, it's fine, you can have a product that rejuvenates something, but you can't say it's going to not kill you. Because aging is not a disease, and we don't need to kind of, you know, so there's a really gray space, that's why they get away with so much I think, for the time being. So in terms of the strategies, very early on, you might be familiar and listeners might be familiar with the biosphere study that was conducted very early on in the 90s as Biosphere 2 it was called, and it was set up by a researcher in the US.

So this facility was built in Arizona, and essentially, it was developed, those two big funders essentially built this environmental system, so they built this environment where people were able to live and see if they could live off their own ecosystem and build and grow their own foods, and they were kind of leasing it out as such to researchers, and they leased it out for the first experiment with one particular researcher, Roy Walford, and he did this particular study in 1991 I think. So they were the first people to go and live in this enclosed space and be self-sufficient for two years. So there's eight researchers, different researchers and scientists who went to live in this research facility, they lived there, they grew their own produce. And Roy Walford, he was a pathologist, but was really, really interested in the idea of longevity and calorie restriction. They lived there, they grew their own fruit and veg and legumes, it was very much a plant based kind of environment, and full of good oxygen, all of these things that they were trying to test to see if this was the best way to live in terms of like self-sufficiency and longevity and good health span. They stayed there in this isolated environment for two years, they calorie restricted, I think initially this kind of – he reported that he told them that they wouldn't have enough food to survive, so he got them to reduce their calories for the first year and they lost – or their

intake for the first year, so they reduced their calories. They stayed there for two years, they lost on average 16% of their baseline bodyweight from when they moved in, and kind of stabilized during the second year, they were able to kind of stabilize their weight, but they reported kind of being constantly hungry, but this was a very much a nutrient rich, just calorie poor diet, so they're still eating quite well. And they did lots of testing then afterwards, and they showed that they had lots of improvements in terms of metabolic and cardiovascular health, so their blood pressure was in a better range, their fasting glucose levels were normal, but they were all – they all left the biosphere very malnourished and underweight, so they physically probably didn't look as healthy as maybe when they went in. And what they determined kind of from that was like that fasting is potentially a good approach, but it shouldn't get to the stage where you're malnourished or nutrient deficient. And this is one of the kinds of very early studies, and they went on to do a lot more studies after that, I think, in monkeys, and in animal studies, and then we'll probably get into more of the research done by Valter Longo, which he's very well known in this area, and he was one of the students of Roy Walford, so he continued on in this area of research to look into, maybe not calorie restricting so much, but the fasting side of things. So I can describe the different fasting approaches, I don't know if that would help kind of the conversation a little better to help understand it, because it did start off very much so being around calorie restriction and dietary restriction, whereas now the research has moved more into fasting periods, and that's the part of the approach that will actually provide most of the benefit.

DANNY LENNON: Yes, I think, again, here's an area where there's kind of gray area, because there's a lack of definitions of what people are saying not only by things like longevity, or anti-aging interventions, or even you hear talk of reversing biological age, and using a number of different biomarkers to indicate this, and it's all very difficult to kind of tease apart. And then, even when someone says about fasting, as you know that there's various forms of fasting that all look very, very different, and so, if we're trying to be kind of precise on what are these things doing, it's probably useful to

do that. So maybe very briefly, yeah, if you give a kind of quick overview of how we can differentiate between different types of fasting regimens, and then, we can maybe mention them throughout the studies later on which one we're talking about.

NIAMH ASPELL: Yeah, I think that the most popular one and the one everyone's kind of familiar with or have heard of is intermittent fasting; and essentially, it's an umbrella term for a few different types of diets, but it's restricting your food intake for certain bad times and certain periods of time. So the diet could include kind of fasting for a couple of hours or over a couple of days, traditionally. They don't specify what foods you should eat, and common approaches are kind of 16-hour fasts where you'd kind of stop eating in the evening time, and you don't resume eating till the next day. Some people recommend doing shorter fasts of like 12 hours because they are more sustainable long term, so people will be more likely to comply if they only have to fast for say 12 hours. But the effects, the health effects are thought to kind of occur at a much slower rate if you're fasting for only 12 hours. So I think most people are probably familiar with 16:8, which is where you're fasting for 16, and you have a window of eating for eight hours. And in that window of eight hours, it's not that it's like a free for all, it's just that you would kind of eat as normal again. And then, there's alternate day fasting, where you eat for one day and skip the next day time restricted feeding, which is very similar time type of thing, it's limiting a daily eating window during the day, so it can be – we typically, and Alan you probably know a hell of a lot more about this than I do, but I think we typically eat for about 15 hours a day, so it's restricting that that we're only eating for maybe eight hours. An older one that I'm not sure if it's as popular anymore, but there's a lot of research done into the five-two diet, I think that was a researcher in Manchester University where they tested a diet where you essentially for two days of the week, so not consecutive days, would eat around 500 calories and these are your fasting days, and then you'd eat as usual or as typical on the other days. The only other one that, I suppose, is worth mentioning is the fasting mimicking diet, and this was designed by Valter Longo, who had mentioned previously after he had tried to do a lot of experiments with water fasting

diets in oncology studies, but he found that there was very poor compliance from the patients and also oncologists were very concerned about their patients doing water fasts. So he developed this fasting mimicking diet, which is technically a medical diet, it's about 30 to 50% of your normal calorie intake for four to seven days, and you would do that typically three or four times a year. So it's almost like this, you know, refresh your week, so it resets – they believe, it resets your body or cleans your body and restarts your system, and you only need to do it maybe three or four times a year, and this is very much a standardized, it's manufactured, it's prescribed product. There's a lot of medical oversight with it as well. I think they're typically the most popular ones, and then calorie restriction and dietary restriction, the only differences there is that there's not these time windows of when you're totally fasting. It's just that you're reducing your daily intake of food, but you can still be eating kind of adlib over the day. It's just you're eating less, you're not having this period where your body is not consuming any energy whatsoever.

DANNY LENNON: Great. And, of course, there's some commonalities between all of those, but also some distinct differences, and those differences become more worth talking about when we start hearing what mechanisms people are suggesting that this is going to have an impact on longevity or our lifespan, particularly, if we're comparing something where there's either some small degree of restriction, but people are still eating throughout the day, versus some of these prolonged fast for multiple days. And, of course, I think people listening will be familiar with people in this area talking about the impacts on autophagy, the impacts on mTOR, IGF-1, all these different types of pathways that mechanistically build this picture as to why different forms of fasting are so rejuvenating or good for, let's say, either lifespan or health span extension. So maybe if I asked you, Alan, when you see the kind of discussions around, mechanistically what's going on, either on some areas where we have some legit aspects, other sides where it's maybe an over extrapolation, what are some of those mechanistic reasons that people commonly may hear, and then, any other commentary you have around the mechanistic rationale for such interventions?

ALAN FLANAGAN: Yeah, well, the mechanistic rationale is almost entirely predicated on rodent models and animal models including monkeys, so not exclusively to rodents, but generally, we're looking at animal models, because, again, of the issues that we discussed at the outset with what's your actual outcome; and as Niamh highlighted as well, that that factor of it like aging not even being recognized as a kind of disease, creating this kind of gray area where claims can be made. So the majority of the evidence is in relation to animal models, and most of it is using forms of ongoing energy restriction, and with animal models, particularly rodent models, you can even look at kind of generational effects as well. So a number of the more kind of researched potential mechanisms, one that you mentioned that probably in terms of the kind of wider Gen Pop conversation on this gets a lot of attention is autophagy, which is a process of the immune system surveying and getting rid of essentially damaged cells. So it's the ability of the immune system to detect damaged cells, and to essentially ensure that they're processed out of kind of the system and out of circulation. So at one level this is what's really attracted the potential kind of hyperbole around fasting in humans, because people have taken some of these kinds of data from rodent models, in particular, and assumed that an extended fasting period will result in an upregulation of autophagy in humans, and, as a result then that this is a good thing to do, fasting is going to kind of internally take out the trash to use a kind of crude analogy. The reality is in humans measuring autophagy as an outcome is difficult, and it also may potentially vary as far as like what threshold of fasting is likely to actually achieve that outcome, and I think, in this regard, it's important to stress that autophagy is still a perfectly normal, physiological process that will occur in individuals.

So what this claim is kind of focusing on is the fact that this particular strategy is going to upregulate this process, kind of beyond what you would normally get, and that that overregulated process is going to keep you kind of, yeah, like, in better underlying physiological health. And that's, of course, where things get tenuous – it is easier to study in a rodent

model; it's difficult to extrapolate either the fasting period or the degree of caloric restriction from rodents to humans because of the sheer difference in the size of the respective organisms. At 30% energy deficits, for example, in an organism the size of a mouse is a much more severe and energy deficit for that organism to an experience, than a 30% energy deficit in, for example, an 85-kilo resistance training male. So they're not the same exposure necessarily, even though on paper they may read as such, so it's difficult to say that, for example, a 16-8 intermittent fasting regime, which is one of the ones that need mentioned, is a popular strategy. That may be eight hours of a window that an individual is eating, but people forget the postprandial process may extend, and when people are eating meals within an eight-hour window, if they're eating larger meals, that postprandial period of processing that meal may be extending for five to six hours after the given meal. So if someone stops eating at 8:00 p.m. and has their large dinner at 8:00 p.m., and that postprandial process may extend to midnight or a little bit thereafter. So the idea that it's a full 16-hour fast, so to speak, is not quite technically accurate, and as a result then, it becomes difficult to kind of extrapolate and say that there's a particular hour period at which we will see autophagy upregulate in humans. So I think that's a claim that at this point is not really something that's very well supported as far as we could infer a kind of a deliberate outcome of any of these kinds of interventions.

There's some other mechanisms as well that, again, are interesting, but confined largely to rodent models; one is in relation to what are known as heat shock proteins, which are these types of proteins that protect other proteins in the body against damage, against oxidative damage, and either just straight calorie restriction in rodents, or indeed, an intermittent fasting protocol in rodents will increase levels of these heat shock proteins, and that is shown in these models to protect against damage. For example, if you're looking at rodents already with diabetes, there's protection against some of the adverse effects of glycation and elevated blood glucose levels. There are some, as far as fasting and the brain goes, which is always a big one, the bros will always

talk about fasting enhancing cognition, again, there's some evidence in animal models that energy restriction, caloric restriction, or intermittent fasting might enhance brain derived neurotrophic factor, BDNF expression; and we know that BDNF is involved in kind of regulatory processes associated with learning and memory. And then, there's also what is a very common point of focus for longevity in particular is the effects on insulin like growth factor 1, IGF-1, and insulin itself. And so, there's a lot of interest in the longevity kind of space and conversation that maintaining very low levels of IGF-1 and insulin is a positive. And so, the bros have started sticking in continuous glucose monitors to try and maintain blood glucose levels within certain ranges the entire time. And again, a lot of this is quite interesting and speculative as far as human data goes, in rodents, yes, you can see that various caloric restriction protocols and intermittent fasting regimes can lead to a reduction in IGF and insulin, but really extrapolating that to an effect in humans is, again, a kind of a tenuous jump to make, because, like I said, the 30% energy deficit in a rat is not equivocal to the 30% energy deficit in people. So there's a number of mechanisms affecting various body systems, but the weight of that evidence is in animal models, and that's where we get into some of the interpretive and extrapolative issues with applying this thinking to humans.

DANNY LENNON: Yeah, I think we could spend probably multiple hours talking just about some of the mechanistic claims in this area, and as is always the case with most quackery, that is where most of the focus gets placed of an over reliance purely on mechanisms and not much else. And, of course, some of those terms is where you see most of that occur, whether that's autophagy or some of these other areas that you just mentioned. So we won't belabor the point too much, other to note for people, because I'm sure they've heard of these things discussed elsewhere is that these are real processes. So autophagy does take place, but noting that is very different from saying a specific intervention like fasting will increase this process to a greater degree than other things one may do in normal day life to the extent that it will have some sort of end result on a health outcome. That is the real

question we care about as opposed to mechanistically if you restrict something, does a certain process get affected. So again, maybe that's another place we can talk about at a later quack asylum, because there's many claims made in that area, but for now, I think with that setup, we can maybe start working through what evidence we do have. And again, we don't need to spend too much time on some of the experimental models, but I think it really sets the stage for what has been now looked at in humans. So with some of the animal data particularly, Niamh, with some of these trials, which ones do you think are actually the most interesting and ones that can maybe that were able to provide us with useful hypotheses of what might be going on or that there may or may not be benefit or just interesting ones to bring up amongst all of the animal data that has been published?

NIAMH ASPELL: Yeah, so there is an abundance of animal data currently out there. I think there's some really interesting studies in rhesus monkeys in the US, so there's two particular studies, one of these studies came from the back of that initial biosphere experiment, and they've done a couple of different studies. This is in the Wisconsin National Primate Research Center. There's a professor there called Ricki Colman, and she published a really good paper in Science in 2016, looking at its calorie restriction, and how it delays disease onset and mortality. So a lot of these animal studies were either showing longevity, or they were showing improved health span, or reduction of age related diseases. What's good about the animal models as well in monkeys is that they've been followed up for very long periods of time, so this particular one, by Colman, the monkeys were followed up for a 20-year longitudinal study, and they showed that moderate calorie restriction reduced the incidence of a number of different age related diseases at this current point in time, so some of the animals are still alive. So in terms of actually, and like what we'd mentioned earlier, determining longevity, most studies don't follow up either humans or, well, it's different when it's a mice model, but with humans it's more difficult for us to kind of show those documented increases in longevity. But in this particular study, they showed a reduction in the incidence of age related diseases, and that was at the

time of reporting that. But, in addition, they observed changes in terms of their glucose metabolism and reduction in diabetes, cardiovascular disease, neurodegeneration, but this was following another study that was done by the National Institute of Aging back in 2012. This was published in Nature, I think the author was Madison al, and they looked at the impact, again, same thing, calorie restriction on the health and survival of monkeys. And this was again another long study, so 23 years, they conducted this particular observation, and they initiated calorie restriction instead of early life, but in kind of middle or older age of the animal.

So that's one thing that's kind of challenging a lot of this research as well is when we define when is a good time to intervene, so I think when we talk about preventative interventions for aging, there's still no understanding of when we start preventing, because essentially, we're always in this kind of aging process. But for this particular study, they looked at older age animals, compared to controls, so they calorie restricted monkeys, and they demonstrated again that they had improved metabolic profile, and that they may have less oxidative stress, and they checked this or used kind of objective markers looking at different plasma and inflammatory markers. And when calorie restriction was initiated in younger monkeys, there was a trend for delay of this age associated disease onset, but there was no improvement in their overall survival rates, whereas the longer the older monkeys seemed to be able to, there was more demonstrated effects in that later stage of life. But it was very much dependent on the environment and the genetic factors with the particular monkeys as well, so there's one other research study that was done in monkeys, and it was the same that they showed the total opposite, but they were looking at a different type of monkey, and they felt like it was the genetic factors that played an important role in that. So I think there's lots of evidence in mice, there's an awful lot – a lot of the Valter Longo work initially was done in yeast and bacteria. Then he did a lot of animal models, and they have some really, really interesting data on anti-cancer effects. So they demonstrated in a number of studies, I think it was – there's a paper published in 2014 by Cheng et al, which is part of the Longo group,

and they demonstrated that mice given that fasting mimicking diet, the one that I mentioned previously, where it's kind of a very prescribed standardized diet, became protected after six cycles as they were receiving chemotherapy, and also a fasting mimicking diet. So these particular mice were given these FMD strategies in midlife to reverse the effect of aging on their white blood cells, so that's what they were focusing on as the target. And during that middle age, they were twice monthly given this FMD, so I'm not sure how that, again, in terms of translating that then to humans, what does that mean, in the case of humans, if you're twice monthly giving mice FMD diet. So there's two cycles of this four-day fasting, and at the starting point, they had an impaired white blood cell profile, and then they show that their white blood cell profile returned back to normal levels, or what was seen in the mouse's youth compared to mice who just had a normal regime. They also then demonstrated that the mice that followed the FMD strategy had 50% less tumors later in life and they were more likely that those tumors that they had later in life were benign, so they were in cancers. So the same lab provided similar evidence a couple of years later, where they looked at FMD alone or in combination with chemotherapy, and it was shown to be effective in short term starvation again, in reducing tumor progression that was cancers in mice. So that was a lot of their kind of initial work, and since then, we'll probably get into these other studies they have done more clinical work in humans to demonstrate some of these outputs as well.

DANNY LENNON: Yeah, we'll definitely circle back to the human trials, looking at cancer, and also some of the other human trials that looked at the FMD, particularly. I think with the two rhesus monkey studies it's quite interesting, because on one side, we're using something like rhesus monkey, which is obviously much more similar to a human than is going to be in a mouse model, or certainly, in a yeast or fruit fly or so on. And then also the length of time that they had these trials going on, and the degree of control you can have in that particular situation, and that these trials were basically done in parallel, but – and one of the things you talked about in the statement that is quite interesting is you see these very different kind of

set of results of in the Colman study you see from Wisconsin, where you actually see a kind of clear benefit on the longevity and also the risk of these age related diseases, whereas you don't really see that in the Madison study. And you mentioned there's some of the reasons are the limitations around why comparing those two directly is challenging, even though they're both done in rhesus monkeys for as long period a time, and we probably don't have time to get into all of these, but one of those was differences in diet, and that's kind of interesting then as you start looking through of how they formulated the diet in the two different studies, and essentially, if I remember from memory, because of the way they formulated diet in the second trial of basically just what nutrients they need, and we kind of put this together in a formulation, it was so unpalatable to the monkeys, they had to like just load it up with loads of sugar. And so, now you have this kind of very formulated high sugar diet that's quite unpalatable initially, versus a diet that was more similar to their typical chow that you'd see in experimental conditions, and has been suggested as one of a number of reasons as to why there may have been differences in there. So I don't know if any of you had any other aspects of the two rhesus monkey studies that you found interesting, or if we can glean much from the conflicting results.

ALAN FLANAGAN: Well, I thought one of the points that was raised, and like the paper contrasting and comparing the effects of the studies was the age of initiation of caloric restriction. Again, it's easier to take, in one of the studies, they were initiated to a 30% energy deficit after weaning. It's very difficult to, again, take a model like that and extrapolate to humans as far as like long term caloric restriction goes, even the various cohort studies that have kind of looked at caloric restriction or tend to caloric restriction, like, there's a lot of assumptions built into them as far as like we would expect behaviorally that no one is maintaining a 30% energy deficit every day of their life for a 30-year period of time. And as Niamh discussed at the outset, even the short term kind of results over a couple of years in the biosphere study as far as like health outcomes and wasting went. So yeah, the experimental model in terms of the sustaining of an

energy deficit over a period of time that you're able to do when you're controlling monkeys is obviously going to be difficult I think to extrapolate to free living adult humans.

DANNY LENNON: So you're not recommending to calorie restrict children after breastfeeding?

ALAN FLANAGAN: Yeah that's it!

DANNY LENNON: 30% deficit.

ALAN FLANAGAN: But that's it, calorie deficit for life now, that's it.

NIAMH ASPELL: Yeah, they know no better, yeah.

ALAN FLANAGAN: Yeah, exactly. They don't want enough, that's the thing, those damn babies.

NIAMH ASPELL: Yeah, I think that's the thing in a lot of the fasting diets as well, and you can – there's a bit of, not confusion, but I think people think, well, the amount of fat I'm taking up a fasting regime, so that means I can just eat in this eight-hour window, I think that just means I can eat whatever I want, so I'll just go wild for those eight hours, and then, sure, of course, your fast is fine, because you're absolutely stuffed from having just been through eight hours. But I think when you look at the FMD diet, or the diet in biosphere, the ones that they recommend, they're very much, they're very nutrient dense diets, and they don't go beyond – I think the calorie restriction comes as a byproduct of the fasting, it's not that they're so much saying that you should calorie restrict, it's just reducing that window of time. But if you continue to eat kind of well, and you're not trying to overcompensate for the time where you're not eating, then that's where you potentially see a benefit, but it should still be good quality food within that time period. So like going back to that where they had to, if they wanted to restrict the monkeys, and they had to bribe the men, they were like, look, you can have food for this period of time and release it with sugar so that you'll...

ALAN FLANAGAN: They'll come back...

NIAMH ASPELL: Be compliant with the intervention, and I think – and that's one of the challenges with fasting as well, that it might not suit some people, because if you are depriving yourself for a majority of your day, sometimes people are more likely then to make poorer choices or to use that time period to kind of eat what they kind of want. So we can probably get into the flaws in fasting diets or some of the limitations, but I think with the animal studies, what they have to get an animal to do based on their environment and their behavior isn't the same environment and behavior that most free living humans will be living in.

ALAN FLANAGAN: And there's something really key in that, because what one of the key questions that we have to ask if we're kind of trying to glean something from comparing rodent and monkey models to potential application in humans is – and this is a big question, generally in the kind of time restricted eating and intermittent fasting literature, not necessarily related to longevity, but certainly related to potential metabolic benefits is, is there an effect independent of energy restriction, is there an effect independent of weight loss, and for some metabolic markers that has been shown. So from a longevity perspective, what becomes really difficult is we have these models in rodents and in monkeys that are almost exclusively relying on the effect of some form of calorie restriction, however, that is achieved, whether it's just linear calorie restriction day to day, or whether it's the creation of an overall energy deficit through a time restricted feeding or intermittent fasting type of protocol. And so, the question then becomes, well, could, for example, the extension of a fasting period of some description and of some duration, be sufficient to create an environment physiologically that results in some of these kind of beneficial purported effects without necessarily having to create this kind of linear daily restriction and energy. And I think that's a question that is going to be very difficult to answer, I mean, if we're talking purely from a weight loss perspective, most of the quality studies would suggest that there's no real difference between linear energy restriction and a form of intermittent fasting, there's no extra advantage conferred. It's the overall creation of a reduction in energy by whatever means that appears to then underpin the actual outcome. So I

think there are some big questions that we need to kind of ask then about, well, is this even applicable if it's not necessarily about the model of how the energy restriction is achieved, rather than the magnitude of that energy restriction per se in organisms that may have similar pathways to humans and rodents and monkeys do, and monkey aging certainly would appear to be a more proximate model for human aging. But we've got some big questions there as far as taking studies that are really predicated upon energy restriction maintained over time in these animals, and then, assuming that some sort of extension of fasting for however long and using whatever protocol may actually achieve those similar effects in humans, and I think that's where the quackery comes in, because people take that and make these huge deductive steps. And the reality is, as far as human evidence, there's very little there to allow us to make those deductive steps.

DANNY LENNON: Yeah, and you say that despite the anecdotal reports of people seeing themselves get younger through fasting.

ALAN FLANAGAN: Exactly, yeah.

DANNY LENNON: Fantastic

NIAMH ASPELL: The director of the National Institute of Aging was asked about would he take some of the supplements that David Sinclair currently sells, and he said, no, he wouldn't, because he's not a mouse. I think that's just the best way of...

DANNY LENNON: Yeah.

ALAN FLANAGAN: Yeah.

NIAMH ASPELL: I'm like, okay, well if the director of the National Institute of Aging isn't advocating, and I think that says a lot...

ALAN FLANAGAN: I don't think I'd be wearing a CGM either just for my day to day data collection.

DANNY LENNON: So with that, let's maybe turn to the human intervention trials that we do have and actually

investigate, well, do we have any good quality evidence to go on, what is actually there, what, if anything, can we glean from that seeing as thus far we've suggested that there's maybe not as much strength in them as people may suggest. So there was a number of studies done in humans that you had mentioned in the statement, Niamh, and maybe one of the first ones I think we can start with that's quite interesting is the Horne et al 2008 study that was looking at members of the Mormon church. Can you maybe give an overview of that particular study and why you thought it was useful to bring into this conversation?

NIAMH ASPELL: Yeah, I suppose, this is one of the kind of first observational studies and the objective of this study was never to kind of look at calorie restriction, so in this particular study, they examined fasting, and they were also interested in major adverse clinical outcomes in humans. So it was a population based study of fasting, and they wanted to also look at reduced tobacco use, and their main kind of target of interest was low coronary artery disease in this particular population. So this particular study was conducted, let me get this right, the Church of Jesus Christ of Latter Day Saints, on Mormons, I needed to say that when slowly, so I didn't get any of it wrong. But initially, this study was conducted, they were essentially performed to see if they could challenge the assumption that low coronary artery risk was attributable to exclusion of smoking in this particular population. So the study found that this particular group had a lower general risk of coronary artery disease than that of other religious preferences, despite after adjusting for smoking. So they still had this though coronary artery disease and it wasn't so much that it was related to the fact that not many of them use tobacco. So they wanted to better understand why there was low heart disease essentially, and fasting history was evaluated in a number of people in this study. So in 448, this group then were of unrestricted religious preference that wasn't based on religious or driven by religious reasons, but the patients were reported in routine fasting, they had a lower odds ratio of having coronary artery disease than those who didn't fast. So interesting they – so they say these religious

preferences, those who reported kind of continuous routine fasting system, those implemented daily kind of into their lifestyle or periodically into their lifestyle had much lower risk of coronary artery disease, but then also of other metabolic diseases such as diabetes. They followed up, it was similar, there's another observational study, and they wanted to confirm and expand their fasting association with coronary artery disease and diabetes, and they use the same fasting survey as when that was implemented in the previous study. And they evaluated a new group of patients who had cardiac history, and that primary outcome for that one then was looking at regulation of other metabolic markers, and they showed that it was not significantly associated with fasting. And so, the second study found that patients who routinely fasted whereas the first didn't, the second study showed patients who routinely fasted had lower odds of diabetes, and they reconfirmed this first study where they showed that there was lower risk of coronary artery disease. So the fasters had lower blood glucose concentrations and BMI. So there is similar evidence for changes in their BMI and fasting like behaviors, and they would typically fast for periods of 18 to 19 hours, so there was no breaking of their fast within that time period, so they were quite strict fasting regimes, I suppose.

ALAN FLANAGAN: Yeah, couldn't stop giggling, but the Jesus Church of Latter Day Saints is the Book of Mormon, if you haven't seen it, so just the line cut into my head, I am Nelson Mandela's tears. So if you haven't seen the Book of Mormon, it's really worth it. But it's the same with the Adventist Health Study in terms of there's a challenge in teasing out some of the wider potential influences have kind of more strict religious observances, and generally speaking, there is research that suggests that people who are religious and are part of an active religious community, for example, live longer anyway. And that may be because of all of these various ancillary factors like community and otherwise, I thought the LDS study was interesting, because it seems of all of the various kind of modeling that they looked at as far as other aspects of their behaviors went, the only one that seemed to be robustly significantly associated with artery disease was the religious worship associated with fasting. And

so, there are likely some kind of unmeasured factors, I think going into these kinds of outcomes when we're looking at very religious communities, and there's potentially some additional factors going on with the methods and the kind of overall prescription of their fasting, so that's where the Adventists are quite interesting to look at, because in the Adventists who are more, who do have some form of kind of extended fasting, it's not just a random window, so their traditional meal pattern is they rise very early, there's a very early breakfast, and then a large meal then kind of like the afternoon. And then, so it's these two big meals in the early part of the day, and then an extended 16 to 18-hour fasting period from that. So if we're looking at human research on time restricted eating, for example, where energy is front loaded to that early part of the day, there may be some extra stuff going on there as well, such as, it could, yes, the fasting duration might itself be a factor, but it also could be the elimination of evening eating that has a beneficial impact on blood lipids and certainly blood glucose levels. It could be the duration itself, it could be the kind of aligning of the meal intake with a period of the day where there is kind of a more optimal metabolic responses to food intake from gastric emptying to digestion, absorption, and metabolism of nutrients. So, this is one thing that is yet to be teased out as well in this research is, is it the duration of fasting itself, is it the restriction or elimination of evening energy intake, is it the kind of enhanced potential kind of metabolic effect of distributing the majority or indeed all of your energy too early in the day, or any combination of the above. And then, I think, from the religious standpoint, if you really add in some of these other factors that you see in terms of associations between community, religious practice, and observance, and indeed kind of health span, which exist as associations independent of nutrition, it becomes a difficult, albeit, very interesting kind of set of observational findings, but certainly a difficult mix of potential practices and exposures to disentangle.

DANNY LENNON: So therefore, one could say, if you wanted to enhance longevity, you could indeed join the cult of lifespan extension in that community and worship their gurus

and have this kind of religious fervor around, and actually will benefit you.

ALAN FLANAGAN: Yeah, or just go vegan. You've got a whole new church, got a...

DANNY LENNON: There's so many choices in nutrition.

ALAN FLANAGAN: A whole new God to pray to.

DANNY LENNON: Nutrition is not short of cults for you to join.

ALAN FLANAGAN: Yeah, there are so many belief systems you can adopt really, yeah, you've come to the right place.

DANNY LENNON: But it's interesting, those remaining questions on fasting generally, because I think we've talked about this before in any fasting research for any kind of outcome, and particularly, some of the chrono stuff that we still don't know, like, of all these potential regimens, there's probably an endless way to set it up in terms of how long you're fasting, where you place those calories in that fast, the duration of each one, etc. and really, we don't know which one is, quote-unquote, best, because it's very difficult to compare all those things in time.

ALAN FLANAGAN: Yeah, and because the fields just kind of like got boring, and people just seemed to be content to just reproduce the same TRF study is the one that came out last week. So there's a real kind of creativity/lack of imagination issue, unfortunately, that's kind of acting as a bit of a barrier, and there aren't really any robust studies looking to try and actually have meaningful comparisons against some of these; and the ones that do exist that have kind of attempted, for example, looking at a difference in the timing of the window, haven't particularly been well controlled. So yeah, there's a huge amount of scope for some additional work to be done in this area, but yeah, as far as teasing out the component parts go, there's a lot that we're left with open questions.

DANNY LENNON: Yeah, there may be a lack of imagination in some of it, but there's no shortage of imagination in the internet generally to make up for that by filling in the answers that we don't know.

ALAN FLANAGAN: Yeah.

DANNY LENNON: That's easily done. Maybe to round this out, I don't know if we want to touch on any of the RCTs that were done in this area, because, again, a number of different acronyms we can look at here, we have the calorie study, the feel good trial and InterFast trial as well. Even if we don't get into the details here, is there any kind of big takeaways you would have from these Niamh that are worth mentioning in relation to the actual RCTs that we do have, currently?

NIAMH ASPELL: Yes, I think these are all kind of merged together when they're evaluating fasting or calorie restriction. I think there's a couple of things we can kind of take from them. I think the calorie study, maybe there's like an overall reduction of like 11%, no, that was, sorry, the calorie study, so they did a reduction in calorie intake of around 12% data daily calorie intake, and then you've got the InterFast study, and they had a much greater reduction overall in calorie intake. They had, on average, 37.4% reduction in calorie intake in that population, so there is a calorie reduction component to all of these interventions. We still need to understand how much of a reduction is required, and how much of a reduction can we realistically expect research participants to adhere to. When it comes to longevity, we can't follow them up for long enough or subject them to some of these extreme diets for so long to really test those things out, but I think as long as the metabolic responses are there, then that should be kind of sufficient to that extent. The InterFast study is a really well designed study actually, I think it is, I think it's quite good in the sense that it's designed quite well, but it's a pilot study, so it's not statistically sound. But in terms of what a study should look like, if you are to recruit a lot more people, I think it's a good example of that.

So this study was conducted in Austria, where essentially, they had a great – it was a cohort study, prospective cohort study, where they had 60 people either doing alternative day fasting. So this is a hard thing, I think, to get a participant to commit to, but they ate normal one-day, fasted the next day, and continued to do that for six months. And then, there

was a controlled group who just ate as normal. And then, once the prospective study was over, they did a randomized controlled trial in a smaller group of participants, and again, they induced the alternative day fasting approach. I think the biggest thing around this, irrespective of what the results were, so they showed things like what you'd expect, if they're eating 37% less calories, there's a reduction in body weight, and also what you'd expect and seeing from other researchers that the body weight loss was fat around the abdomen, there was very minimal loss in terms of lean muscle mass that improved their fat to lean mass ratio, so there's good results in that sense, whether you need to not starve yourself half of the week to get that, I'm not sure. And again, there was improved lipid profiles, improved metabolic profiles, really marginally though, because this is one of the things that this study, it was – and usually with these pilot studies, as a first demonstration of safety of the diet, they have to recruit healthy volunteers.

So if you have a healthy volunteer at normal blood glucose, would a very normal, like, their actual baseline blood pressure levels were very, very normal, like below 120 over 80, and the average is 117 over 70 something, so they were like peak condition, and they were trying to improve on that. But I'm not sure if it is improving on that, if you're reducing their total cholesterol below a level. So in terms of actually demonstrating positive benefits in this kind of population for a short period of time, it is kind of challenging, but what they wanted to show, essentially, from this was compliance, could they stick to the diet, it looks like they did, the controlled group did reduce their calories on average as well, but not by as much, by about 10%. So it goes back to that calorie restriction, so maybe the 10% reduction in calories is not quite enough, maybe you do need a bit to reduce it a little bit more to see some of these particular changes. In terms of the actual, just overall differences between the groups, they are observable, I think in terms of the statistical analysis on it, I would say that, you know, look at it very, very cautiously, so the sample size is only 60, and they – I went on to look at the – they published their protocol a couple of years beforehand, and they have 20 endpoints, which is quite inappropriate for a sample size of 60 people to

just throw everything at it and test absolutely everything. They did try their best to follow good protocols in terms of statistical analysis, and they did apply like Bonferroni corrections, which will help reduce some of the risk there, you know, it's kind of a more conservative way of analyzing outputs if you've got loads of tests that you're actually looking at, so they tried to do that, but they didn't have a power calculation to see if what they were actually applying was appropriate. And I think that's a bit weak, because there's plenty of evidence to show that what the effect size should be, so you do have all of the materials there to do a power calculation. So I think it's obviously a restriction around actual just like either like with research, we either are poorly funded in nutrition research, so you can only recruit a certain number of people on your study, because they're very, very costly, but it did show some hints at certain things, like not a lot of things, like a lot of they have so many endpoints in this particular study, but it does point to some things that might be important and should be explored, kind of, more of a long term. The thing that annoyed me about this study though, it's a study in midlife, and it started at age 35, which I was like pretty, pretty annoyed about, like, I'm nearly there, and I'm like, I'm not midlife, so I think defining these age...

ALAN FLANAGAN: Don't call it midlife, yeah.

NIAMH ASPELL: I'm like, midlife, these youthful young creatures...

ALAN FLANAGAN: Yeah, pretty mean, yeah, started in infancy.

NIAMH ASPELL: Yeah, that wasn't the main issue, but it was midlife, so it was 35 to 65. But if you think about physiological changes that someone who's 35 will experience compared to somebody who's 60 will experience, and you put them all into this tiny group of 60 people and wait to see if they're aging, slower, better, faster, whatever it might be, that's a very muddled sample, in my opinion. So I think their design was good, but they should just duplicate the size, and it is really hard with aging studies, and my own PhD looked at preventive strategies for aging, and it's very hard to pick that point if you're only going to follow up people for a certain period of time to pick that point where you're

most likely to be able to intervene, because we don't know that's different for everybody, I suppose – it's very person dependent. But I think it's a nicely designed study apart from that, I think that would be good, and then, what they're trying to do, and I couldn't find their results, I don't think they've published that yet, and I'd say probably COVID threw a spanner in the works for them, but they published the findings at the end of the six months – at the end of the intervention, which was four weeks, so there's six weeks perspective, and that four-week intervention, and they published the findings from that, and the next plan that they had was to follow them up for two years, and then, to publish, if they, after the intervention, maintained any of these improved metabolic markers, or they maintained their weight loss. And that's what I think's interesting, because I would imagine they went back to their normal eating patterns, regained the bit of weight that they lost more than likely, and probably went back to their baseline profile. They haven't published this, I'd imagine the follow-up was probably supposed to be last year, which probably made it difficult for them to do that, but that's the thing with these fasting interventions, are you likely to alternate day fast for the rest of your life in order for you to have a cholesterol one point lower.

ALAN FLANAGAN: Yeah.

NIAMH ASPELL: Like, you'd be really sad and miserable, and I'm not sure – well, maybe not everybody, but depending on your lifestyle and your behaviors, if you're opting out of food Tuesday, Thursday and Saturday – tricky.

ALAN FLANAGAN: I'm really underwhelmed by the ADF research overall, I have to say, for the magnitude of what's being asked to participants, and not just the recent study, like, I mean, like you said, that point about the power calculation is really important, because there's a big body of literature – Krista Varady's research in Chicago, like, the ADF diet, going back several years now, so it's not like this is some sort of novel intervention, and this was kind of the only study to try this. There's a literature on ADF, and, in fact, it was one of the earliest intermittent fasting protocols. There was research on the ADF way before there was

any of these 16-8, or other kinds of early time restricted feeding protocols, and I think for the magnitude of what's being asked, so when we say, alternate day, I think it's important for listeners to grasp that that means not a 24-hour fast, but 36 hours. In effect, you're going from your dinner on a Monday evening to your breakfast on a Wednesday morning. And if you look at some of the prior research, the attrition rate tends to be quite, quite big from the studies, and overall, the actual magnitude of even when studies have used more clinically at risk populations, the magnitude of the benefit from a metabolic standpoint is largely small – for how extreme the protocol is, the return on investments is really not anything that is overwhelming at all. In fact, I would say, it's rather underwhelming, particularly, once you then compare it to just kind of linear energy restriction or some more moderate, but daily time restricted eating or feeding protocols. So yeah, and that may be because of the nature of the intervention that either during it or indeed after cessation of the intervention, there's just kind of a compensatory comeback, so to speak. But I think when we synthesize the body of ADF research overall, including the recent stem the InterFast study itself, I have to say, I'd find it very difficult to justify telling someone that there is a metabolic or physiological return on investment that's worth the effort of not eating every second day.

DANNY LENNON: Yeah, I mean, this area, and this is more of a broad general point, but if someone is looking at interventions related to longevity, if someone's going to start including things that are aimed at, say, the health span aspect, and using that to support something like fasting, well, we already know a variety of dietary patterns that work in terms of prevention of the main chronic diseases that typically are going to kill someone before the, say, median life expectancy. So, let's say, cardiovascular disease, which we've talked about a million times on this podcast around, there are things that are known around dietary patterns which will, say, reduce that risk. And so, is the claim in that by fasting in some way, you're going to reduce the risk of that or a neurodegenerative disease or something else to a greater extent than what we already know through other nutrition

research, or is the claim that even beyond that, that you're actually extending the lifespan? And I don't think we can really see evidence for either of those where you can reliably extend lifespan in humans to an appreciable degree, or that it's doing something unique in terms of reducing that morbidity time at the end of life of some of these main age related diseases, beyond that which would be achieved through other dietary changes that we already have an abundance of evidence for, but that seems to me to be where things are at. I don't know if there's a difference in how you guys see it, but yeah, just seems to be grasping at straws much of the time.

NIAMH ASPELL: I think so, there's a really nice infographic that the Lancet Commission published a couple of years ago, around dementia prevention and risk factors for dementia, and it says like life course model, and it gives an attribute to the most potentially modifiable risk factors for dementia, which is kind of one of the most prevalent age related diseases, and it attributes a certain percentage to different behaviors throughout your life, so the first model that they presented included like APOE, which is the genetic variation that predisposes you to dementia. But apart from that, they've included a list of others, based on all of the evidence, and this is a worldwide type analysis, and they present in that that diabetes contributes 1% of your risk, and obesity contributes 1% of your risk as well. But things like social isolation is up as high as 4%, dementia is 4%; hearing loss is a really big one, that's 8%. Education, early life, so these are much more heavy hitting risk factors for dementia, but we're putting a lot of emphasis on something like dietary restriction as having a major impact on health related or age related diseases, when I think their contribution isn't as significant. I think social isolation or depression, I think, if those components are a factor in someone's life at older age, and then you say, well, to live longer, to make things a bit easier, you could also just stop eating every second...

ALAN FLANAGAN: Calorie deficit world.

NIAMH ASPELL: Yeah, I'm kind of like, it's balancing all of those things, it's kind of, I think it's getting those basic things right, and then having those traditional diets

where we see where these groups of centenarians that have been evaluated, there's typically, like, there's obviously a genetic component, but then they also have these quite kind of just general healthy diets, and they seem to be able to avoid obesity or avoid then diseases that can be related to obesity or comorbidities related as well. So I think it's bigger picture.

ALAN FLANAGAN: They have behaviors, if we're really looking at some of the kind of components of like Blue Zones, the traditional Mediterranean diet research, it's things like communal eating, they eat these meals together, and again, it's that social aspect, it's the community aspect, there's a lot of intangible factors that are going into, I think the relationship between the nutrition side of things that are not necessarily to do with what's on the plate, although that is important, and I think there a lot of the component feeds into the wider psychosocial aspects and behavioral aspects and communality and community aspects of foods in these cultures, in these Blue Zone type diets, and in these kind of Mediterranean longevity populations. So I think you're right, Niamh, I think an emphasis can be overegged, as typically happens with the want to eat side of things.

NIAMH ASPELL: Yeah, there's a lot of really rich and successful people at the moment who just want this cure for life where they can just live forever and ever, and they're kind of I think really pushing some very strange supplements and drugs and stuff, and I think what the Twitter CEO said a couple of years ago, he just eats one meal a day, he has seven meals a week, and that's it, and that's what keeps him sharp. And then you just have people who aspire to kind of obviously to be really successful in their career, they look up to these people, and they're like, oh well, if this guy's eating one meal a day and he owns Twitter, that's got to be the way he did it.

ALAN FLANAGAN: Brings into question the more philosophical aspect of why would anyone want to actually extend their time on this planet, but, hey...

DANNY LENNON: When I posted on social media about our longevity statement, a friend of mine...

NIAMH ASPELL: “I'm trying to get this over”.

ALAN FLANAGAN: Yeah.

DANNY LENNON: A friend of mine, Hugh, is a psychologist, and he just replied to me, saying, what people really need to do is just make peace with their mortality. And I was like, yeah, that's right. You don't need to, how do I eat for the rest of my life to extend it by a month.

ALAN FLANAGAN: Yeah, trying to get out of here early.

DANNY LENNON: Wait, I have to stay here longer?

ALAN FLANAGAN: Yeah.

NIAMH ASPELL: Yeah, if you put so much stress and pressure on yourself to get to, so it's a race, isn't it, like, someone who wants to get to this certain point and achieve that, and like, yeah, but you need like, are you enjoying your kind of ride there, like, probably not, I don't know. And then also, if we don't have that health span increase as well, like, to get really bored on it, and we're all retiring under 70, but we're living till we're 120, like, every economy is just going to crumble, we're just going to have a lot of really old people knocking about nowhere to put ourselves, we're not having kids anymore, no one's going to look after us, and we're just an absolute drain on society.

ALAN FLANAGAN: Exactly.

DANNY LENNON: Pension starts at 100.

ALAN FLANAGAN: Let's make a pact.

NIAMH ASPELL: I am not working until I’m a 100, not a chance. I'm clocking out at that average life expectancy of 82, I don't want to be exceptional in any way.

ALAN FLANAGAN: Yeah.

DANNY LENNON: So before we finish up, I know we're coming close to time here, but there is this one area that we haven't really touched on that I think is worth discussing because of its specific nature, and that was some of the trials related to the fasting mimicking diet from

Valter Longo's is group where, as you noted Niamh, much of that has focused in around cancer treatment or as an adjunct to typical cancer treatment, and could this potentially lead to better outcomes in a few different, in specific cancers or specific tumors even, which is an important caveat here. So can you maybe just give us an overview and, again, people can read this statement for all the specifics, but an overview of what has actually been done in humans related to the fasting mimicking diet, particularly in relation to using that in conjunction with typical cancer treatments?

NIAMH ASPELL: Yeah, so there's lots of work been on there, and that's where I'd mentioned previously that there is a particular lab, we're trying to do some of these fasting interventions in oncology, so with cancer patients as an adjunct treatment, so they would have been receiving either radiotherapy or chemotherapy as well. But they were initially starting with just these water only fasts, but they find that the oncologists thought they were too dangerous to do it, and then, the patients going through such kind of treatments didn't want to then, on top of that stressful period of treatment, to just drink water. Okay, so it wasn't like they're obviously their priority at that time, so that's where the fasting mimicking diet came about. So it's a low calorie diet, around 50% less calorie intake, and it's predominantly plant based, so it's a medicalized diet, and there's obviously a lot of oversight, because these are patient populations. And there's a couple of studies, and I think I've linked the DiRECT study as an example there, and there's another ongoing study at the moment, and these are RCTs on the focus, they're following the usual pattern of how these research studies should be done. So there's initially focusing on safety and tolerability, so in cancer patients who are currently undergoing treatment, they want to be able to see if it's safe for them to do this FMD diet at the same time, and that it's also tolerable. So what you want is to have very few adverse effects related to the FMD intervention, which is really challenging to analyze and to assess in these studies, because we know, obviously, there's a lot of metabolic changes when a patient has cancer and they're undergoing chemotherapy. So it is quite challenging for them to demonstrate that, but they have done a

number of studies in women who are either stage 2 or stage 3 breast cancer, and they show that FMD exerts some protective effects. So it's not only to the toxicity of chemotherapy, but also to the people who are getting radiotherapy and pathology kind of responses. So what they have shown in their animal models for this is that the FMD, the fasting process seems to be able to target cells that aren't being affected by the chemotherapy, and kind of repairing and cleaning those as such, so it's not interfering with that process. So the clinical investigations in terms of effectiveness, there's not been much work done there whatsoever; there's a new trial that was registered last year and they reported only a few side effects from giving patients a five-day MND intervention, and that was administered in cancer patients with malignancies, with solid tumors as an adjunct treatment. So this is in combination with them actually receiving medical treatment, which I think is really important, because sometimes you hear kind of these horror stories of people who will use fasting as a means to kind of self-treat themselves in the event that they might have a cancer, which is obviously not what these types of studies are trying to demonstrate; they're trying to demonstrate that in conjunction with chemotherapy, that you might see greater improvement if you're also fasting as well. So patients in this particular study, they received the five-day fasting on an average, they had – so it was once per month that they received the five-day intervention, so it will be based on your routine or whatever the strategy is in terms of how often you're receiving your cancer treatment, and this was over a cycle of a couple of weeks. So on this particular study, on average, over the whole duration of their therapy, they fasted for five days, six times throughout the whole period of receiving the chemotherapy, which is kind of tricky with the outputs for this is they had reduced fat mass, which is hard depending on the side effects that the patient was also having from receiving the cancer treatment as well. It's hard to distinguish between where that resulted from. They also had a reduction in some inflammatory markers, which is positive, which I think it's hard to filter out at the moment, the efficacy side of things, because that is an exploratory outcome for any of the trials that I've reviewed, most of them are much more focused on the safety side of things, so

I think the next round of interventions are clinical studies that are registered, the primary endpoint of those are the efficacy markers to see if it actually improves medical outcomes, and in conjunction as well. So I think those findings will be really, really interesting, but we'll be still, I think we'll be waiting on those, but there's a very big belief within the medical and oncology community that work with these a lot of these researchers that they really do have a lot of belief that there is potential, and to include some of these strategies.

DANNY LENNON: Yeah, this is almost like a golden example of a case where you have some really good quality, exciting research, some really great work being done in a very specific context of certain types of cancers, certain types of tumors with certain types of patients, being evaluated for a very specific intervention, and that's all fantastic. And then, as humans, what we often do is do things that are disgusting, as is what you see in this area, where you get someone who's a nutritional therapist, or some other kind of non-qualified title starts recommending to everyone that, oh, if you have cancer, then fasting is something that can help you, and it's beyond unethical. But unfortunately, this happens, like, this happens regularly, and I've seen it happen, and that is where the kind of quackery side stops being funny, and it's starts like, oh, there's actually people who are talking about this, when they actually don't understand what they're talking about at all, and actually is probably kind of illegal to be doing it.

ALAN FLANAGAN: Yeah.

NIAMH ASPELL: Yeah, it's extremely dangerous, particularly, when, during cancer treatment for a lot of patients, your body composition can rapidly change for a number of reasons, and the interaction of all of those drugs, and then to put on top of that some uncontrolled or unregulated or unsupervised fasting, it's just really, really concerning. A lot of these interventions as well to have recommended to offset some of the negative consequences of induced sarcopenia or muscle wasting in these populations to combine the fasting with muscle training, and I'm reading these kinds of, thinking, you're forgetting who your target audience is

here, these are like cancer patients undergoing intensive chemotherapy; and I think they need to be careful in how this is communicated to these patients, because it's very much saying, you could do much better on your treatment if you also fast and go to the gym, like, it's around proportionality of ability and expectation, and it's also not going to work for every patient, and I think that's what at the moment, they're looking at different stages of cancer, and it might be more appropriate for certain cancers and at certain stages, but I think it's that medical supervision that is the most important thing.

ALAN FLANAGAN: Yeah.

DANNY LENNON: Excellent. I think that has everything that we had planned to cover, so maybe just to round this out, I don't know if either of you wants to end with some general thoughts in this area that you want to leave people on, if there's anything on your mind that is outstanding or anything that is particularly important that you want to leave people with, or anything else that you'd like to say in relation to this topic before we probably finish.

ALAN FLANAGAN: Don't worry about sticking around.

NIAMH ASPELL: If you're fasting just like, yeah, just don't go on about if you are fasting. If I meet you for lunch, don't tell me you're fasting, like, that's grand.

ALAN FLANAGAN: Yeah.

NIAMH ASPELL: Meet me in your window of time where you can eat, and you can tell me about your – don't tell me about it.

ALAN FLANAGAN: Yeah.

DANNY LENNON: Don’t tell me your biological age.

ALAN FLANAGAN: It's the least interesting thing about you, yeah.

NIAMH ASPELL: I know. I think David Sinclair declared to the world his biological age, but it's also he got tested with a company that he owns, so like, how likely was it for

those employees to tell him actually you're much older than you are.

DANNY LENNON: Yeah.

ALAN FLANAGAN: Yeah, you on the way up.

DANNY LENNON: Yeah, great. I really enjoyed that discussion, and I think related to this topic, one thing that we do have planned for a future podcast episode is going to be focusing specifically in on neurodegenerative disease, cognitive decline, and the role of nutrition there.