DANNY LENNON: Tommy, thank you so much for joining me on the podcast today

TOMMY WOOD: Thanks for having me. It's a pleasure to be here.

DANNY LENNON: Before I get into any of my particular questions, what is usually the best way that you like to introduce yourself at an overview level so people have some context for where some of this discussion will be coming from?

TOMMY WOOD: Sure. So my main day job currently is I'm a professor of pediatrics at the University of Washington. I work mainly in brain injury research, actually, neonatal brain injury research, but I think a lot of those principles translate over to adults which is probably the majority of the people listening. However, at the same time, I do a lot of work with various athletes and chronic disease populations, so I work with Formula One drivers, endurance athletes, some collegiate athletes here now, and a large group of people who are just trying to optimize their health through diet, nutrition, and various lifestyle practices. So essentially, what I try and do currently is create a framework whereby people can optimize their health and minimize the disease risk essentially over the entire lifespan, that's what I'm trying

to do and that's what my research will go into for the next few years, hopefully decades.

DANNY LENNON: Sure. And I definitely want to touch on the many aspects that relate to chronic disease risk over time and looking at how we can look at a health span and promote beneficial health over the long term. But to pull back on the brain metabolism piece, because I know you mentioned your work you're currently doing and your PhD was also specifically in neonatal brain metabolism, can you maybe just tell me a bit about some of the specifics of that because I find it quite interesting in terms of what that research focused on and maybe how that leans over into the work you're doing within the hospital too?

TOMMY WOOD: Sure. So my PhD was in a fairly narrow field as they tend to be, in a condition called neonatal hypoxic ischemic encephalopathy which is essentially when a baby goes to a full-term during pregnancy and then something happens around the time of birth and they come out, and there's some evidence of brain injury and that can either happen over days or hours before the birth or sometime during the birth and often the baby comes out and you don't really know what happened and you have to treat it. The treatment that we currently use is therapeutic hypothermia, so we cool the baby down for three days to 33.5 degree Celsius. And my research mainly looked at all the different aspects of the physiology of the response to brain injury in a rat model of this condition and particularly looking at the degree of hypothermia, looking at how actually the body's own physiology temperature responds to the injury, so the more injured you are, the lower your core temperature goes, and then this sort of translates out to various aspects of adult brain injury because hypothermia has been this treatment that we've tried to apply to almost every brain injury that we can think of, so after a cardiac arrest in adults, a traumatic brain injury obviously a very big one, and it hasn't really translated very well. And that's

because the population that we treat, the timing of the injury, makes it very difficult to apply that, it's much easier to apply that in the neonatal setting. But equally, we also see things like getting too hot or preventing getting too hot is definitely very beneficial to the brain after a brain injury, and that translates again traumatic brain injury, adults after cardiac arrest, all the way down to babies. So regulating temperature and how the body responds to injury in terms of its own temperature and then the temperature that you try and impose, say on the patient as a clinician, that was where most of my PhD was focused.

DANNY LENNON: Super interesting. Maybe a good place to get into this is what is it that's specific about either the brain or brain tissue and metabolism that goes on within the brain that we should know of first that relates to some of the things we may discuss around brain injury and treatments interventions and so on?

TOMMY WOOD: So I think the most important thing probably is how the neurons and then the other inflammatory cells in the brain respond to a specific injury and how – particularly, there seems to be this timing of how well the mitochondria work after a brain injury. And you have this period of time where you can instigate some kind of therapy and then see benefit, and it's probably in the six-hour range, that's about as long as you have after the injury. And if you instigate a treatment before then, you can essentially try and help the brain match the amount of energy it is capable of producing to the amount of energy that it needs, that's one of the reasons why we think hypothermia is beneficial. And again, this hasn't worked in adults sadly, but preventing hyperthermia, so preventing the body becoming too hot and basically you increase metabolic demand when the mitochondria are unable to match that, so that's essentially making sure that the mitochondria are producing as much energy as they can and

there's various ways to do that and then also making sure there's not extra demands that the mitochondria can't match. That seems to be a big part of seizures after brain injury, you know, how many cells in the brain die after injury, and so making sure you're matching that properly, that seems to be a big area where we start to see neuroprotection.

DANNY LENNON: Essentially, mitochondrial dysfunction is part of that injury cascade we would expect to see after a traumatic brain injury. And so maybe just if I take a step back on that, when we're talking about traumatic brain injury, obviously that covers a wide gamut of things – what do we classify as a traumatic brain injury?

TOMMY WOOD: Yeah, so you're right. Traumatic brain injury has a very wide potential range of things that come under that umbrella. So anything from a mild traumatic brain injury which would essentially be some kind of concussion that you frequently get during sports, you see it also very frequently in the military, car accidents, and then you might see some reduced cognitive function, executive performance, obviously you might see some differences in sleep habits and these various other ways that we can measure how the brain is functioning, and that can be from very, very mild where it might be very difficult to pick up a deficit, all the way through to massive traumatic brain injury where somebody has multiple skull fractures and you have bleeding into the brain, essentially, you have that entire range. When you have a single mild traumatic brain injury, like I said, you might not be able to pick up much, but there certainly seems to be a compounding effect. So one of them the models that we use in my lab is a repetitive mild traumatic brain injury. So imagine somebody who does a fight sport or somebody who plays American football and you're getting small concussions where you're getting knocked to the ground, you're getting your head hit maybe once a week or once every two weeks, and even though there's some time to recover in between, there seems to be this

compounding effect. And we're seeing more and more that people who engage in these activities for long periods of time, maybe decades or at least 10 years, depending on the athlete, then they start to see some negative effects, again, 10-20 years later after all of this sort of injury has accumulated.

DANNY LENNON: So how does that injury cascade, that we've just described, compared to, let's say, the pathophysiological events that occur with some neurodegenerative diseases, are they kind of two sides of the same coin, are they distinctly different, how should we think about something like a TBI versus neurodegenerative disease?

TOMMY WOOD: Yeah, that's a really good question. And I tend to see them as two sides of the same coin, and I think different people will have different cognitive models for how they think about these things. But when you're looking at neurodegenerative diseases, the most well-known or described is probably Alzheimer's disease; and the amyloid pathology that you get – amyloid being a protein that accumulates in brains of people with Alzheimer's disease, and that's the sort of, one of the hallmarks of the disease. And then there's also tau, another protein that aggregates and tau hyperphosphorylation is something that you see in Alzheimer's, in later stage Alzheimer's disease, but you also see it in chronic traumatic encephalopathy, so when people who've had repeat concussions over time. In my mind, these proteins, as they aggregate, there are basically a neuronal response to some kind of stressor or injury. And that sort of ties together all the different ways that you are able to injure your brain cells, and that can be from concussions, it can be periods of hyperglycemia, so type 2 diabetes is very closely tied to an increased risk in Alzheimer's disease, it could be heavy metal toxicity. There are multiple different ways that you can injure your brain cells and the brain seems to respond via the aggregation of these proteins. And if

you get a lot of them, that can sort of propagate the injury. But in the middle there seems to be that they might have some protective effect. So amyloid has some antimicrobial, potentially antioxidant effects, and there's a possibility that this is the brain, it's an epiphenomenal marker of neuronal stress, and these are your neurons responding. And eventually, they'll accumulate and aggregate if you're not taking away the thing that caused the injury in the first place, and then that's what we end up seeing in the brains of these people either on MRI scans or various other imaging or, again, sort of, if you look at their brain after they've died. So I think if you can think about all the different ways that you can potentially injure your brain and then there's a variety of responses that happen, but I see them very much as interlinked, and it's very difficult to sort of unpick how each one affects the risk of a different disease – but in reality, you have all these inputs throughout your entire life that cause stress or acute injury to the brain and then so there are these multiple different downstream outputs that end up resulting in the various neurodegenerative conditions that are becoming increasingly common.

DANNY LENNON: Sure, and I appreciate that we're not just talking about maybe tau or amyloid in the progression of some of these diseases, but they are some of the most looked at markers here. And so I'm just wondering, with that, in terms of what we specifically know about some of these proteins, is it like a threshold that once a certain amount has accumulated that we are beyond that, that we've almost done irreversible damage, and that the onset of that disease can no longer be halted?

TOMMY WOOD: Yeah, that's another really good question. And in reality, if you're thinking about the proteins as they accumulate, and again that's the thing that has been focused on from a research standpoint, that doesn't necessarily mean that's the best thing for us to focus on in terms of long term treatment of the disease or these

diseases. So again, Alzheimer's is probably the best for us to discuss here, even though I think all these are interlinked and that's because something like a chronic traumatic encephalopathy has only really been something that the field has been interested in for less than a decade, probably, yeah, five to eight years, and that just means we don't have as much data as we'd like to look at those. It's now become a very big thing and people looking more and more at NFL, American Football players, boxers, other fighters, and so I think we'll know a lot more about that in the next few years. But if you think about Alzheimer's disease, the amount of amyloid beta that you have in your brain does not seem to correlate with the symptoms of the disease. And again in both animal models and in humans, if you do things, like you give drugs to try and reduce the amount of amyloid in the brain, that doesn't really seem to reverse the disease. So there's probably not, for an individual, a certain amount where we can say now that the disease is definitely irreversible, however, you can get to a point – and again this is mainly from work in mice mainly – that if you have a huge amount of accumulation or you create a genetic manipulation, such that they accumulate a load of amyloid beta, at some point you're going to just cause this sort of fast forward loop of whether the amyloid starts to cause its own damage.

So there's going to be a threshold, I don't think that there's any way that we can say right now this is a person where things are too far gone from a protein aggregation standpoint. However, there is some interesting data, again, from the Alzheimer's disease literature where people have been able to reverse a lot of their symptoms of cognitive decline. And again, most people probably don't care about how much amyloid beta is in their brain, they care about remembering where they put their keys. So that focusing on symptoms I think is probably where you're going to see most of the benefit. And once you're still in the arena of

what we call mild cognitive impairment, there seems to be a lot of capacity for improvement, whereby, again, it's largely case studies because the large randomized control trials are sort of being implemented now, but where people had to quit work and maybe they had to have some outside care because they weren't able to look after themselves as well as they could before, and actually they may be able to go back to work because they've managed to improve their cognitive function so much. So I think there is a lot of capacity for repair and we know the brain can regenerate cells, there's plasticity, we can have new cells in the hippocampus which is probably something we think about in terms of memory. So there's a lot of capacity for repair, but you have to make sure that you're removing whatever those stressors were or whatever those injurious factors were and then sort of support everything else as much as possible. But sort of for an individual saying there's a threshold here, I'm not sure we're at that point yet, but I think there's still a lot of hope for people to be able to improve function if they're at a point where they've started to see some impairments.

DANNY LENNON: Sure. So when it comes to prevention and maybe looking at some interventions, again, there's probably a spectrum of two ends that we could look at – similar to what you just described, we could have specific metrics like the amount of a certain protein or we could look at a metric of a subjective marker or even an objective marker, let's say. And the same thing may be happens here, if we're looking at an intervention, we can get really drilled down mechanistically and look at things that would say influence some of these potential markers or accumulation of proteins. On the other end, we can maybe look at large-scale observational work where we're looking at people who are typically more active, might have reduced risk, and so there's probably two ways we can look at, and really both those things are probably linked I'm guessing anyway. But in terms of what we do know right now, how do you tend

to talk people through that from a perspective of neurodegeneration prevention which is I think a big and growing focus for a lot of people? Where do we start that conversation of things that were fairly sure from actions and behaviors we can take now that are likely to be of benefit?

TOMMY WOOD: Whenever I'm approaching some kind of chronic disease process, I always try and think of the basic lifestyle and environmental factors that we have control over, because then there's actually something that you can do there, and luckily, there are quite a few things that we know are really important for human health and that's important from disease prevention all the way through to athletic performance, you can apply the same principles, but sort of related to what you were saying previously, I don't know 100% know how they work or I don't know the mechanism down to the detail because it's complicated and there's multiple aspects, but I'm fairly confident that the risk of you implementing them is very low and the potential benefit of doing these things is very high. So that makes it very easy for me to say these are the things that people should try, and it's not something that anybody is going to be really surprised by, but really actually implementing them is probably creating the behavior change to put these things in place is probably the most important thing. So I'm stealing some terminology from a friend of mine, Dr. Josh Turknett, who's a neurologist, and he calls these things game level interventions. So you're playing the game even though you don't know how the game works, you don't know how the code underneath is working but you know that it's going to help you win the game.

So things like optimizing sleep, incredibly important for both recovery and for eliminating waste products from the brain, movement exercise, both resistance training and some kind of aerobic exercise are incredibly important. And then social

connection, again, having that kind of interaction with humans in real life seems to have a dramatic effect on people's cognition long term, and then dietary components I think avoiding large swings in blood glucoses is really important, making sure that your blood sugar regulation is optimized as much as possible, that's probably the easiest one. I mentioned things like heavy metals earlier, it's not such a problem in Europe, but in the US there's a huge amount of lead in some areas of the municipal tap water and lead seems to be associated with neurodegenerative conditions. So filtering your water if you live somewhere where you're not so sure about your water quality can be incredibly important. And then doing things to actually engage those plastic parts of your brain is also really important, so learning new skills, learning languages, learning to play an instrument even late in life, you don't have to be great at it, but those learning processes really seem to help stimulate repair and then growth of the brain. So all of those things, again, none of them really rocket science, but those are the places I'd start.

DANNY LENNON: If we're presuming we are aware of those and we can start trying to get people to focus on them as the center of the bullseye, for a lot of people in the audience who are interested in nutrition, either they would be wondering is there something that could be done or will at least on some places on the internet have seen various types of more specific nutrition strategies advised or hypothesized at least in relation to prevention in this context, we'll talk, say, specifically about neurodegenerative disease, but this probably applies for others too in relation to neurodegeneration, speaking from my own experience at least some that I have seen hypothesized, would relate to, one, there's kind of talked about various different fasting models for various different reasons – one, probably just because fasting is quite popular now. But then from a mechanistic point, I think, people can start discussing cellular senescence, and if fasting can have

some sort of role there, maybe we can have some benefit, others would look at, again, maybe where ketogenic diet comes in and again that would make mechanistic sense based on what you said about excursions in blood glucose, and maybe there are some others. But right now, do we actually know anything from a nutrition perspective of types of strategies that may be useful in this area or where we left as our best guess right now?

TOMMY WOOD: Yeah, so you mentioned two big ones, which understandably there's a lot of interest in, and I think there's things I was talking about earlier, they sort of come from what I see as an evolutionary framework which is that the things that we probably were exposed to regularly are the things that we expect and are part of creating a robust human, so, as well as avoiding things that are going to cause large spikes in blood sugar which again probably is something that we've only been exposed to in the last few decades – if fasting absolutely is one of them, and that's just occasionally, just don't eat, there would certainly have been times that we didn't eat and we certainly weren't eating 24 hours a day which is what is common nowadays, how that directly relates to the brain in terms of autophagy, mitophagy, removing senescence cells, I think that's still a very active area of research. And it's worth thinking about the fact that, at least in the peripheral tissues, aerobic exercise is probably the best way to initiate autophagy. So if you look at people who fast, I would say, for 24 hours, they may not have kicked in their autopsy processes yet, but if you get them to do 30 minutes of aerobic exercise, then those things start to kick in. So there are these other things that the anaerobic exercise being the easiest one, if you think about what autophagy, actually that's probably the fastest way to get those processes going, so it doesn't just have to be fasting. Ketosis, particularly in the injured state is something that I'm very interested in and I actually recently wrote a paper on the use of exogenous ketones for neonatal brain injury,

but I think it translates, and people are very interested in it, it's been researched,traumatic brain injury and models of Alzheimer's disease, and that's probably because they can increase mitochondria efficiency, again, maintaining blood sugar levels. They also have various potential neurotrophic effects and anti-inflammatory effects, so there's a huge amount of interest there. And people have asked me, if I had a TBI crash in the car or somebody punched me or something, what would I do, and actually getting myself into ketosis as fast as possible is something that I would just do – do I have evidence that it's definitely going to work? No, I don't. But I think there's enough to say that that's something really worth doing, so you can – exogenous ketone esters, periods of fasting, that's something that I'd implement for myself.

Other things, and probably the next most well-researched, omega-3 and omega-6 fats, so DHA which you would get from, you know, it's the long-chain omega-3 fatty acid you get from fatty fish, that really has been quite extensively researched in brain injury, pretty much again across the lifespan from preterm birth all the way up to Alzheimer's disease. And I think, again, it's quite a complicated picture because it's not just that single nutrient, it's that nutrient within the picture of all the things that you eat, and there's certainly some competition from other omega-6 fatty acids for the downstream metabolites of DHA. So it's not necessarily the DHA itself, even though that's very important for membranes, mitochondrial membranes particularly, it's the fact that they're metabolized by various oxygenases into compounds that are, what we call, pro-resolving mediators, so things like resolvent, maresins, protectins, and these have beneficial anti-inflammatory and reparative effects. But things like linoleic acid from vegetable oils, rapeseed oil or canola oil over here in the US, soybean oil, they can directly compete for those same enzymes and then also produce different metabolites called ox-lambs or oxidative

linoleic acid metabolites, and they actually have some pro-inflammatory, some damaging effects. And there's some evidence to suggest that they may be part of the problem in, say, Alzheimer's disease, particularly because there's been a dramatic increase in those in the diet recently. So DHA, Omega 3s, I think are important, getting a source of those in the diet, but then also reducing some of those others that might compete. And some people have looked at giving those downstream metabolites, those protectins or resolvents in animal models of brain injury and they seem to be very promising, and there are some products that you can get now where you can take some of those precursors, and I know people who are using them after, say, concussive or TBI in the military, there's no real evidence to support that, but again it's a very interesting area of research. And I would say that, if you're trying to prevent or increase your resilience to injury, then again reducing some of those oxidizable or more novel omega-6 fats in the diet and making sure you're getting enough omega-3s is going to be very important.

And then beyond then, there's probably going to be various different strategies that people can implement, other nutrients that are very critical to brain health. Obviously, choline, B12, most of the vitamins, particularly B vitamins, and people can certainly test for those or they can just make sure they're getting a very nutrient dense, nutrient rich diet, animal products, vegetables, and you are probably going to get most of those things. So that's kind of the framework that I generally use.

DANNY LENNON: Sure. A couple of things to dig on. I definitely want to come to the exogenous ketone use and TBI, or in the aftermath of a TBI, one final thing on the fasting because, again, when we look at this mechanism and you mentioned autophagy, which tends to be the route people go when they're hypothesizing why there may be a benefit there. But I think I remember

seeing something that in certain neurodegenerative disorders, you actually see greater autophagy going on in the brain tissue as it is, it kind of muddies the waters if we look at this in a black or white situation of well, just more autophagy is better. Is that accurate? Am I rendering that correctly?

TOMMY WOOD: No, that's absolutely right, and autophagy is one of the responses to a brain injury. So you see that on various models of brain injury, and then in acute brains, and also neurodegenerative disorders, because you're getting this, either you've damaged cellular components directly or you're getting an accumulation of proteins and the body's response is to try and initiate autopsy to get rid of those. So it's a very good point to say that just increasing autophagy by fasting or exercising isn't necessarily a good thing, but equally, I don't think that there's a risk of doing those things is suddenly going to increase autophagy in the brain and that's going to be a bad thing I think the – is the fact that autophagy is a natural response to a cellular injury and that's been fairly well described in the brain. So it's one of those things that cells die with autophagy happening rather than a bio autophagy or because autophagy is happening. So it's just another one of those hallmarks of neurological injury, which again, it just comes back to your point of saying that it's not a good thing or a bad thing, it's just a thing and you want it to happen when it should happen.

DANNY LENNON: On the exogenous ketone use and ketogenic diets in general, we have worked with a lot of combat sport athletes at Sigma and one of the things we've tried to think through is how do we allow for the fact that, particularly after hard sparring sessions or if we can at least mitigate it in those, definitely after a lot of competition, there is high risk of some degree of some sort of trauma to the brain, is there anything we can be doing to help athletes. And I think particularly after competition or a fight is probably a good time because they're not

going to be competing for another while afterwards, and so we maybe can make some changes. And just on what you would typically do with athletes or advise in those scenarios when there's either a concussion has happened or there's at least just been a lot of trauma through repeated punches to the head, you mentioned there's probably a timeframe you really want to focus on getting some ketones into the system, what does your protocol look like in terms of supplementation? And do you also try and do that with, say, diet in the days afterwards and what does that look like just in practical terms?

TOMMY WOOD: Yes, so you're right, there does seem to be a time window generally across acute brain injuries. In that sort of, after somebody has had a concussion getting, say, ketones in quickly, that hasn't really been looked at to the extent that I'm confident in saying, this is exactly what would happen or this is exactly what you should do. But I'd probably take some kind of exogenous ketone ester, the human ketone ester developed by Kieran Clarke and Richard Veech is probably the one that's most easily available, and the one that's been best studied. So taking that immediately or within a couple of hours after the fight, and that's going to keep your ketones elevated for a few hours, so I'd probably take two or three doses a day for a day or two afterwards; and then you don't necessarily need to go straight into, say, carbohydrate restriction or extended periods of fasting afterwards, but I would really make sure that the athlete isn't eating any carbohydrates that cause dramatic spikes in blood glucose. So at least reducing the glycemic load or, particularly, if you have athletes where you've done some blood sugar testing, you know how they respond to certain foods, because again that's very variable from person to person, focusing on those foods that aren't going to cause large swings in blood sugar, I would certainly do that while there's any suggestion that there's some effects ongoing. And then, as you know, getting back into very

light exercise as soon as the person is able seems to improve or speed up recovery. And then again, not getting too hot, it's certainly something that I've recommended to a few people with various severities of traumatic brain injury, particularly as they try and get back into training so you can – obviously, if you're starting very light in your outdoors, it's unlikely that you're going to overheat depending on where you live, but using ice vests or ice packs if you're sitting on a bike or a trainer, just try and make sure that you're not suddenly shunting a whole load of really hot blood into your head in the most technical way. It's probably something that I do. Again, it probably just needs to be a day or days or maybe a couple of weeks after the injury – again, sort of, whenever you're still seeing ongoing symptoms. But yeah, so heat and glucose are probably some things you want to try and minimize the amount that you are sort of exposing your head to while it's recovering.

DANNY LENNON: Right, yeah, and it's interesting. I was talking with a friend of mine recently and it's kind of, we were just laughing about how that would seem like a few core things we can do with athletes, but for some that would be almost impossible to implement when we look at their usual post-fight routines of, I'm going to go out, eat foods I haven't been eating in a couple of months, go and have an after party, get some drinks and there's probably a degree of sleep restrictions.

TOMMY WOOD: Yeah, absolutely.

DANNY LENNON: Probably like a menu of everything we wouldn't want them doing, but that ends up being the case oftentimes.

TOMMY WOOD: Yeah, I think, additionally, so you mention the sleep and obviously getting that sleep back is going to be really important, and most fights happen at night, so these guys may have been training late at night, they've been up in the middle of the night, their circadian rhythm is

probably completely out of whack. So getting light during the day, darkness at night, if you need to support sleep with melatonin or various other things just to get people back into a robust circadian rhythm again, I think that's going to dramatically improve recovery. But of course, it's going to depend on the athlete in terms of how interested they are in doing that.

DANNY LENNON: One thing before we finish off Tommy that I wanted to get to is some stuff around genetics, and particularly if we're looking at neurodegenerative disease, at least from what I think I remember seeing a few times, one of the genes or genotypes and alleles that gets talked about a lot is related to the APOE genotype that someone may have and whatever alleles of that gene can make them more or less vulnerable. What do we know in relation to ApoE4 and how that plays into risk?

TOMMY WOOD: Yeah, that's a great question, and it's one of the genes that I'm most excited about or that I would be most interested in for a given individual in terms of their outcome. And ApoE4, if you have one copy, it probably increases your risk of Alzheimer's disease two or threefold; and if you have two copies, again, depending on the study, it could be anywhere from three, four, five, six-fold, up to 20-fold. And again, it's not having the gene itself causes damage, it's that it seems to exacerbate the response to injury. So it seems to increase inflammatory responses, it causes altered phospholipid handling, it causes changes in cholesterol handling. So there are all these things that are supposed to happen to repair after an injury, and ApoE4 seems to sort of exacerbate some of the damaging processes and inhibits some of the reparative processes. So if somebody is exposing their brain to repetitive injuries, it seems that having ApoE4, being ApoE4 carrier, seems to increase the long term risk of neurodegeneration. And again, if you look at the literature, people have looked at athletes after concussions, and some say that if you have a concussion as an athlete and you're

ApoE4, you're more likely to see worse symptoms. Other studies say that's not the case, and I think it's much more in terms of the long-term risk of neuro degeneration rather than how quickly you recover from an acute concussion, and that's just because of how it interacts with long-term inflammatory and reparative processes. And again, this is something that people are really interested in currently, so the literature isn't all out. But there are cases where, say, NFL athletes who have been arrested or imprisoned for violence or have committed suicide, who have CTE, chronic traumatic encephalopathy, those who are ApoE4 carriers, seem to get more severe disease and more severe symptoms earlier. So again, it's not a perfect correlation, but if you look at both the mechanism and you look at some of the studies and cases that we're starting to see out in the real world, it certainly seems that the long-term risk is increased if you're an ApoE4 carrier. So then really looking after your head, if you're a carrier, I think is going to be important for long term help.

DANNY LENNON: Sure, and I think that leads me to – I wanted to talk a bit about your presentation that I actually got to watch which was – I really enjoyed watching genetics and statistics that you got into, and you had made really good points and were able to demonstrate really usefully I thought, through that presentation of understanding what certain statistics around certain genotypes actually mean for risk of onset of various different disorders, and can you maybe give – and again we can link to full presentation for people, but can you give maybe some of the overview point that you would want people to be at least aware of when they're coming across some of these statistics from certain papers related to genotypes, certain genes and risk of certain disease?

TOMMY WOOD: Absolutely. And I think it’s very common now, I'm sure, perhaps even a majority of the people listen to this have done something like 23andMe to look at their genetics, maybe

they've run it through some kind of third-party tool to tell them about the risk associated with certain single nucleotide polymorphisms or SNPs, that's really what I covered in the talk. And you'll see that with each SNP that you might have, so FTO, the fat and obesity related protein, which is the common SNP that's most associated with being overweight, that's probably, I think that's where I started in the talk. And you'll see that on average as you have either one or two copies of a specific SNP in this gene, you see an increased risk of increased BMI and obesity. And that is true on average but when people are looking at this data and they're looking at large population data, these are studies in Nature Genetics, done by experts in genetics with hundreds of thousands of people – yes, on average that is the case, however, what they don't show you in the paper, and I had to sort of back construct the dataset based on the data they presented, and you see this huge variability. So the actual likelihood that you have an effect of having that gene in terms of your weight is a few percent. So more than 90% of people would just have no overall effect of having that genotype and that's not how the data is normally presented, it's normally presented as you have 40% increased risk of the chance of obesity and that's not really your true risk. And for that particular protein, it's interesting that FTO SNPs are only associated with increased BMI after the Second World War. So it's definitely an expression of the environment that people are exposing them to and I think that's really what we see again and again and again.

So people are very interested in MTHFR and methylation, and when you look at your gene function which people have done, and you look at some marker that we can measure that we might care about like homocysteine, the effect is so small, like, you could have huge losses in protein function and somebody will say, oh your MTHFR isn't working properly. I hear that all the time and it drives me crazy because, in reality, the percent loss of your gene

function, whatever they might tell you, so for me, I have more than 52% loss of my MTHFR protein, that sounds pretty bad. But if you measure that in a test tube and then you measure something in blood, there's almost no correlation or the correlation is so small that in reality what's going to be much more important are all those things we talked about in terms of general health and lifestyle factors, nutrient availability and your genetics have, I mean, I can't say no role because they do have a small role but it's almost not worrying about, not worth worrying about for most people. And again, I think almost all of it is an expression of the environment and the environment most people are putting themselves in nowadays is very unlike the environment that you might originally have been exposed to, and it's interesting. So in some cases, things we might think are bad might actually be good, so ApoE4 is a really good example of that, so there's a hunter-gatherer group called the Tsimané in Bolivia and they recently looked at the ApoE4 genotype and their risk of cognitive decline. And in this particular group of people, they can have quite a high parasitic burden, so they have a high burden of parasitic infection. And in those who have a very high burden of parasitic infection and high numbers of eosinophils is the white blood cells in the blood which is associated with a parasitic infection, in those people ApoE4 is protective of cognitive function.

So there are all these different ways that these genes interact with the environment, but the environment really dominates. So I think that the most important thing to take away is that when somebody says X gene is associated with X risk, you have to think about the population that was looked at. And so most of these studies, if they're being done on populations in the US, current best estimate suggests that probably less than 10% of people in the US have good metabolic health. So then when you're looking at how genes affect disease risk, it's in that the setting of poor metabolic health

because of the environment that people have exposed themselves to. So a gene by itself doesn't really tell you very much, and most of the studies where people are looking at genes and disease risk, it's in an environment in the population which may be a lot of the people who listen to this have worked hard to create a better environment for themselves, and then those risks no longer apply.

DANNY LENNON: Right. That's it. They kind of wash away once you've taken care of a lot of those environmental factors that you mentioned. And I would hazard a guess that probably more people right now are getting maybe some genetic testing than are actually covering off all the big rock lifestyle things you mentioned earlier first. And so, they're still getting...

TOMMY WOOD: By the time you've done that, the genetics don't really matter that much, that's really what – if you sort of analyze the data, that's really what it suggests.

DANNY LENNON: Right, and not to mention the psychological stress and anxiety that you could cause yourself by telling yourself you are at a 50% increased risk of some disease that may not really correlate to any pragmatically meaningful risk. Super interesting. And like I said we will link up to that talk if people are interested in that topic. But we're just almost out of time here, Tommy. So before I get to my final question, where can people find more about you online, more of your work, are there any places you would divert their attention on the internet?

TOMMY WOOD: Sure, so on social media, I'm probably most active on Instagram. So I'm @drtommywood. Also occasionally on Twitter @drragnar, and I have a website by the same name, drragnar.com. And I don't post a lot of stuff anymore on there, so there's some old blog post from several years ago, but usually, if I'm on a podcast, that will go up there and I think my Instagram post there as well. And it's also got sort of the more professional side of me, so you

can see all my publications and all that kind of stuff if people are really interested in digging into those things.

DANNY LENNON: Awesome. And so with that that brings us to the final question I always in the podcast on. And this can be to do with anything even outside of today's discussion. If you were to advise people to do one thing each day that would have a positive impact on any area of their life, what would that one thing be?

TOMMY WOOD: Yeah, I was thinking about this all morning because I knew you're going to ask me, and there's obviously loads of ways you could go. Usually, when somebody asks me this question, I would say, you should squat and you should get a dog. But that's essential for human health. In reality I think one of the most important things that I recommend to people and some of the best advice that I got when I was training as a doctor was be nice to people and there's so many reasons why this is important. And again, it sounds like something that's just so simple that it's almost stupid to mention, but as I spend more and more time interacting with various people in various fields, being nice to somebody even when you're having a bad day or you don't agree with their viewpoint or giving your time for free to somebody who could really benefit from it, I think that's going to not only help everybody else, but also help you. You can think of it selfishly if you have to as well. So just like being nice is probably, again, it's one of the best pieces of advice I ever got. Not that I thought I needed it, but anyway, just hearing it is incredibly important, and I think that's probably the thing that I'd tell people to do. It's actually quite easy to do and incredibly both rewarding and beneficial.

DANNY LENNON: Right, yeah, that's the thing, we often need these little reminders of when we do it, how good it feels for us as well. It's not just an inherently good thing that we should be doing anyway, but we also get that payback from it too, so it's a nice way to keep that circle going.

Tommy, this has been great conversation, I've really enjoyed chatting through some of this stuff; and whilst we can only scratch the tip of the iceberg on some of it, it's been really interesting to dive into some of these ideas. So thank you for coming on the podcast. It's been really enjoyable.

TOMMY WOOD: Thank you for having me.