AACP Australian Chapter – 2015 March Conference
Breakout 2 Transcript

Paul: I think this is going to be a great way to end it. We are going to be doing sleep and exercise then we are going to be talking about the gut microbiome and nutrition. That's what we are going to be finishing up with. So we will go ahead and get started.

So I post the question. Are we becoming more well-rounded. So interesting point yeah tough crowd wow!

So what we are looking at is the research produced by the President's council on fitness. So again in America like in most countries we are seeing all kinds of sad like a collective sign, and I think not a good one. Colorado finally actually crossed over the threshold of having over 40% of their people being overweight. So Colorado was the last one of the states in America basically holding out I think to not actually have a significant part of their population being overweight. They now have crossed over that threshold as well.

So this idea is that the President's Council on Fitness revealed that less than 5% of the US adult population participates in 30 minutes of physical activity per day. So when you really think about it, this is really kind of a staggering statistic. So 5% of the US adult population basically participates in 30 minutes of physical activity, and don't even participate in less than 30 minutes. So this is their accounting like you know walking to your car, to your work, upstairs and things like that. The average American has become very sedentary. For children it's far worse. It's actually you know from when you are looking at it long term on the cost on the medical system and such, basically because of all these technologies for our kids. Basically they are glued to the computer and to some kind of electronic device most of the day. In my generation, we talked about TV and we always say you know kids like in our generation watched 3-4 hours of TV a day and then using my average my parents they don't do that. They basically sent us out of the house on any day if they could. So we were very fortunate. So again it's always that funny thing. You want to go back and hug your parents after the fact when you feel like they were mean when you were going through that time period. Later you come back and you want to hug them. But basically we are seeing and this is again from the President's Council, that kids spent around 7 hours per day on computer screens, cell phones and TVs. I would even say that this is even more than that. Literally our kids come out of class and they immediately go to their cell phones. In fact we have cell phone policies, right, we have it all the time in our classroom. To be honest with you, I have given up. I used to try to be hard core with this and say you can't take your cell phone out when you are in class anymore. I don't even fight it. I feel like they are paying the dime to come to lectures. They are supposed to be here to learn. If they want to play on their cell phone, as long as it's not disruptive to somebody else, I let them do it anymore. Because it's so rampant. It's really out of control. I mean you go to movie theatres right, go anywhere out in public. You basically have to tell people to turn off their cell phones. You have to keep reminding them.

I love when people go to the ball game, you know they go to ball game, they watch a basketball game or something, and they are on their cell phone more than they are watching the game. This is the age we are living in. And my oldest son is in computer science. And he keeps informing me it's even going to get worse because he seems like he's going to some of these expos and they have… have you seen … almost like star trek… oh crazy… I mean literally these things project out, so you can watch you know and it's just right here on your arm so you are going to be like connected to everything. Have you seen the glasses? Aren't those crazy? I mean these glasses that have the little camera thing on it and stuff, and it's amazing that you are going down the street you look out and you see some, you know like one of these buildings around here, one of these really cool buildings, it will identify it for you. And it will tell you that in your screen as you get these glasses on, it will identify the buildings that you are passing and it will even tell you some history about it if you want to, while you are driving, while you are walking. And being a neuroscientist, I really worry about this. I worry about this sensory overload this is creating… Now we have sensors that will tell you you are going to hit the car, right? So like now, you can be distracted like that because now you have sensors that will tell you before you actually hit the car in front of you. That's what we are moving to. It's brilliant, right? It's like … yeah… I don't know if you follow this, but in LA, there are literally hundreds if not a thousand or more than a thousand of them. But see… the idea

is that we are becoming very robotic and we are not getting basically the exercise that we are supposed to be getting. So again this is a problem because it starts in the school system.

You know, we don't emphasize exercise anymore. I know that when I went to school, you'd go to school you know early, because you want to go to the playground and you started playing. And then you went to classes for a little bit, then you have recess, then you go to play again. Then you went into the school, ate lunch you have lunch break, and then you went outside and played again. Then you have an afternoon recess period and then you played sports after that usually. Right? So we were outside almost all day long playing. And I have to love it in Missouri, you know coming from Iowa and Illinois where my boyhood friends came from was much colder. We moved down to Missouri and one of the funniest things that happened was I was coaching soccer. I coached soccer for about 16 years. And one of the rules I cannot get used to is if the wind chill gets below 40 degrees, this is Fahrenheit, we had to call off practice. It was too cold for the children to play. I am like seriously? And they don't even let kids go out for recess. And the problem, which is really amazing, is that it is really because a lot of parents don't send their kids with proper clothing. And that's why they had to do it. Because you know my soccer team is amazing. I will show up for practice and I would even send out emails saying OK guys the weather is going to be changing. There's going to be a front moving in. Bring something warm. And they show in shorts and a t-shirt with the temperature going to be you know around 40 degrees Fahrenheit. And so again the schools are trying to be more proactive.

But the bottom line is they change the curriculum so much. I'll give you a sad story about my children. So my children went to high school in Nixon, this little community outside of Springfield. And you know they were on (the) track (oval) to take AP classes to get college credit and stuff. They actually all took their PE classes, their requirement for physical education in the Nixon school system. Basically you have to take 2 classes and they took both of them in the summer back to back. One of them was called basically skills for lifetime. It was actually their physical exercise class. It includes things like bowling and things like that. It wasn't anything aerobic at all. It was amazing to me. They walked the track, they didn't run the track. They actually got to walk the track for half hour. That was considered OK. So again it's the whole change in mentality within schools and stuff that we don't even have our kids exercising at schools anymore. We don't really encourage them to do that.

So biologically this is getting back to the whole idea taht when our brains evolved, basically around 160 thousand years ago, this is what we were doing. We had a feed basically, we had a very nutritious diet which we will talk about. But basically what they say is that we were able to walk 5-6 miles per day. That should be what we should be doing under normal conditions. This is what we should be trying to achieve because that's what our bodies evolved to do. When you eat food and stuff, what tissues should take most of that energy? Muscles, muscles by far. So I am teaching a diabetes class right now. And basically 60% of the food that you incorporate, the glucose that you bring in should be going to your muscles. Why? Because you should be active. Right? So our system, if you think about this from a very basic set up, our systems are actually designed for 60% of the energy to go to the muscles first. Because that's what we should be doing, yeah, survival, moving and stuff. And yeah, the second half of the energy goes to the brain, it takes about 20%. So think about that. Muscle and brain takes up 80% pretty much. Now you have 20% left. And that gives provides energy for everything else, ok. That's kind of how we are designed. Basically how we are setup.

When we look at this again, we are designed to actually have moderate labour, manual labour for about 4 hours a day. And like I told you before. Going to gym and lifting weights for an hour is not even sufficient to actually get to this level. You really have to do you know basically manual labour. Things like even gardening, pulling weeds, all that kind of stuff, all counts. But we are nowhere near this kind of lifestyle anymore. This minimally active lifestyle falls very short. So this is the point I was supposed to make. 4 out of 5 adults, so 80% of the adults basically lead a sedentary life, or minimally active lifestyle that falls short of the recommendations. All they are asking people to do is to do 2.5 hours, you know 2 and a half hour of aerobic exercise each week. Right? Each week! And 4 out of 5 adults are not even matching this. They are not even getting that done. I mean it's really ridiculous. I remember again I was coaching soccer all those years and everything, and it was just dumbfounding me that the parents will come down and they will literally bring their big energy drinks and they sit on the sidelines and eat their food and stuff and you know what you guys really should be doing? You should be walking the sidelines, you know, spend the time walking round, and

they just kept getting bigger and bigger. So again, it's the whole well-rounded thing. We have a lot of well-rounded people in America.

So what are the benefits of exercise? So as dumb as it sounds, when I was actually trying to prepare this stuff, it was very difficult to find any epigenetic evidence of the benefits of exercise, which seems retarded but that's the way it is. I really couldn't find much and I will show you the ones that just came up just recently and some of the data. But one of the things that we, you know, have pulled from some of the literature was exercise basically has very positive effects on the cardiovascular system. We know that. And the immune system. Again people who exercise on a regular basis have a stronger immune system. And even the nervous system. And of course it's going to have that really huge benefit and effect of reducing the risk of obesity and metabolic syndrome. And we will talk about metabolic syndrome later on. It enhances cognition. I think one of the most remarkable things that one of my sons sent me one time was he was looking at nobel prize winners. Just people who have done incredible things in their lives. And he was looking at what their lifestyles were like. It was a really interesting paper. So it was basically saying what was the common factor with people who are brilliant, who actually have solved some of the greatest problems for mankind. And you know what was critical? Everyone of them walked everyday. They exercised.

One of my favourite stories of all times is Thomas Edison. You know Thomas Edison? All the patents that he's had and everything. The remarkable work that he did. Thomas Edison went down to visit his home, and what was really a great thing is that what he did, is he would take his walks everyday. But the other thing he loved doing was fishing. Ok? So he would go down to the boondocks everyday, and he said there are only two times when really people don't bother you. It is when you are in church, and they really don't bother you when you are fishing. So he took to going fishing down there. And what was really interesting about this is it was only years later they discovered that he never put bait on the hook. So you guys, this is the plan for you. You know if you want some time, just go out there and pretend you are fishing. Nobody will know the difference.

But again it's like what this paper was saying was that almost every creative genius whether it was in arts, was in music, or it doesn't matter what it was, but what they did was they built in walking everyday. And it's not running. This is again I think where we get in trouble with America, as we always want to be driven. Everything has to be like tight triple A personality type stuff. But actually doing the walks is really what you want to do. Walking actually activates the sympathetic system. Very, very restorative for the nervous system and everything. Well, the 10000 steps, has anybody done the maths on that? So it's 5-6 miles per day. Yeah most people will take probably an hour and a half to do that. So you probably need to walk an hour. It's actually really difficult in our lifestyle. The way that we live our lives right now is very difficult because my wife and I have been trying to abide by this. Em… it's really difficult. You really have to make a commitment to exercise. When we lived on a farm, it was not a problem right? Cause we have to go out and feed the cattle multiple times per day, we had to walk up sometimes you have to walk you know half a mile just to get there. Yeah.

That's a really good point. That's a very valid point. And again, a lot of people will exercise at the end of the day because that's the only time they can fit it in. but then it ends up causing them to have sleep disorders because they are basically increasing their metabolic system at the end of the day, and honestly what happens then is what are they going to do. You will see the statistics it is going to blow you away later on about the symptoms we talk about when we eat food at night. I mean it's crazy. Like again there's actually a whole syndrome where people actually eat their meal their major meal comes after 9 o'clock at night. And again some major problems because you shouldn't be eating your food at 9 o'clock at night when you are trying to go to bed at 11. Yeah.

About the 1000 steps. It's the whole day. Right, it's just being active. Right. And so, it's really easy. Again, you can talk to your patients about this. It's not as complicated as it sounds. It's like you just park your car further from work. Instead of taking the car. We call it elevators, you guys call it a lift. Em.. you don't take that. You take the stairs, right? But again it's like a very simple thing. You go to the store and just park further out. Park in the furthest spot of the parking lot and then walk all the way in. And it's amazing how if you build in just like little things like that, you can actually achieve pretty much the goal everyday.

One of the things that we see with exercise is this genome Y DNA methylation changes. We will come back to that. Metabolism changes tremendously with exercise. And so again the type of exercise you want to be doing is you want to be doing more exercise like I said walking you know low impact type of stuff. It's going to be better for your joints long term. But again what we are saying is even simple walking is more beneficial actually than running. And especially from a metabolic point of view. It depends on a certain culture, but some people actually will eat a meal and what do they do after that, yeah, they have a walk. Go for a general stroll. You know. It aids in digestion, I mean you know we talk about the peristaltic movement of the gut, I mean you see that's one of the ways that you can stimulate peristaltic movement. I always like when people say my muscle blocked out I can't do anything. Well you have been sitting around the whole day. You know why don't you go take a walk? And it's amazing because they will come back it's kind of embarrassing and they will pass gas when they do that. So I always tell them to do it outside you know away from people. But I mean it's one of those funny things. Part of this is it's waking up that nervous system and it's actually helping you with digestion and stuff. The idea is that this is not only changing your muscles, but it's having an effect on multiple tissues in your body. So again, when you look at this, the long term benefits are incredible. Em… you know from exercising and again what they have shown in almost every condition is that it reduces the incidence and severity of pretty much every disease if you exercise. And again even those neurodegenerative diseases, people who exercise are going to be much better off.

So what is it actually doing? Well, this is the kind of the over- arching thing that we talked about before and this is coming from one of those musculoskeletal journals. But basically they are talking again about the environment. So what does exercise actually do? And this is one of the first papers I found but it really didn't say anything other than just saying oh, well there is DNA methylation pattern change, so I was like oh this is good but not kind of helpful.

This paper was a little bit better than the other, it went into a little bit more detail. What they actually showed is physical exercise and basically muscle contraction actually changes the muscle itself. And one of the things that is really important about what this does is it changes the expression of glut 4. Does anybody know what glut 4 is?

Yeah, basically what you have is … well… actually on every cell on your body pretty much, you have these glucose transporters. Glucose itself cannot pass through the cell membrane. It can't get into the cell directly so it has to have a receptor that actually is going to help bring it into the cell. One of the things that actually happens and this is really important to consider is when you exercise, glut 4 actually gets brought to the surface. Ok? And this is again really going to be important because if you can see how metabolic syndrome occurs, this is part of the underlying pathology. So you eat a meal and you go for a walk, so you are now metabolising those sugars. Where should those sugars be going? The muscles. How do they get into the muscles? Well, what it does is it up-regulates the glut 4. So it's bringing the receptors tot eh surface. See how clever the system is? So it brings the receptors to the cell surface of your skeletal muscles and to what? Take advantage of the sugar. Ok? So let's say you don't do that. You don't go for a walk right after lunch, instead you just want to go play your video games and you sit down and you pop yourself down in your chair and you don't do anything. Well where does the glucose go? Yeah… which organ does it go to? Goes to the liver first. But if the liver is basically full, because it's already got enough glycogen storage, where does it go next? Right so basically what's going to happen is instead of getting metabolised and stored as basically glycogen, now it's going to basically start to be used to make fat. You know basically it's being transformed into a different structure. So again, we are bypassing the major thing that we should be using the glucose for.

So again we are for eating in a sensible way. This is what should be happening. And then you look at this and it's like again physical exercise actually changes basically the cellular activity. And it changes that through the histone deacetylation patterns. So it up-regulates the expression of the glut 4. So if you have a regular exercise pattern, you maintain a high level of glut 4 in your muscle tissue. What that means is that your glucose is being utilised in the right way. So it's actually not being diverted to the liver and other tissues. It's actually going to the place it's supposed to be going. Ok?

Now when you look at this. The other thing that happens is other type of changes. Em… like I said not only does it happen in the muscles, it also happens in the nervous system. I was talking about these creative genius people. And again, they figured out a long time ago that if

they exercise, if they did their walking and stuff, that's when their ideas will come to them, I don't know how many of you have any had this experience with even breakthroughs with your patients and stuff. Sometimes it's out more in the grass, or taking a leisurely walk, you are not even trying to think about your patients right, and all of a sudden you have that aha moment, you go oh my gosh! This is how I should do that. I mean it usually doesn't help when we are sitting at the desk and making it try to happen. Right? I mean it's an incredible thing about the neuroplasticity about how the brain works and about how it functions that we sometimes have to go do something relaxing like that, just go take a walk you know and you guys I know you guys do this everyday the coogee to bondi walk I could do that everyday. But again, it's like your brain just free flows at that point in time. And what they showed is that when you exercise, basically you get epigenetic changes, you increase brain plasticity, so basically you are changing the fundamental circuitry again, of your brain. One of the things we will talk about is that when you do this, you are much less dependent on other types of drugs, right? You don't crave as much alcohol, you know again we are going to have examples of this but the thing is that really fundamentally changes the architecture of the brain. It promotes neurogenesis in a way that is actually healthy, so it promotes learning and memory. And it actually causes stress resistance. So when you exercise, you actually change the brain so it modulates stress. So things that are maybe will cause you stress actually you will be able to buffer that much better. And you will better respond to that because you are changing to chemicals in your brain. The composition of it. The BDNFs and things like that. That really are important and actually minimising stress levels and such.

So there are a lot of benefits from exercise.

So when you look at this physical exercise, there are positive influences on neurogenesis as we were just talking about. So it happens in the hippocampus, so again normally we think of it helping skeletal muscles exercise and build muscles and stuff. But that's really not the goal of it. You know when you really think about the goal of exercise, it should be to actually allow all these other things to happen. And one of the things that's interesting about exercise is it doesn't have to be strenuous exercise, like I keep emphasizing. Because I think that especially in your patient population, especially if you tell them they have to do 10000 steps a day, they are probably going to freak out. So it's probably not what you want to do, you probably want to just ease them into it. And if they can walk around their house one time, right? Whatever they can do at their level of comfort, just have them doing that. But one of the things from a neurodegenerative point of view, it's one of the things that happens, and we talked about is that ageing all these other things basically change what is going on in the hippocampus.

Basically physical activity is a very positive thing. So while stress and ageing are going to basically influence neurogenesis in a harmful way, things like an enriched environment … simple things like reading a newspaper everyday just being mentally active you know engaging in conversations with people. It's always one of the saddest thing for me is to go to nursing homes. I worked in nursing homes when I was younger. It's one of the most depressing things I think you can experience. Incredibly brilliant people right, are sitting in a wheelchair and nobody talks to them. All day long. You know they have no input. And then we wonder why they get depressed. I mean these are really intelligent people. But what you are doing is you are putting them in a basically negative environment. They have very little chance of actually having neurogenesis. I was saying this the other day that one of the things that is actually has played a role in and it's kind of a fun thing to watch is they are trying to bring in video games and stuff to some of the nursing homes now. And music. So music therapy has been huge for these because it gets them into a different zone. Yeah… they will get up and start dancing. But even like video games, it's just to keep the brain active. You know, it doesn't have to be video games like we are thinking like sudoku, and those kinds of things. Any kind of things that you can do like that for like your patients basically is going to help them actually maintain their neurogenesis and basically suppress things like depression and anxiety type of disorder.

And so when we look at this again, all this is actually feeding in and actually helps with learning and memory I think most time we forget that. So this goes back to my point about how you know you have to use the word moronic. But that's what I think it is. How moronic are school systems. Right? So we just have been talking about how there are tons of evidence that walking and exercise actually promotes neurogenesis and what do we do now? We pretty much eliminated that out of our school systems. So when I think of one of the

primary ways that we learn is we sit in a classroom, we hear things. And then we go walk around, you know, we go move. And then that's when the neurocircuitry changes, And also exercise also improves stress coping behaviour responses right? So they cope with stress much better so again when you start talking about all the problems we have with children in school nowadays they can't sit still they can't do this I don't it's necessarily always their fault. I think if we mandatorily make them go out and actually exercise they would be a lot better off. I don't know if this happens.

Are there any companies in Australia that has mandatory breaks where you have to exercise? This again is an interesting thing. I know in Japan mitsubishi and some of the companies when they go on breaks they mandatorily have to walk so when they get a 20 minute break they can't go outside and start smoking a cigarette. They can't go outside and do whatever. They physically have to exercise. So again in so many companies in the US are doing the same thing. They are moving towards this model because what they are finding is when they do that, (a) it makes them more productive. But (b) the other thing is the big thing from the insurance side of things is it cuts down on injuries. So when you are on an assembly line doing the same mindless tasks again and again and again, all of a sudden you have them go walk and do something different, they find that when they do that they come back more refreshed. And they come back to it minimising the injuries to the workers. So again I think hopefully this is going to coming back into vogue and hopefully will change the school system as well.

This idea of physical exercise increases motivation and decreases depression. I think this is a really important thing. This is something that is very much attainable by any of your patients right? In rats when you have free and social access to a running wheel they basically will do it. They will just naturally jump on that wheel and they will go. I don't know if you guys have ever had rats as pets? Our kids have had rats as pets. You sometimes have to take the wheel out at night. Don't you? Otherwise you don't sleep at night. Because that rat will just run all night long. What it increases is the same compound that we talked about before. BDNF this is brain derived neurotrophic factors. It is a growth factor that supports the nervous system. So these are growth factors that are actually really important for supporting the hippocampus and memory. And then what it does, is it changes the cells in here and increases motivation and performance. So as crazy as it sounds, if you allow an animal to just run, to exercise, it actually does much better. We actually have protocols. We take better care of animals than we do ourselves.

So we have special diets for our rats. Right? We feed them special water. We have to keep the temperature right. We give them the right kind of lighting and stuff like that. And we even go so far out you have to enrich the environment for them. We have to change almost on a daily basis the enrichment that is in there. We have to provide different ways for them to exercise everyday. And when we do this, what we find is the rats are much more calm. They are much more balanced. But we don't even do this with our own population. Right? You know maybe we can learn something from this. So then you look at clinical depression in women. There was a study done which says that the number of minutes of exercise per day, I love this, starts with less than 10minutes, I don't even know how you do that. You go from the bathroom to the TV and then sat there for the rest of the day. But with less than 10 minutes per day, basically what they looked at is there was clinical depression. Then they started saying OK if you start exercising so 20 to 90 minutes per day, I am sorry 10-29, you can see a significant drop in depression. This is I think pretty important to realise. That a small change, right, up to between 10-20minutes per day, that really maybe doubling the amount of movement that you do per day. It's actually decreasing the clinical depression in these individuals. And then you can go through and you can see that as you increase this further the depression goes down. So rather than treating them with drugs, maybe just exercise. So what they wanted to do is to understand if you look at people who are clinically depressed, they are comparing exercise versus medication versus the combination. Exercise was actually y better. OK? So these clinically depressed people had almost 90% recovery by exercising. Ok? Without medication. There are other ways to do this.

Basically it's bottom line is saying basically I'd rather take drugs than do this, exercise 30 minutes per day. It's kind of like the Dalai Lama thing. You know, if I can take a pill to achieve this nirvana, I will do that rather than trying to work through it. And this is the culture we live in. it's basically people want to be fixed with a pill rather than taking responsibility for themselves. I think most of you had this experience. It's very empowering if you have ever

been overweight or something, and then you lose weight and gain control of your life again. And basically you feel fit again, you change the wardrobe and you just feel so much better about yourself. And I have watched this happen with a lot of college kids, that whole freshman thing. Where they literally come into college and gain 15 pounds they are all depressed. I gave them my classes second semester and I go here's what you want to be doing. You want to look at this and then they get empowered with it.

[question asked in the background]
The paper didn't elaborate on it. The sedative effects is maybe what you are saying. Ok that makes sense. Yeah, this is like gloss over the point. Yeah, but this is actually interesting. That exercise alone was better than the combination. Yeah they are actually lower if you are taking medication with exercise you actually get a lesser response. Yeah and it's pretty remarkable. So when we look at this. One of the real benefits of physical exercise is actually on Alzheimer's disease and Parkinson disease. This has been worked out and it goes back to the idea of oxidative stress and oxidative damage. And we have talked about this before, so common mechanisms leading to Alzheimer's disease and Parkinson's, again we think of these as inflammatory diseases. You get this oxidative stress and damage to the DNA, the lipids, and the proteins. Again there are some genetic mutations that predispose individuals to this. Iron, too much iron actually, can cause some of these to happen. And then basically what you are looking at is what they call mitochondrial damage. And this is what we are going to be talking about what happens when you go into deep sleep. This is where you repair your mitochondria. This is when the mitochondria actually the supraoxide dismutases and the other enzymes come up and you basically reduce the free radicals that are in your system. So again if you are just metabolising, you are going to generate free radicals. What you have to do is give yourself time to recover, basically get rid of the waste products so to speak so the system can reboot appropriately. And what happens is under these inflammatory conditions if it stays persistent, you get neurodegenerative diseases and you get selective death of neurons and then ultimately dementia and then movement disorders follow up.

Now it's interesting about that you can really delay this process by diet and caloric restriction. And exercise. So the combination of this actually promotes neurogenesis as we talked about. Neuro regeneration basically delays the onset of this. And again this is just something really easy for people to achieve. It's not difficult. So you have you know if people have ethis in their family line, then this is something they are susceptible to, and basically just get them up and exercising.

And then one of the things we will come back to is this idea of diet and caloric restriction. The biggest problem I think is that we have is that we have an abundance of food and so it's really a bad combination when you have too much food and not enough exercise. What is remarkable about it is how our bodies are actually able to overcome some of these pathological states just by doing simple things. We always talk about if you want to live longer what is the one thing you should do. Yeah it's kind of a funny thing from a nutrition point of view. Basically eat less. Almost every animal we have looked at on the planet, if you calorie restrict them, they actually increase the time they live. Because it minimises oxidative stress and reactive species, and actually it increases the neurogenesis. If you want to live longer, the moral of the story is eat less.

Now I put this up here because I think this is a problem. And I think it goes across almost all disciplines and almost all countries. It's the idea that most people come from work. Are they physically tired? Now I mean the bottom line is the majority of the people do not do that much physical labour anymore. We have minimised that. We have tractors that do a lot of the heavy lifting and stuff like that. So even for construction jobs, there is not enough physical work. I mean it used to be we used the hammer right? Now you use a nail gun. It's completely different. So even a lot of the construction jobs, jobs that we think you have to be really manual to do, you don't have to be using that much muscle anymore because we have machines that do a lot of the heavy lifting for you. So what you look at is most people are really not physically tired. They are mentally tired. This is similar to little kids. Right? Little kids are so tired. You were saying about how these little kids come in and they are tired all the time. We basically have it at all levels. You know, adults, people who are students, we have it in athletes. We have it in our pets. You know? I am just joking about that. And then even the poor little mice. We run them to death.

So everybody is tired. We live in a culture where we are overstimulated. We don't really know how to manage our sleep anymore. So we are pretty much chronically tired. I think exercise and sleep go hand-in-hand. If you are doing appropriate exercise, my dad always said this, he said if you did a good day's work you never have to worry about having a good night's sleep. And that was always what I grew up with, and I always lived by that. If I am not sleeping well, sometime it's as dumb as it sounds, I will actually go up get a cup of water, do something that is more physical. I don't know if you guys do this. It's a coping strategy because like all of us would, we tend to go 24/7. We have a lot of stuff going on in our heads but one of the ways I cope with that is I should do physical work right? Because when I do physical work, it takes my mind off everything else, it reduces the stress and I am pretty much able to go to bed at night pretty free of any peripheral activity.

So I mean I think everybody has to figure out what works for them. But with all the cram writing we have to do and managing the lab and everything, basically they say how do you ever sleep. And I say oh quite well thank you. But I have figured out ways to really quiet my system down before I go to bed. And I think you just have to do that. And again if you have trouble going to sleep sometimes the best thing to do is to go out and walk. Allow yourself to get physically tired and then that will help you. Honestly it will quiet your brain down as well when you do that. So we talked about this before. The idea of how this happens. And this is why this is really remarkable. This is a study that is just came out. You know this last year. And basically it's the evidence of the benefits of physical exercise. And in this case they just looked at skeletal muscles. But they are looking at trained legs versus untrained legs. And they are basically looking at basically the productivity of them. And what they did is they looked at the epi-genome of them. And the scriptome. Which is basically the messenger RNA products they make. But what they are doing is basically showing that in an exercised leg, the skeletal muscle will get rewired differently at the epigenetic level. The DNA and the way it's packaged actually gets changed. And what they showed is basically there's differential methylation and it happens in multiple ways. And this is one thing I really want you to focus on. These changes occur at the molecular level. They occur with biological processes and the cellular components. This was a kind of really in-depth over the top type of basic science article. They were looking even at the architecture of the muscle itself, like do myofibres change? Do contractie fibres change?

The bottom line was is yes, when you use muscles, all these things change. And the changes are happening in a certain way. Your regulation of glycolysis, again, glucose metabolism actually changes when you exercise. So when you are using your muscles, basically you are imparting this knowledge onto the muscle and now you are getting changes at the DNA level to cause expression of genes that actually allow the muscle to function correctly. That's really I think the take of this. Basically you know the major take home message was a lot of these things that were changing actually just aid in muscle function and stuff, and in metabolism. I won't really go through all the details but the bottom line is they don't really know again what all these changes mean. They just know that in an exercised muscle, these are the things that we see.

So these are the kind of changes that we are seeing at the epigenetic sites. And what they did is a really kind of a major analysis. They call it an integrative transcriptional network analysis with DNA methylation and they basically want to talk about this coordinated training response. So what they were looking at is all these different genes and all these different factors and seeing how they come together, and the bottom line was that they basically said that this kind of exercise program induces changes that allow for phenotypic adaption. So when you exercise on a regular basis it causes cellular changes that allows the muscle to actually perform well. I mean in a nutshell that is what they are showing, but it's kind of sad that we haven't got anything to demonstrate this kind of micro-level change. And it's kind of like I said I spent a lot of time, a lot of energy doing this really just to say that you know basically exercise influences the expression of genes in the muscles.

OK, so now we are going to look at sleep. So again one of the functions of sleep and I think one of the primary ones is the fatigue reversal. So again this is the idea we all get run down and this allows us to recover and re-energise. And it does it at multiple levels. The physiological level, the cellular level, and there is what we call the biochemical refreshment. So sleep promotes synaptic efficiency. So this is the whole idea. This occurs in some medical schools where they have intensive training the whole morning. They have a nap and then they take a nap in the afternoon. And what they found in those individual students that were

going through this kind of model that they actually remember what they learn in the morning much better. Because it actually allows them to shut down, and allows neuroconnectivity to happen. So again the power of sleep is to promote neurogenesis and to promote neurocircuitry. And again it promotes protein synthesis, and neurogenesis and restoration, right? It will allow the metabolism to get restored as we talk about when we go through this. The mitochondria are able to function correctly.

What it does for the immune system is reset the protection. We all know this. Sleep deprived your immune system doesn't function as well. You are going to be very susceptible to viruses, bacteria, other types of infection. And then memory, I think being a professor, this is actually really important for me. Always disheartened by how many of my students are so chronically sleep deprived. They are in college right? And yet they come to class and they they fall asleep most of the time.They can't even stay alert for 15 minutes because they are so tired all the time. And how are they going to learn if they are coming in with this kind of background. So again, this idea that memory consolidation actually occurs during sleep is really important. And then the psychological wellbeing, we can't say enough about that, right? I mean if people are having mood swings, my daughter is going through this, and we are like wait a minute, she really wasn't managing her sleep pattern very well. And we realise she has to go get sleep, right? And then it was funny because it was like she actually had a couple of good nights' of sleep then the whole household was good again.

So it's an amazing thing. The restorative power of sleep. A little basic sleep cycle. So again, one of the major points you want to make about this is the typical cycle is about 7 and a half to 9 hours. So if people are put into dark rooms that's what it comes out to. Most of you are familiar with the different stages you know. Stage 1, you know again, decrease brain activity by 50%. Muscle movements stop. In stage 2, you have eye movements stop. Muscle activity stops. Basically the brain waves become slower and then sleep begins. Deep sleep starts. You begin to produce very slow delta waves. Again these are the part that is actually important for metabolic restoration. So deep sleep is really important. Now there is no eye or muscle movement. Difficult to wake the sleeper. One of the important parts of this is when you are in deep sleep like this, you turn off your sensory neurons. So think about what we were saying here. So during this part of sleep, you are incredibly vulnerable, right? Because basically the sensory neurons all get turned off. So you are not getting any stimulus from anywhere. So in this situation you literally can pick an individual up and move them around. And they won't even remember being picked up and moved around, right? So it's almost like they are like in a coma. But think about how important this is for the nervous system and for the tissues. Right? Think about what this is saying. There is no eye movement or muscle movement. But this is when it gets really restorative. Because you are not doing anything. So all that metabolism that you have going on during the day, all those metabolic products all get taken up and removed at this point in time. So this is why this part of sleep is so important. In stage 4 again you produce these delta waves. No eye or muscle movement again. And they may be disoriented when they are waking up but again, a key point is there are no eye or muscle movement. So again very restorative. Now this is repairing a lot of the tissues in the body. Allowing you to heal muscles and do other types of things.

Now you get to REM sleep. And again now, you get changes characterized by the rapid eye movement. That's why it's called REM. The blood pressure rises, breathing becomes shallow, muscles, torso and limbs are paralysed. So basically these parts all get basically inactivated. And you begin to dream. The major part of this is this is the part of sleep that actually restores the nervous system. This is the part where we consolidate and we basically start connecting things. And this is why this is very important time. And the most important thing I want to point out is as the night progresses, the length of REM sleep actually increases. So again the length of time spent in deep sleep actually decreases as you go through the cycles. By morning, almost all of it is just basically REM sleep. So you really spend a lot of time in REM sleep on that last part of your cycle. So if you are actually sleep depriving yourself, what you are really doing is you are really not doing these stages any longer. So you are really just doing these two. And these are very quick stages. But again when you think about sleep deprivation, what you are doing is you are losing the benefits of that REM sleep, which is longest on the last cycle. That's the major take on on that.

Ok so, sleep deprivation. Is it a recent phenomenon or problem? This is the cover of TIME magazine 1990. The sleep gap. Too much to do, too little rest. So back in 1990, we knew this was a major problem. Have we done much about it? No, we really haven't. We haven't really

addressed it. I think it's a major epidemic that we have going. Significant impact on public health is obvious. This is a weird one. This drives me nuts. So when you go to the hospital, right, I had this conversation with my mother because she had to go for surgery a little while ago. And I told her I said can you actually talk to the physician at the time and actually have them not wake you up 6 times right after you had surgery. I mean think of how ludicrous this is. You just got through major surgery. And what did they do? They wake you up repeatedly all through the night. You know. How was that even make any sense? Right? But they try to get statistics on how many hospitals patients actually have sleep deprivation. They are saying 20-60%. I think it's closer to probably 100%. I really do. I don't know of anybody who comes out of hospital feeling refreshed. You go home to recover from your hospital stay, right? So again I think we can do a lot better within the hospital systems, hopefully with some of the monitoring they have. They more automated monitoring system and stuff. Might actually allow people to sleep. And recover before we start bothering them? Probing them?

It's about 20% of the population has sleep deprivation. And again I think the number is grossly under-represented. I think if the definition is you are waking up to an alarm clock on a regular basis, that's the definition of sleep deprivation, or mostly sleep deprived. And again there is alarming prevalence and increase of this in the youth and the young adults and what are the triggers of this? Well, you start seeing things like mood alterations, social irritablility, dysfunction, complaints of bodily pains. So again you can kind of tell when people are going in to this sleep deprivation mode, we all been there and done that. We know we are basically compromised. And so it amazes me that we actually don't have more murders and crazy things going on. Given the fact that we all have these nervous systems that are basically over-stimulated and we are not getting enough sleep or exercise.

This is kind of a funny cartoon. One of the sleep deprivation causes. You can see here's the worry centre, you got the curse control, you know, I love this one. Basically it's showing down here, here's a sleep plan. This is how we live our lives. It's kind of comical if you can actually read it. Like the bragging centre, the distinguish quiet from not too quiet. I mean basically again it's the link of every children's video to the second. We have all been there, we have all lived through a lot of this stuff. When you look at the consequences there are a tremendous number of health consequences when you are actually undergoing sleep deprivation. And this is what we are talking about in our model.

So one day of sleep deprivation allows your system to become sensitised. Like we showed in the animal models, by the time you go through 2 or 3 nights of sleep deprivation in an animal, basically you can't even touch it. It is so irritated and agitated with which you have done to it. They will try to bite you just to get out of the cage at that point in time. They are that upset with you. Now the causes are psychological, physical, life style and environmental. All these things are contributing to sleep problems. One of the things you might not be aware of. Do you know what kind of light you should never have in your room? Yeah, blue light. And if you think about again about how clever or not clever all these manufacturers of all these electronic devices are. What do they put on the LEDs down there? Blue lights! Your brain can't shut that down. Your brain cannot turn that off. So if your children are in rooms that have blue lights in any of the electronic devices, then they literally are not sleeping in a dark room, because your brain can't shut that off. You know. There's actually professors at Missouri state that were working on light pollution. And the idea is there is so much light pollution that we don't live in a dark environment almost ever. So again if you have patients that are having trouble sleeping, one of the things you can advocate for them is buy blinds that actually block out the light. Right? How many of us have blinds that actually really do get the room to pretty much dark? But I mean most people don't. Most people have blinds that are artistic or basically you know they are nice looking and stuff but very impractical in the sense of what are you trying to achieve is good sleep. So the idea is how do we minimise? We talked about this before and we have this in the discussion about what you can do to actually help this.

But this is the thing I want to drive home is sleep quality and quantity and the pain. We are looking at the vicious cycle. It's what comes first. You know so basically a bad night sleep we said can enhance pain, but pain disrupts sleep creating a vicious cycle. So once you have an injury or something, think of even a knee injury, an ankle injury, whatever it is, now all of a sudden you try to get a night's sleep, it's going to be very difficult to do that if you have the ongoing pain in those joints. And then you don't sleep well and the pain starts exacerbating and gets worse and worse. So again what does sleep deprivation do? Increase hyper-vigilance, and pain. So again we are creating this vicious cycle and the pain perception of

course is dependent on the activity of the ascending and descending pathways. And the bottom line is when you sleep, you activate the PAG (periaqueductal grey) and basically this is actually descending modulation. This actually quiets the nervous system. Helps buffer the nervous system. This is active when you are in the parasympathetic mode. When you take a walk, you are activating that system. And it sends signals down and blocks the descending pathway which is the nociceptive pathways. So you might have other things going on in your body like different aches and pains but for the most part the joints are actually affected. When you start moving like this, you are going to activate the system and you block it. Remember we talked about you rub something, the A beta fibres, basically this is another mechanism that is going to pry open the brain to allow you to modulate the incoming barrage from the trigeminal system or the dorsal root ganglion. So what you want to do is you want to have the inhibitory pathways basically dominant over the stimulatory pathways and then that's how you can achieve basically a loss of pain.

I don't know if this is a good example or not. I always think about people that get in car accidents or basically something happens to them, and they have a tremendous amount of pain. What's one of the things we bring them to the hospital and they have tremendous amount of pain. Broken bones and everything else. We actually induce a coma. Why do we do that? It's rest. You know it's long term rest. And then what they can do is they can allow the body to heal. So what you do is when you put someone in a coma like that, what you are really doing is facilitating this process. You basically shut down all the information coming in and what you are allowing the body to do is actually use the energy it has to actually fix itself. Ok? And this is very important. That works like being in a coma. If someone has severe injuries like that, they will drop into a coma. And sometimes, it will be 3-4 days before they come out of that. But they won't come out of that until basically their body feels basically it's ready for it. It's a natural process. So this is always going on. Always available to us. We just have to take advantage of it.

So potential mechanisms contributing to sleep loss and inducing pain enhancement. All things like you know opiates, HPA, melatonin, and these inflammatory systems. There are lots of things that actually can contribute to sleep loss. Basically the other things we should put on this is nicotine, caffeine, all the different stimulants that we have. And I think you were talking earlier about sugar. You know minimising the amount of sugar you take in. We try to push as much in the day as we can. But they were trying to make this big deal about these overachievers. These people who can get by on 4 hours of sleep. Ok, and then how much they can get done. They work for 20 hours a day and blah blah blah… only sleep for 4 hours a night and then blah blah blah. The thing they leave out of that is how long do those people live? Not long. Yeah, when you are 20s, when they are running on 4 hours and 6, they can do that and they are highly productive. So then they are applauded for all their achievements and stuff before the age of 30. What you want to do is see how they are when they are 45, right? They are medical wrecks. But they never follow those people up. I called the radio station that was running the thing and actually said I want you to interview people that have actually been like this when they are 45 and give the whole story and they wouldn't do it. That's not the focus of our story. Then I said you are not giving the whole story. You are actually misleading and you are actually precipitating a culture in which now you are trying to applaud these people who really can't get by on that. But I mean what's the minimum they really do say most people can get by on. About 6 hours. Right? I mean 6 hours is about the very minimum. One of the things that was really crazy was I got approached when I was doing the sleep section. We had somebody visit us from the government agency in the US. And one of the things they were hoping to achieve was basically the super soldiers because they had rumours about how you can actually change the sleep architecture of individuals and somehow this is where people get off tangents. It's like a James Bond type thing. But this is where I get really disheartened with where we sometimes throw our money.

There's an investigator at the university at San Diego who had actually convinced the government that he can actually basically he can achieve what we have in other mammals. And that is if you think about birds of flight. How do birds of flight not sleep? When they are migrating. They basically have two hemispheres that are disconnected in that sense. So they can use one hemisphere to continue on and they basically have a duplicate, right? It's like a duplicate hard drive. So they can shut this one down and keep upgrading on this one. How do whales do it? Pretty much the same way. But he convinced that this is the way our brain was organised. And he actually got 3 million dollars for this study to actually do this. He tried, he said he can do this in dogs. I think the thing he left out is his dog became crazy, right? So

what he was doing was he was trying to train these dogs to actually stay up for extended periods like a week at a time. You know? And he had these guys convinced that he can do this in humans as well. And I remember visiting this person and I didn't get the grant I was supposed to get because I think I made him too mad when I told him this study was crap. But it was amazing to me. I mean they literally bought into this whole idea that you can actually take a human being and train them to basically stay up for seven days at a time. And then you have the super soldier. The soldier who will never have to reboot now you can just overcome all this biology. They are really convinced that you can use one half of the brain and switch off. Are they both equivalent? Are they both identical? No they are not. So yeah, it's amazing sometimes what people try to come up with. They try to get around this whole idea of how important sleep is.

And we have mentioned this before sleep loss increases the pro-inflammatory cytokines. Oh, peri aqueductal gray. It's a really long word. The association again with TMD and migraine as well was established. We know the TMD patients exhibit enhanced responses to painful stimuli. There is actually a genetic polymorphism that predicts all of this. Basically what you are looking at is again this idea that sleep actually is a major player. When you look at risk factors, you have to look at whether or not it's the quality versus the sleep quantity. Again those are sometimes confused. Again this is where I get frustrated with sleep tests. Sometimes they will come in and say I am asleep 8 hours but they are taking a sleep test. Is that the same sleep? No. it's not the same sleep. So again sometimes in our culture we are looking at the quantity of sleep but not the quality. I think quality is much more important. Much better to get 6 really good hours of sleep in which you get most of the stages, than it is to have an extended period when you never really go through deep sleep or REM sleep in a normal way. Ok? 77% of orofacial pain patients have reduced quality, or quantity of sleep. And then 75% suffer sleep bruxism. 43% were diagnosed with 2 or more sleep disturbances. And the primary one was insomnia. You know people having difficulty getting asleep and then of course with I think this is actually on the rise is obstructive sleep apnoea I think most people would have agree with that.

So what we did is again we are trying to actually build models that help us understand the pathology that is going on in this conditions. The idea of this perfect storm. And this came from visiting Roger Cady. Roger Cady was talking to us about how does the system become sensitised. And the idea with this perfect storm is that basically it's different risk factors coming together to create the situation. So what we have is all these different risk factors. Things like changes in weather, poor diet, relationships, muscle tension, we have things like our sick child. You can see what's happening to the floor down here if you haven't been watching that. And basically you have lack of sleep on top of this and then there you go. You are done. And so what happened was we were trying to build a model that we call the perfect storm.

Roger Cady made this video of this lady who is explaining what a normal day was. And she was saying basically she was someone who you know has a stressful job, so she was carrying a lot of neck muscle tension. She hadn't exercised recently. She was eating poorly because she was trying to get her 3 children to all their activities. And then her husband had left the country to go somewhere so she now had even more stress to take care of everything and get everything done. She had deadlines at work. And all these risk factors were piling on top of her. And then she gets into an elevator and what happens is she smells strong perfume and that perfume, that strong smell was enough to trigger her migraine.

The perfect storm is different for different people. But I think you have to understand all these risk factors actually contribute to the sensitisation. But what I am going to do is bring it all together for you and show how sleep deprivation, neck muscle tension and the smell triad actually can mimic what we see in a clinic. We are just going to cause low grade inflammation in these neck muscles. And then what we are going to do is basically look to see what happens if we use our water model here on sleep deprivation for just one night. And then use the mechanical sensitivity model. And of course California bay leaf (?) to actually trigger things. The idea is that none of these things will work alone They don't change the system. But then when you start putting them in combinations, they really do start doing that and that's what I want to start to drive home with this. When you start putting these risk factors together now they become able to activate the system. So independently they do not. We just did the muscle pathology and added our pungent odour. This is showing you how it works. This is sleep deprivation and pungent odour. Doing the same kind of thing. So again, different

combination of risk factors when we put sleep deprivation with the odour. But it's the sensitised system. These pungent odours are enough to cause these offensive responses.

This is the one I want to show you and this is where it gets pretty squirly. This is I think more realistic to where your patients are. Now we are going to take muscle inflammation, and REM sleep deprivation together. So now we are going to have this highly sensitised animal and then we are going to add the pungent odour. So what we are predicting is basically they were going into hyperalgesia, right? So we have ongoing muscle pathology, tension in the neck, we have basically sleep deprived this animal for one day, so REM sleep for one day, we waited 7 days for it to recover, ok? So there is still ongoing muscle tension, we sleep deprived it for one day at the beginning of the week, and now we are going to add the pungent odour, and what we were really surprised with, is basically we got a migraine phenotype. What happens in a migraine again? Is the animal able to do anything? Basically it becomes incapacitated. Believe or not, that's what happens with these animals. We thought we were going to get hyperalgesia, but the animal became unresponsive. It completely shut down. It was in so much pain that it basically didn't even move. It put its head to face the corner and it did not want to be touched. It did not want to be handled at all. It had a complete change in the level of sensitivity. So we were using these sixty grams, these hundred grams of filaments, and we were expecting this to go into hyperalgesic mode. It basically shut down. We were poking it with a 180 grams filament. We couldn't get the animal to even respond. It was basically what you see in a migraine patient. When they are going through a migraine, they are in so much pain, they can't even respond to any kind of stimuli. And that's what we are seeing in this model. And it happens in the V3 region even more. And the V3 region we couldn't even get a response on these animals. When we palpated the masseter, they were in so much pain they couldn't even move. We started doing this looking at what is this doing to the other parts of the system, right? We are out past 21 days and it's not resolving. So it's 21 days past just doing this, and the system is still highly sensitised. And it's still pretty much messed up ok? So what we want to know is what is actually happening.

So what we decided to do is to look at the gut microbiome and see what effect this has on that. I will come back to this a little more detail these two lectures are going to run together because I am going to run over time again.

But basically this is overwhelming numbers. We have over a 100 trillion commensal bacteria. Commensal meaning the ones that are the good guys. The ones that are supposed to be living in our gut gastrointestinal system. But they used to say 400 species, now we know it's over 1000. The number just keeps getting bigger. So it's over 1000 different species of bacteria in our gut that are just normal residents of us. They are supposed to be there. So in addition to diet, pollution, infection, our intestinal microbiome is another epigenetic factor affecting gene modification. And again disorders in the system do increase risk and aggravate symptoms of a whole host of diseases including allergies associated with this. Inflammatory bowel disease, autoimmune disease, even metabolic syndrome really ties back to the gut microbiome. And again what the hallmark of this, all these diseases are, is excess inflammation. Starting in your gut. And then these molecules are going out into the circulation and then sensitising the whole entire system.

We are going to talk about why that is so important because that leads to insulin resistance. So global information like this actually leads to insulin resistance. And that again drives diabetes. So this is what we are looking at. The commensal bacteria and your immune system have to be a symbiotic relationship, but I won't go through all the details of this. But basically what it is you have certain bacteria that are going to play well within your intestine. They are going to release factors that actually can work together with the epithelium to maintain the integrity of the epithelium. We talked earlier this morning about autism. And one of the things that happens in autistic children is they have inflammation of the gut. The gut becomes leaky. That means instead of these being tight junctions here, they actually become dissociated. So now things can get into the system that should not be able to. So they basically start having more infections and other things. Because their digestive tract isn't protecting them anymore.

Ok. So basically it's really important to maintain commensal bacteria. So we have friendly bacteria, and we have unfriendly bacteria. And you have to recognise that fungi and other types of organisms actually can be a problem too. Like yeast can be a problem. And fungi can be a problem. And think about when you go on a broad spectrum antibiotic and you are

wiping out some of your bacteria. What does that give favour to? Now you are creating an environment so that now you can have opportunistic yeast and fungal infection. Right? So those are very difficult to get rid of. So this is why balance is so important. So commensal bacteria we knows play really important roles and regulate basically the inflammatory conditions. But they are also going to provide metabolites to our brain to actually help us keep healthy. So we took these animals that were actually control animals, and then animals that were basically sensitised so that are actually treated with muscle pathology or sleep deprivation. So they are sensitised animals. And then we do the DGGE – the gradient gel electro freezes and basically what this allows us to do is to get a fingerprint of the major classes of bacteria that are basically in the digestive tract of these organisms. This is based on the control conditions and these commensal bacteria they are really strong bands. And you see these changes and I am going to go to the next slide which actually highlights this. You look at it in this pattern right here. What we see is the alteration of the gut microbiome.

Like I have been saying. I can't show you all the data that we have with this. We actually worked with several companies on this and they weren't really willing to let me share all the data. This is some of the preliminary data we had. The bottom line is this when they go into that chronic pain condition we just talked about with the two risk factors plus these things. Basically their whole gut microbiome changes. And a lot of the commensal bacteria, the ones that we should see here that are normal, get lost. These are the commensal bacteria bands. These are bands that we should have. These are bacteria that are just lost. And then what we pick up is these invasive species. And what we can actually do is a DNA analysis of this point. We can actually take the DNA out of this and we can clone them and identify what these bands are. And so we can actually look at what bacteria are actually changing. And we can see certain bacteria have been lost and other ones are overgrowing. Some of the commensal bacteria are lost, remember it is so important we were losing those good guys.

Lactobacillus we talked about that being a really good guy. That is actually how a lot of yoghurts work. It's increasing lactobacillus and a chronic sensitised animal like this is losing lactobacillus. I mean It's not like you are down regulating but in these more chronic animals you can't even find it there. It's getting overwhelmed by invasive species. And here's the scary part. Guys, it's that we don't know what these invasive species are. Because we can't culture them. We don't even know what they are. So while we know all the genes that are in our human genome, we don't know all the bacteria that are basically in our gut. We just know there are thousands of them. We have no idea what the function of a lot of these are. And why is that? Any microbiologist in our group?

What percent of the gut microbiome can we actually culture? Probably about 1% is what they estimate. So out of all the bacteria in your gut, we can only study about 1% of them because that is the only ones that we can actually take out in a culture dish. So you see what this is getting at. What you are looking at is we have all these invasive species. We have no clue what they are even doing. And how they are changing the system. One of the things that we know is that one of the metabolites is basically an inflammatory molecule. So we know that one of these bad types of bacteria that we have actually is involved in promoting TNFα (Tumour necrosis factor alpha) and cytokine production and actually promotes that formation. So we do have some evidence that we are shifting from basically an anti-inflammatory state to an very inflammatory state. And actually when you actually take out the colons of these animals, you can actually see the intestinal tract is all inflamed. And again it's very profound what we are seeing.

How do we actually fix this. And again I try to get these companies to allow me to share the data we just found but they won't really let me share yet. But I can tell you there's good news on the horizon because there's actually products that are on the market today that are already available that actually can reverse this process. One of the things that is remarkable is we have been doing this feeding study for about a year and a half now So we are looking at nutritional ways to change the profile of these sensitised animals. Remember we talked about the migraine model and how severe that was. If we feed them for two weeks these certain nutritional products, that again if I tell you what it was you would be dumbfounded because it is very common. And then you do the migraine model, but they never go into the sensitised phase. And it blew us away. I mean think about that. Just changing the diet you are putting a new nutritional component in your diet. You are adding to the diet of these animals and it's actually water soluble. We are putting it directly in the water. And so they were drinking it for about two weeks. We do this injury model and what do we see. We see nothing.

We see just complete blocking. Blew us away. We have over 20 animals that we have done this way. We never ever see this response. So these animals are completely protected from actually going into the sensitised state. If they have this in their system. And what is remarkable about this is that it's something that is very common. And it's something that you know people ingest all the time.

What we are moving towards is try to understand how it works. I wish I could share. We signed a disclaimer on the grant. We actually recently have two patents on this. Yeah. I would say people from certain populations probably eat a lot of it. Other cultures do not. I would say. I know it's terrible. I wish I could tell you. The good news is it is going to be something that I think is going to be hitting the market. One of the things we have actually done now is we moved it one step further and what we are doing is try to figure out how it is anti-inflammatory. And what I can tell you is it increases the lactobacillus so you know how like taking yoghurt is a probiotic and is really good. I tell you it's not yoghurt that we are working on so I will give that a break. It's not yoghurt. But what this product does is it actually increases lactobacillus over 10 fold. So it actually shifts the balance of the bacteria so if you are taking yoghurt or active yoghurt you may maybe bump your lactobacillus about 4%. We are seeing over 10 fold almost a 12% increase in lactobacillus which is probiotic. And then what we are doing is we are showing in this product one of the things that makes remember I talked about those solvents the short chained free fatty acids that's what it promotes production of.

So putting this nutritional supplement in, we are shifting the microbiome so that it actually produces those short chain fatty acids that actually called resolvins and they are anti-inflammatory. And that seems to be what is responsible for what is protecting these animals from going into the sensitised state. So it's really kind of cool. We actually with all the pharmaceutical studies we have done, are finding things that we can just put in the diet of these animals and see these pretty remarkable changes.

I won't say it's better because cocoa and grapeseed actually work in this model as well. But it works differently because it's something you can put in your diet. And it's again something you just have in there.

I would, as soon as I find out from the company that we can actually let it out. I will do it. They are actually telling us that we will get permission soon after all the patent actually gets filed. But they want us to actually start publishing on this. And we have multiple papers we would like to publish. Yeah, it's been fun.