Prof. Simon Carding, Leader of the Gut Health and Food Safety Research Programme, Institute of Food Research and Norwich Medical School at the University of East Anglia, describes our current understanding of the human gut and its relationship with its human host and introduce the provocative proposal that gut microbes influence when, what and how often we eat and whether we stay healthy or succumb to disease.

TRANSCRIPT:

Prof. Simon Carding:

Right, well. Thank you Rich for the introduction. So as Rich said, I'm going to try and inform you a little bit about:

- **What goes on in your gut and in particular about all the microbes that live in your gut,**
- **Why they're so important for your health, and**
- **Why under some conditions, they can actually cause quite severe disease**

So there's been a significant shift in our understanding of what causes disease. I think, you know, traditionally we've always thought of it to do with who we are – our genes, and then the things we do as we go through life – so lifestyle, and what we eat and what we get exposed to in the environment. It's those two that come together, to either keep us healthy or to cause disease.

But what's apparent now is that in the middle of this and that, may be involved in interpreting a lot of these things that we do and eat, our gut microbes. They're a direct link to our genetic material and they can in turn influence how we react, and respond to things in the environment and how they can keep us healthy or not.

Really, the understanding of gut microbes has really taken a fantastic leap since around 2000. This graph here shows the number of scientific articles that have been published about gut microbes. You see they really started to take off here around 2002 and that's because of technology.

So before 2002, the only way we could really identify and characterize our gut microbes was by what we could culture on a petri dish. And since we now know that about 80 percent of our gut microbes can't be cultured that really isn't a good representation of what's in our gut.

But then with the advent of gene sequencing technology we can now identify microbes according to their genetic blueprint. What's apparent is that different types of bacteria have a unique genetic fingerprint. So if we can identify the fingerprint we can say whether or not they're present or absent.

And this, as I said, has led to this huge explosion in this area of research. We can now identify microbes we can culture. So this has led to massive interest in gut microbes and some of these are very recent.

So the Daily Mail thinks that healthy gut bacteria might be linked to anxiety and then we've got others that are linking gut-brain connection – Autism, probiotics as a means of treating diseases and then a couple of books.

This one has just come out and those of you in the Institute will notice the significance of broccoli on the front as the Institute is responsible for generating strains of broccoli that have lots of nutrients — good beneficial nutrients in them. But really the message here is that what we eat influences our microbes which in turn can influence our brain function, and keep it normal.

But as always we have to be aware of the hype, okay. So whenever we read these articles we need to have a couple of things in mind that allow us to determine whether or not, you know, there's some factual basis to it or whether it's hype. And these are some of the questions that I would say you need to ask.

So the obvious one is, well, *"So what do these differences they're detected do they really matter are the changes, a cause or a consequence of the disease?"* And of course we want to know — *"How it works? What's the mechanism?"* So is there anything in this article that allows us to understand how it actually works?

Then a lot of experiments are carried out on animals because we can't do many interventions in humans for ethical reasons. So another obvious question is well – *"Is a mouse – a small human?"* No it isn't. So we've got to bear that in mind.

And then obviously we've got to think *"All is there something else they haven't looked at which could explain what they're describing?"* So behavior and lifestyle are two important things.

So I'm going to try and sort of touch on some of these things in the rest of my talk. So this is what I'm going to cover. I think I need to introduce the gut to you. I'll talk a little bit about

microbes, some interesting facts, a little bit of trivia and then how gut microbes may play a role in determining what we eat and what the consequences of what we are for our health, well being, and then how we actually might manipulate they've got microbes to improve or restore our health.

So that's what I call LawnCare, right start with so did the guts mouth to the anus, it's a long tube. Here's a picture taken with an endoscope and you can see it's not a smooth tube. It's got these ridges to it, the muscles. This is what allows food to be propelled through the guts. But it's not a smooth chew. It has lots of finger-like projections that we call villi that stick into the lumen to capture nutrients and absorb them.

So the tube is quite long — it's like nine meters from mouth to anus. And somebody has taken the trouble trying to calculate what the surface area of all these villi are. And the outcome of that is it's probably about the size of a badminton court. So it's an incredibly large area and it has to be large in order to take up the nutrients that are in your diet to keep you healthy.

Gut – the Bioreactor:

And then we also consider the process of digestion. And the gut is in fact a massive bioreactor. so we take in food plant material, for examples, and they've broken down first of all in the small intestine.

Here's where the small simple sugars are absorbed, and then the larger more complex plant material that we eat in our diet passes through into the large bowel or the colon where it's fermented. And it's fermented by the bacteria that live in the colon. And the end product of all of this is something called **short chain fatty acids** which are very important because they can provide about 5 to 15 percent of our daily energy requirements. In some animals it's up to 30%. So this has to be a very efficient process to keep us alive basically.

And the enzymes that are responsible — the proteins that digest these food materials and the polysaccharides. Now we only have about 20 genes in our whole genome that will allow that encode proteins will break down these carbohydrates.

But one bacterial species – this one in particular – Bacteroides has 260. And you think there are a thousand species. So that's a vast number of proteins that can digest our food. So the bacteria that live in our colon are ideally suited for processing our food and extracting the maximum level of nutrients from them.So it's a bioreactor.

Gut Microbes:

A little bit about the microbes. So the gut is packed full of microbes. There is no space that endoscope image I showed you. They've displaced and rinsed out all the bacteria. Normally that will be jam-packed with bacteria – most of them are floating free in lumen.

But a large number of them actually make physical contact with the cells that line our gut. So there's actually some intimate association of these microbes with our gut. And there are two terms that we you may come across we use to describe these microbes:

- The microbiota — which is to describe all the microorganisms that live in the gut and
- There's the microbiome – (and) that's all the microbes plus all their genes combined.

So microbiota-microbiome, as you may have come across in a lot of these articles. But individually bacteria are incredibly small. So this is a head of a pen under an electron microscope and each of these orange dots represents one bacterial cell.

So you can see that you can get lots of bacteria on the top on the tip of a pin. They're incredibly small but well though they're small they make up for that in their vast numbers. So we have about 10 trillion cells in our body. But we actually have ten times that number of bacteria in our body. And so on this scale here we have enough cells it would fill half of one of our legs. All the rest of the body will be filled up with microbes bacteria and then if we think about all the DNA that we have.

Oh this is an interesting quote. sorry I forgot about this, this ninja just gives you an idea of the scope and scale of the numbers here — of bugs and bacteria in our colon. So just one linear centimeter contains more bacteria than all the humans that have ever been born. It's a vast number of microbes and then the DNA elements. This is the big toe okay and that represents the DNA in our body that is actually ours okay. So everything else — more than 99% of the DNA is bacterial DNA.

So you know, just think about that, that's actually quite amazing really. So we are carrying around a lot of DNA. But very little of it is our own.

Okay, now this is the audience participation bit. Some trivia – *"How much do you think all the microbes in our body weigh?"*

Don't be shy! PhD students at the back, come on. How much? What? That's not conferring su nope. Anybody else? Kilogram. Closer to kilograms. Two to three kilograms. A lot right. A couple of bags of sugar and if you put it in a volume size about one and a half liters and

there’s about a thousand different species thousand different types packed in there.

And this is what they need to keep them healthy – about 50 to 65 grams of these things, which are sugars, to keep them healthy. So that amount is needed every day just to keep your microbes healthy. And then you’ve got all the other things that you need to keep your body healthy. And so a product of all this metabolism is gas.

So, how much do you think we expel every day? And this is everybody. So it’s not just old men and teenagers, everybody in this room expelled gas. How much do you think we expel every day? How many liters? How many? Five. That’s a bit high. Anybody else? One, two, four – that’s a lot. And of course at the end of all this we have waste.

So 60% of your stool is made up of bacteria living and dead okay. So that’s trivia, interesting thing just before you have your meal. You can run through some of these facts and figures but they are very very important and we know they’re very important, because of animals that we can keep germ-free.

So these are animals that have never been exposed to any microbes. They’re sterile, and when we examine these animals they’re clearly compromised. They’re deficient – so they have nutritional deficiencies, they don’t grow. But interesting – they live longer. So if you want to live longer, don’t eat. That’s the bottom line.

- They have a defective gut, so their gut is not poor properly formed, so it’s leaky.
- And their immune system is very poorly developed, so they’re very susceptible to infections. And in fact, if you introduce a pathogen to these animals it can kill them very quickly, because they have no protection, no immunity.
- And also their development is affected as well.

So clearly. we’re already starting now to move into the gut brain. So there are really poor animals — very sick.

Your microbes are unique:

So the microbiota and the microbiome are very important. So your microbiota is unique to you. It’s your identity, it’s like your fingerprint. Your microbes are unique to you.

However, the microbes you have are shared with other family members, so there’s some commonality there. And interestingly looking at the microbiota of monozygotic and dizygotic, that identical and non identical twins, you know, there’s no difference. So even if you’re an identical twin you’ll have similar differences in your microbiota to non identical

twins.

So what does that mean? Well it means that genes are important. Who you are is important. But also nurture/ nature. The nurturing is also important in shaping the microbes.

But we now know that we all have a core microbiota. So there's about 57 species of bacteria that we all share and there are two types that predominate in all of us here, and not unsurprisingly. These are concerned because they perform important functions such as ones here — degradation of carbohydrates or degrading our plant material we eat. They also provide these fatty acids that we need to keep us alive every day. And also amino acids and vitamins which we can't produce but our gut bacteria can.

So it's not surprising there's a core that all of us need to keep us healthy.

But then everything else all – the other 800 of 2,000 species are all unique to us. So where do they come from? Well your parents – in particular your mother. So if you think you have bad bacteria you can blame your parents fully justified okay.

Infants' Gut Microbes:

Now originally it was thought that we were born sterile but that's changing slightly. We've now evidence that we can in fact. Babies do get exposed in the womb to bacteria that the mother has and that can be through the placenta and also by other routes.

But by far the biggest source or time point at which you get exposed to microbes is soon after birth. Because if you believe we are born still then the bacteria can colonize very very quickly. So the first few months after birth you're rapidly being colonized by bacteria. The types of bacteria depend on the delivery.

So if it's vaginal delivery then most of the microbes that will colonize the baby will come from the mother. If it's a C-section then the bacteria actually come from the people in the operating theater handling the baby. And most of those will be skin type bacteria. And that's important. Because there are now evidence that links later onset of various diseases and disorders back to whether or not you are vaginally born or from a C-section and the types of microbes that initially colonize the body.

Other things that will impact on the types of microbes that will colonize this infant are delivery. So is it a normal birth or does it just require intensive care? The age at birth is also important – is it a full-term birth or preterm birth? And hygiene obviously – where you're born – the home versus the hospital at a very different population of microbes that can

colonize the infant.

And then after that things that will impact and cause alterations in the microbes are antibiotics. And again it depends on how many, what types and for how long?

And also very important is nutrition. Whether or not the infant's breast or bottle fed? And again the breast milk contains lots of ingredients including microbes which can colonize that baby and keep them healthy.

Influencers of Gut Microbes:

But as we go older we get exposed to microbes, some other sources and by different routes so via the nose and lungs we breathe microbes in the mouth and the gut obviously the things we eat and through the skin and these are the sources so water and the food we eat will contain microbes.

We have pets if we live in a farm we're getting exposed to – microbes from the animals that we live with.

Where we live – Do we live in the country or do we live in the city, the population of microbes? Again, they are very different.

And then the type of accommodation or the dwelling that you live in, you know. Is it single dwelling? Is it multi-dwelling? All these people are contributing microbes that you'll be exposed to. And then are you indoors or outdoors? Are you active or inactive? Are you an Xbox fan or are you out playing football?

These things will all expose different types of microbes. All of these are important. Because beyond three years of age your microbiota is pretty much set for life. So the early years of life are critical for the development of a healthy microbiota. However there are cultural things and social things that will also impact on the types of microbes that populate us now.

Here's a fact most of you probably didn't know, okay. Interesting one to experiment on. So intimacy and you know it's across the animal kingdom. Different types of interest, transfer of microbes grooming it's another one nurturing food sharing right. We often sit down at the table and eat together and we can be sharing food. It's a good way of transferring microbes.

And then there's something that's slightly less, you know, pleasant. But animals do transfer microbes to their offspring via this route by regurgitation of food and transfer food as well as microbes. So the message here is if you have some good bacteria you need to share it.

Because there are some of us poor, less fortunate people. Scientists, for one right. I mean my wife is very fond of telling me I have very little culture. So maybe my culture is my bacteria. So share your good bacteria if you have them right.

Aging affects gut microbiota:

So we have our microbiota we've been exposed to. We've got a stable population but it's not the end of the story. They do change. And here we've got a representation of aging. So here you can see these circles. The different colors represent different types of microbes. As we age you can see the colours change as the populations change, and there are some differences between formula-fed and breastfed babies. Transition to solid food is a big one in terms of shifts in microbial populations. And then you can see as we age there is also a shift as well in the population.

Impact of Antibiotics:

Ageing has an impact in itself. But one of the most striking impacts is through antibiotic treatment. And this slide just illustrates the impact of antibiotics. To treat Clostridium difficile, which is a severe infection, that is often acquired in hospital. So as a result of the outgrowth of this bacteria we get sick. So we administered Vancomycin or Metronidazole.

And what you can see is the diversity – the number of bacteria we have in our gut is drastically reduced. Because the antibiotics have killed them all, but it's also killed off *Clostridium difficile* which is a good thing. But you know there's a consequence of this in that. We've wiped out a lot of our good bacteria.

So too many antibiotics for too long have a very profound and can be a long-lived effect on our microbiota. So antibiotics could be described as a man-made catastrophe. However most of the antibiotics that are used are used in agriculture and in farm animals in particular to check infection and solar 8 growth about 19,000 tons of antibiotics are used in agriculture every year.

And of course, Antipodes get excreted by animals and humans as well. So they can contaminate streams and rivers and then get back into the food chain. And also giving antibiotics to our children has its consequences as well.

So in the U.S. by 2 years of age most children had at least three courses of antibiotics. I mean a phenomenal number of doses of antibiotics given out in the US. And what this does is it drives bacteria to become resistant. This is serious, okay. So this particular organism

here MRSA now is resistant to most of the antibiotics that we have in the pharmacy. More than 19,000 people here in the U.S. are killed which is much higher than the number of people dying from AIDS.

I don't know if you just saw on the news today – but there's a UK government review group that recommends pharmaceuticals and it's invest two billion dollars in developing new antibiotics there's a real need for this. But one of the causes is that we administer too many antibiotics, we take too many antibiotics. It leads to resistance – cautionary tale.

Gut microbes altering drugs:

The other side of the story is that gut microbes can actually work on drugs rather than been affected by drugs. They can also work on drugs. The thing to bear in mind is that the vast majority of drugs we take are given orally and so the microbes in the gut can actually alter the drugs. They can alter their structure, they can produce factors that interfere with the drugs and they can alter how the body reacts to the drugs. Here are some examples.

So the bad ones are – these drugs here which are painkillers, anti-cancer drugs, drugs used to control high blood pressure, in certain individuals that have certain populations of microbes administering these drugs will lead to increased toxicity and some antibiotic as well as a similar story well.

There's a good side to this as well in that gut microbes can process drugs to make them more active, more efficacious – such as this antibiotic here and this anti-inflammatory drug.

So what this means is that how you react to a drug can depend on the type of microbes you have in your gut. One of the things that medicine is heading towards perhaps is being able to administer or prescribe you a drug based on the population of microbes in your gut because there's no point in giving you a drug that your microbes will make toxic.

You want microbes to actually help the drugs become better for you, more efficacious. So this is what's been called personalized medicine. The drugs will be given to you because you have been determined to respond best to those drugs.

So then that brings me to really the meat of my talk here in a way, and this is what I'm going to try and persuade you of — that your gut microbes can now influence what you eat, when you eat and what happens when you do eat.

Hypothesis:

So I formulated this hypothesis that gut microbes influence their host's food choices. I sort of put up three predictions in order to prove the hypothesis could be correct:

The first one is that the microbes you have in your gut is a consequence of the food that you eat and how you behave in the environment. So this is interesting. So it's not a map of the galaxies it's actually the results of screening them – the microbiomes – in lots of different animals. This is sort of a zoo collection. Each dot represents similar microbiota in populations of animals, and the lines of separation here indicate how similar or related they are to other microbiomes and other animals.

So we've got these sequences. We know all the microbes. And this is how they all cluster. So you can see different clusters. So horses and rhinos are up here in their own little cluster; ruminants such as sheep and cows make their own cluster; elephants are their own little grouping up here; and then we have the carnivores for the lions and bears again – they're a different cluster in red; and then we have leaf eating monkey serve vegetarian monkeys and pigs; and then the other primates – humans included – we're here.

So we're separate from the leaf eating monkeys. So what does this mean? Well it means that who we are and what we eat determines and heavily influences the microbes that populate our gut. That's reinforced by this study in looking at the microbes that are present in the gut of people that live in Burkina Faso in Africa that have a rural diet primarily vegetarian based diet, and Europeans, and this is actually Italians who have a Western diet.

You can see just looking at the colours they're very different ok. What's interesting is that if people in Africa migrated to Europe to Italy and then adopted the Western they lose this and become this distribution of microbes. So they haven't changed terms, their genes or anything. All they've done is that diets changed and it's caused a profound shift in the microbes.

So the diet really is a driving force in making up the microbes that you have in your gut.

There's another example. This is a Burmese python. So they go through periods of fasting and then feasting. Just looking at three different types of bacteria in the fasting state you can see very low levels but if they're given a meal you know within half an hour you can see these striking chips and expansions and increases in certain types of bacteria. And these will eventually stabilize.

Then hours of the animal goes back into a fasting state, they will decline again. So fasting reduces the overall diversity and then feasting expands the diversity in response to diet. It's

quite striking so–that's diet, stress is another thing we have to cope with in our environment.

Stress influence on gut microbes:

This is some evidence that links stress impacting on our gut microbes so Noradrenaline Norepinephrine and effort in which all poly adrenaline is produced in response to stress. That can have a direct effect on the bacteria that live in our gut. It can cause the outgrowth of the particular types of bacteria.

So here for example ten thousandfold increasing growth in response to Adrenaline's produce under stress. Surgery is a stress and this bacteria here rapidly expands following surgery. If it's not contained then it can cause sepsis. Mice that get exposed to a type of stress rapidly change their microbial populations and that's just shown here. So these are normal animals in most of the bacteria — little circular shapes, but then under food deprivation which is a form of stress, you know, they rapidly changed the rod-shaped bacteria. That was observed over 40 years ago. So we've known for a while that stress is a major factor.

What's interesting is that probiotic bacteria that are present in some of these health foods is well for Morrison's and this is Actimel they contain bacteria that produce a neurotransmitter called gamma. Gammas are normally producing the body.

What it does is — it dampens down excitable neurons, so it relaxes you so. This is being used by the pharmaceutical industry to develop mimics of gamma so they can overstimulate these receptors to make you even more relaxed and in fact even knock you out. Because anesthetics can work by mimicking the gaba that is produced by these bacteria.

So benzodiazepines alcohol — right. We all feel nice and relaxed after a glass of wine or a bottle of beer. Well you know one of the ways that comes out about is that they're stimulating these receptors that gut bacteria can do as well. So the gut bacteria can already you know hopefully take us from a stressful state to a relaxed straight state.

Obesity and Gut microbes:

So one of the other things i wanted to highlight here was this obesity lots of evidence in the literature now and in the newspapers that changed in our gut microbes to make come acres of obese. So gut microbes and obesity are very (related). This is a very interesting experiment, probably the best experiment that demonstrates how microbes can influence

whether or not we are so lean.

So here we have identical twins but one of the twins is obese and one is lean. We've taken the stool sample from each of these extracted bacteria. What we've done is we put them into mice. The mice are then put on a regular diet low-fat high-carbohydrate, I mean, low-fat high-fiber diet. The ones that got the microbes and the obese twin become obese, but the mice that got the microbes from the lean twin stay lean. So that's a direct cause of the link okay. So that's not really height that's a bit more close to fact.

So of course it's my slits not humans. But this is the best evidence we have to date that shows the direct causal link between our gut microbes influencing whether or not we stay lean or whether become obese.

Then this was in the Sunday Times this week. This was from a study carried out by Tim spectra at King's College London and he fed his son — I don't know if his son was a willing volunteer — a high fat diet for 10 days Big Macs and lots of coke. Then he was taking stool samples before and after the 10-day diet and what happened.

What he showed was that first of all is a reduction in nutrients. Because he's now eating these very processed refined foods, there was a loss in number. He's got microbes but he gained two kilos in weight in just 10 days. So the interpretation of this is that highly processed foods present in Big Macs containing grease are toxic to certain microbes and this leads to a loss of diversity. We're losing microbes because of this. If you want to know more this individual has produced his book. I had nothing to do with it so I'm not buying it or anything. But if you want to know more about these books here.

So loss of diversity is a recurring theme. In fact I've already said in aging we have this loss of diversity, we lose richness, we lose microbes.

Other gut diseases:

The same in obesity and it's the same in other diseases like inflammatory bowel disease and Crohn's disease. So the loss of diversity and types of microbes I got is not good, it can have quite profound health effects.

So it's not just gut diseases. All of these diseases shown here are linked by a common theme in a change or shift in the population of microbes in the gut and generally that shift means less diversity.

Interestingly quite a few are linked with diseases of the central nervous system, nearly

generative diseases, the heart, liver fat and rheumatoid arthritis. There's lots. This is a lot of complete lists by any means. So obviously there is one microbe or one population of microbes that can cause these diseases so it's like looking for Waldo found him yeah. The only problem is there are lots of Waldo's.

So it's probably not one microbe, it's the combination of microbes that when they get together you know it's a bit like a gang of teenagers, you know. They could be rowdy or it can be miserable and anti-social. So it's the population when they come together that causes or is probably responsible for the effects on our health. It's not one, it's probably lots okay.

Second Hypothesis:

So moving on to the predictions — we're now at the second one.

So gut bacteria can by influencing how our body works influence our appetite and food preferences. So I'm sure this is a familiar scenario for many of you. You know our mind says 'No, take the healthy option.' But there's something inside of us and 'I really like that piece of cake okay'. It may be that gut feeling, you know, 'I really am hungry for a piece of pie rather than an apple.'

So what is the evidence that normal gut microbes can influence brain development and behaviors – that's what we're talking about brain development behavior. So this is next.

This is a summary of an experiment carried out a few years ago looking at our germ-free mice again. These are sterile Mice and mice that have populations that have microbes. This here shows the expression of an anxiety related gene. So the yellow identifies high levels in the brains of these mice that have got microbes but very little expression in germ-free mice. This maze here is a measurement of how curious, adventurous mice are.

So if they're cautious, timid, they'll spend most of their time in the enclosed section away from the light; but if they're adventurous like this one you know they'll be on the open arms. So what this study showed was that gut microbes can affect normal brain development and make these mice more curious. I'm sorry the wrong way. Perhaps more creative and trying to escape.

So it's this fear of extinction you have got microbes you become a little bit more cautious, reticent, a little bit more anxious. If you don't have got microbes you know it's the Great Escape. You're looking for ways out. More striking experiments like this one shown here. So we've got two strains of mice that we'll call timid and adventurous. So they've got microbes

or anything to do with why these animals are timid or adventurous and what we did so not well?

What this group in Canada did was they took the stool from the timid Mouse isolated the microbes and put it into an adventurous Mouse and that Mouse became timid. The other way around they took the microbes from an adventurous Mouse and put it into a timid Mouse. These are germ-free mice so they're an empty vessel that you can put the microbes into and they became now adventurous. So this is a direct causal link again showing the gut microbes can influence the behavior of mice. At least now is this translatable to humans.

Gut microbes and brain:

I can see probably some people in you always thinking. 'Maybe I could give this to my husband, yeah. Would he still be a grumpy old man, if I gave him some microbes? Would you know if my teenage boy had some microbes from you know somebody maybe they become – bit more outgoing, bit more social?'

Maybe no maybe a few years from now maybe I'll have that but not just yet. But I mean we really shouldn't be too surprised by this. Because we now know that the gut actually contains an awful lot of the neuronal/ neural circuitry that's present in the brain. It's often thought to be the second brain. I mean it has a very large number of neurons – 500 million and it produces lots of neurotransmitters.

You know there's some evidence that sort of links that got to the brain so brain-dead people their stomach functions normally for quite a while. It's almost an inherent activity anybody that's taken paint major pain-killing drugs like morphine for example you know the risk of constipation. It shuts down motility in your gut and emotions and feeling are intimately associated with bowel function, right.

We've all had their butterflies in the stomach that nervous gut action. Well that's all those neurons in your gut that are firing away. When you look at the structure of the nerves in the gut that make up the enteric nervous system, you know, these are the neurons or the dendrites here in silver, the white color. This is our gut tissue.

You can see that when we superimpose these two the nerve fibers actually penetrate and intermix between all our gut tissue and they actually look like they're actually protruding into the lumen to be able to sense – perhaps the presence of factors that they can respond to that are in the gut lumen. That could be made by gut microbes and the vagus nerve is ultimately this the route by which all this signaling in the gut leads into the brain.

So all these signals here that the enteric nervous system responds to are fed into the brain via the vagus nerve. We know that if the vagus nerve is blocked or damaged through injury, profound effects on appetite and eating, in fact, it causes drastic weight loss. So it's clearly a regulator of body weight. Vagus nerve stimulation by hormones and neurotransmitters in the gut could drive excessive eating behavior.

So over stimulation is not necessarily a good thing. Not surprisingly gut microbes can actually regulate how much of these neurotransmitters and hormones are produced in the gut. They can manipulate this to their own advantage by producing things that can block or stimulate the consistent in the gut. So microbes control eating behavior by influencing signals that are delivered to the brain and by the vagus nerve.

Dopamine and Serotonin in Guts:

Two of the most important are dopamine and serotonin. So dopamine associated rewards pleasure compulsions; serotonin regulates our mood, our memory, sleep cognition.

Dopamine about half of the amount of dopamine producing the body is produced in the gut. Some gut microbes can produce vast amounts of dopamine and so you may know that L dopamine is used to treat Parkinson's disease.

Serotonin is even more striking but virtually all the serotonin in the body is made in the gut and gut microbes produce factors that can mimic or block serotonin action in the gut and deficiency of serotonin is linked to depression.

So I hope you can see that microbes by manipulating just these two neurotransmitters can profoundly influence our mood behavior – whether we're anxious, whether relaxed, how much we sleep, how much we eat.

Gut microbes and disease:

So linking this to a disease interest. This is a more recent study now linking gut microbes to a disease that's called autism spectrum disorder. Autism, so we know from looking at a patient's microbiota, is that they have they're disturbed. They have alterations. The makeup of microbes and also there are altered, levels of what the microbes produce and. There's a mouse here that can develop autism like Syndrome. Particular excessive grooming and vocalization is affected as the art as it is in autistic children.

What this group that works with this mouse showed that they could restore or treat this mouse by using ant probiotics – so live bacteria. So the live bacteria altered the gut

composition of the microbes and it looked now more like normal animals. This was linked to resealing of the gut/ So these animals are leaking and it was the leakiness allowing, but these microbe derived byproducts get into the bloodstream and into the brain.

But as soon as the barrier was improved, the leakage stopped and it restored the normal levels that you would find in serum. And it stopped or halted some of the features of autism. So this is animal experimentation, but it clearly shows that it could be a role for alterations in gut microbes that are linked to neurodegenerative diseases and autism in particular – so neurotransmitters.

Hormones role and mimics:

Well there are also hormones producing the gut which regulate appetite and here they said there are appetites that are produced to say, '*Stop eating you've eaten too much!*' Now we have all we need no more tweaks and then there are hormones – it signals to the brain state we're hungry, you need to eat. It's the balance of these two that determines our appetite regulates how much we eat, when we eat.

Not surprisingly, now perhaps, you think, what gut bacteria can alter the balance of these hormones and these hormones are mainly produced in the gut. So we know that probiotic bacteria can raise the level of this amino acid tryptophan and tryptophan is important because it's involved in generating or producing these hormones. Bacteria that live in the gut can produce mimics of some of these hormones in.

For example – leptin graylien pyy – that influences your appetite so they can influence eating and appetite control directly by mimicking the hormones normally produced in the gut. Indirectly they can stimulate things that will block hormone signaling to change your appetite. This is a slightly different one. This is very recent showing how with this information, we can actually use it to try and redress the balance. So here we have this chemical here which is produced as a result of a break digestion of fats is called napes.

As I said these are naturally producing the small bowel as a process of digestion – lipid digestion. Obese individuals have very low levels compared to normal healthy individuals. So what this group said 'Well okay! What if we engineer a bacteria that lives in the gut to produce this factor can we then reboot increase the levels back to normal?' So what they show is when they fed these bacteria producing this chemical to mice you could protect them from becoming obese.

So give them a high fat diet given lots of Big Macs they stayed lean just by giving bacteria

that produced this chemical. What's interesting is this persisted for a very long time even after the bacteria left the body. It was still in effect. So obviously this could lead to a different type of intervention using these engineered bacteria as a treatment for redressing appetite control and maybe even obesity.

Engineered Gut Microbes:

So gut microbes, you know, we can engineer them and we can utilize our expertise in work with microbes for beneficial effects. You know, I've tried to highlight one or two things that microbes produce that influence our behavior. This is a little bit more of a list that shows things that impact on our body's function I've talked about – energy metabolism the equity's factors that help is blood clot blood for blood coagulation new adjustments.

I talked about that sleep and mood. They produce factors that will determine how much sleep we take whether or not. Sleep's beneficial and it's just they produce factors that cause bad breath. So a variety of things that impact on our health and behavior.

Third Hypothesis:

So I come to the third prediction that there is a positive selection system, positive reinforcement if you like in which the type of food we eat selects for specific microbes which in turn then feedback on making us eat more of that. My example here is a seaweed diet. So a stable diet selects microbial specialists that lead to us wanting to eat more of these things.

So there's two types of seaweed diet – this is one but I'm not going to talk about that one. I'm going to talk about this one okay. Seaweed now, In Japan, vast amounts of seaweed are consumed every year – about more than four kilograms per person. But they can process and eat seaweed because they have genes present in their microbes that produce the enzymes that allow them to break down the seaweed okay.

The genes originated from bacteria that live on the seaweed. So as they were consuming the seaweed, some of those microbes stayed in the gut long enough to pass on these genes to the normal population of microbes in the gut. So these microbes that contaminated seaweed, actually transferred some of the beneficial enzymes and genes they had to the normal population migra's in their gut. So this is positive reinforcement because seaweed has lots of health benefits – the exact fication, promotes weight loss, lowers blood cholesterol.

So the reasons to eat it, and the more you eat the more microbes and genes you have, you

acquire that enables you to break it down and get maximal nutritional benefit. So it is positive reinforcement. But you can only do that if you have the microbes there and the genes present in the first place. Japanese population does because they consume a lot of that.

Food Allergies:

So as another type of food preference which is food avoidance and food allergy okay. Food allergies have increased dramatically in recent times. More than 50% since 1997 and they've been linked to the modern lifestyle, so-called hygiene hypothesis — overuse of antibiotics again destroying the microbiota. So we can sort of look at this in more detail using mice again.

If we destroy the microbiota in mice with antibiotics, we can actually give these mice analogy to peanuts just as many children have. But if we reintroduce one type of bacteria into the gut, we can actually cure them of their allergy. That's this bacteria *Clostridium*. So this is direct evidence linking gut microbe activity to food avoidance okay and food allergies.

Not only are the microbes that will encourage us to eat more, there are microbes in our gut that will stop us from eating things which cause harm – smart bugs really and also sweetness and taste. Again if you look at taste receptors that are present on the tongue germ-free mice have different types of receptors compared to mice that have populated the microbes.

So germ-free mice have a sweet tooth. They prefer more sweets and have lots more sweet receptors on their tongues than mice that have populations of microbes in their gut and so near is the knowledge on come on humans is patients that undergo gastric bypass surgery for obesity. Their food preferences shift enormously, in fact, they develop avoidance strategies to stop eating like some dairy products and even meat. This is a company by striking change than they got microbes as a result of the surgery. So microbes can influence food preferences, by altering our taste perception of foods.

So all of this together is summarized here.

Summary:

So what I'm predicting is that food cravings are associated with vagal nerve stimulation by blocking our appetite and we can reduce food cravings by altering our gut microbes. We can cure food cravings and we can cure maybe allergies and then the diversity of our gut

microbiota and what they produce should affect food choices and satiety okay. So if we increase the diversity we have a better chance of controlling appetite and keeping us healthy and not from gaining excessive weight.

So that's great. How do we actually go about changing those that live in our gut?

So this is gut microbe therapy which I'm leading to lawn care. So anything or when's it going to talk about lawn care that's coming right. So message to fix your brain, you need to fix your gut and there are different strategies we can use.

There's the expensive one – pharmacy prescription of drugs. Sorry getting a bit ahead of ourselves here. Antimicrobial therapy. Obviously I've highlighted some of the issues with antimicrobial therapy. Toxicity can cause the outgrowth of pathogens like *Clostridium difficile* and we develop resistance – our bugs would develop resistance to the antibiotics and they're not cheap vancomycin. However it has been used for diet induced obesity to control diet in use. So it's not all bad news. But it's still expensive.

Other approaches rely on biotics **Pro and prebiotics**. Then I'm going to talk about transplants. If we go there I will do probiotics there.

Live microorganisms which when administered in adequate amounts confer a health benefit that is the WHO definition of a probiotic. They are found in a variety of foods. These will be most familiar to you. These are generally for anybody. Then we have ones that are designed for children and even pets. So you can get probiotics for your pets. Evidence says that they work or may work. So there's evidence that they can decrease food intake, they can reduce fat mass, improve insulin sensitivity, stop us from becoming diabetic.

Yogurt is the food that's most associated with reducing weight gain. If you think of the things that we eat to try and reduce our weight, yogurt is one of the things we generally eat. Probiotic treatment in pregnancy can prevent excessive weight gain in the infant after birth. So the other approach is prebiotics and prebiotics can be suited as food to feed your healthy microbes. If you do remember back to my gut trivia slide, I said you need to consume 50 or 60 grams. These are the types of food that will fuel, provide the fuel for your healthy bacteria. There can be lots of things from pre-burn. Even toothpaste contains probiotics, prebiotics food for your gut bacteria.

So this is what they are generally as I said the different types of sugars. Breast milk is a very good source of inulin which is a very good prebiotic. These varieties of foods here but five a day is one of the reasons why we keep saying five servings of fruit and vegetables a

day are a very good source of prebiotics to keep your gut bugs healthy. So you can take probiotics and you can feed your healthy bugs by eating these types of foods.

The more radical approach is okay that's not working let's get rid of everything and replace it so fecal microbiota transplantation so this is it in a snapshot and maybe I'll cure me a my food addiction yeah sounds gross God how the hell could this work but it does work it works incredibly well for treating gut infection against C difficile to come up again you know it's a 94 percent cure rate which is much much higher than all the drugs and antibiotics. Sounds gross. But it works.

So the question is why does it work and how does it work well? That's something the Institute we're very interested in knowing. So it works but you might think well this is something new I've only been reading in the Daily Mail for the last year or so. But in fact it goes back a long long way.

The Chinese were way ahead of us. So two and a half thousand years ago, they were giving people yellow soup to drink to keep them healthy. Vets have been using it for a couple hundred years, a post called transformation – transferring stool from one animal to another to keep it healthy. First real use tested in humans in 1958. It was given to four patients. There were near death from a type of colitis. It cured all four patients and then since the *C difficile* experiment you know we've treated over 500 patients. No side effects whatsoever and success rate is incredibly high. And it's stable so as far as five years out, you know, these people are still free of *Clostridium difficile* infection. So it is very good.

How to do it:

So how do we do it? There are several options okay? There's the craps you'll there's you know things you can have. It's part of your healthy diet for there's the very unpleasant way a tube and if you go on the internet you can get DIY kits that allow you to do this at home, very scary stuff. But you know, I think we'd all prefer the crap show. So what are we going to use it for?

So I've said you know there's some obvious diseases. Obesity, clearly, I've shown giving you some evidence that microbes cause obesity. So if we change our gut microbes can we stop us from becoming obese or even cause weight loss, eating disorders. Again showed it as a link between our gut microbes and what we eat or what we can't eat. So again this could be another application – autoimmune diseases, inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis. They're all potentially slightly more speculative.

Reverse Aging:

But something we're interested at the Institute in looking at can we reverse some of the effects of aging? ooh not quite sure. What that is now I don't want BT burned. So yes can we reverse the effects of aging. So our gut microbes change drastically as we age and that's the search of a decline in our immune system function. We become less resistant to infections and we mostly some people here probably annual flu vaccines right try to boost our immunity. What if we could boost your immunity by giving you a crap seal? Would you rather have a needle or a corruption? Maybe maybe we can reverse other signs of aging, you know. Maybe if we're rich and famous because we've got the youth capsule yeah. Reggie's taking orders, at the frontier.

How does it work? Well this is another example of how it works. So this is a fecal microbiota transplant by a nasogastric tube. So this is you know the way it's been working so far taking my crinkle micros from lean donors given to patients with metabolic syndrome. These are patients at risk of developing diabetes. Six weeks post treatment we can clear glucose from the blood and they're now responding to insulin. This is associated with a drastic change. But they got microbes that increased diversity.

But with everything that's always a bunt and this is the butt. Donor selection is important. This is a very reason a report was published. 32 year old female with a recalcitrant C difficile infection. Remember this is the disease we can cure with FM t! She decided she wanted to take a stool cell from her daughter. As the donor, as you probably would, a daughter was a little overweight but she later gained weight and became obese. The mother 16 months post treatment have been given her daughter's microbes – got microbes, became obese, she gained excessive weight. Despite all interventions, she could not keep the weight off. At 36 months, she weighed 80 kilograms, and a BMI of 34.5.

What this led in this particular Hospital was a complete change in the way donors are selected. So there is the smoking gun. Obviously the clinicians would think well it came from the best patient. We just transferred the phenotype to the mother. Well maybe. But clearly there's a link here. So what we have to think about carefully now is donor selection – what is the criteria we need to apply to a donor in order to be able to use their stool sample for a transplant?

Lawn care:

Here's the lawn care. So if you think about trying to keep your gut microbes healthy, you know, here's our healthy flourishing lon. We can devastate it with antibiotics, we can just let

the weeds grow. So if we've got antibiotics, we might want to give prebiotics – turf food. Or we might want to put new seed down probiotics right. And then the more radical therapy a lawn transplant bacterial therapy okay

So think of your gut keeping Elvis Lawn Care.

And this is my take-home message okay. If you have young children — get them a pet and let them roll around in the mud, let them eat mud, you know, maximum exposure, lots of healthy microbes.

And with that I thank you and I'm happy to take any questions you might have.

Thank you.