#281: Gut harmony: Why the right mix of microbes is important to our health

VOICEOVER
This is Up Close, the research talk show from the University of Melbourne, Australia.

DYANI LEWIS
I'm Dyani Lewis, thanks for joining us. We are not alone, in fact each of us is teeming with bacteria and other microbes. From the soles of our feet to the follicles on our head and every crevice in between, trillions of microbes form specialised ecosystems collectively known as our microbiota. The microbes that live on and in us outnumber our own cells by more than ten to one and far from being mere freeloaders many of our microscopic passengers are essential residents, friendly bacteria that help us digest our food, synthesise vital nutrients such as vitamins and keep pathogens at bay. The rapidly growing field of microbiota research is starting to generate some tantalising results linking our microbiota to everything from our weight to our moods and behaviour. But, how is it that our microbes influence our health? Could we one day start to treat illnesses by manipulating our microbial communities? I'm joined on Up Close today via Skype by a world expert in the field of microbial ecology. Professor Rob Knight is from the Department of Chemistry and Biochemistry, the Bio Frontiers Institute and the Howard Hughes Medical Institute, all at the University of Colorado in Boulder. Welcome to Up Close Rob.

ROB KNIGHT
Thanks Dyani.

DYANI LEWIS
Rob, why is it that we are only now getting an appreciation of the complexity of the microbes that live with us?

ROB KNIGHT
Well, a lot of it is because of the advances in DNA sequencing as far back as the 17th century, Robert Hooke and Antonie Van Leeuwenhoek knew a lot about how we were teeming with a lot of cancer microbes but there wasn't a lot of ability to figure out who they were or what they were doing. It's really the explosion in DNA sequencing technology over the last decade that really lets us figure out what is
When and how do we acquire these microbes?

Well, we acquire our first microbes very rapidly, probably as we are passing through the birth canal, in fact as soon as 20 minutes after birth babies who are born by Caesarean section have very different starting microbial communities from those delivered vaginally. Your first microbes arrive very rapidly, the real question is what's the trajectory of change in these microbes? At what age do your microbes really start to matter? Do the first microbes make a difference to your later life or is it something that you acquire later?

Do we continue to share our microbes with other people in our environment throughout our life?

Yeah, absolutely and also people who you come to live with later in life, you start to share microbes with as well. For example, if you look at adults who are living together who are cohabiting they share more of their microbes than individuals who don't live together. This even extends to your dog, so we can tell what person goes with what dog by looking at the microbes they share.

And can you give us an idea of the ecological landscape of our body, how many different microbial communities do we each have?

That's actually an interesting question and a little difficult to say even on each fingertip you've got a distinct microbial community, what's on the index finger of your left hand is different from what's on the index finger of your right hand. We just don't know how rapidly that varies, so it's a little bit difficult to say how many distinct communities we have. In general though, we know that the microbes on the skin are very different from those in the mouth, very different from those in the gut and very different from those in the vagina. Then even within the gut and the stomach and the small intestine and the large intestine are very different. There's a whole lot of these different habitats, each of which has a completely different microbial ecosystem in it, but then there's a lot of gradations there.

How do you go about picking apart the composition of these communities?

Normally we use what's called micro-gene sequencing, we take one particular gene
and usually we use something called the small subunit ribosomal RNA, there also is a gene for an RNA molecule that forms part of the ribosome. What’s nice about it is that all life has ribosomes, you can amplify it out of every species. There is also a huge reference databases that let you take the sequences that you found and match them up to what’s known already. So, what we do is we use what are called PCR primers to carry out a reaction called the polymerase chain reaction which allows us to make the whole lot of copies of this one particular micro-gene, then what we can do is we can look at the DNA sequences and ask how many different kinds of DNA sequences are there and which of those match up to organisms we already know something about verses which are completely new.

DYANI LEWIS
If we think about that diversity within even just the bacteria, how far down do we need to separate out different species or do we just separate out different large groups or - how finely do you have to define what’s there?

ROB KNIGHT
It depends a lot on what hypothesis you’re trying to test. So, some types of questions like for example, how do microbes vary with diet, you get a lot of the information even the level of bacterial phyla which is a very broad grouping. So, for example an animal phyla might include everything from humans to fish or everything from insects to spiders. Then the bacterial phyla are much more broad groupings than that. Whereas in other cases, like if you want to look at particular pathogens for example or if you want to look at bacteria that metabolise different kinds of drugs, you might have to go all the way down to the strain level. That’s the equivalent of working in very closely related populations of people even within a species. So, a lot depends on what you’re trying to find out and so for some analyses you can get away with very broad classifications which are relatively easy to determine. For other analyses you need to go much more fine-grained.

DYANI LEWIS
If we look at our gut microbes in particular, what are some of the essential functions that gut microbes play in our health?

ROB KNIGHT
The main one that you’re probably familiar with is still digesting food which is really essential and different bacteria have very different capabilities for extracting nutrients from our diets. Beyond that they are doing all kinds of things like metabolising drugs for example, so both breaking them down and reactivating them. They are involved in vitamin synthesis, they are involved in short chain fatty acids synthesis, short chain fatty acids like butyrate and propionate are really important for feeding the cells that line your gut. They’re also involved in stimulating the immune system including things like production of regulatory T cells. They’re even involved in all kinds of things that you might not expect. So for example, ninety per cent of your body is serotonin a neuro transmitter is actually found in your gut, rather than in your brain and microbes seemed to play an essential role in creating serotonin in the gut. So, it’s very different for example between mice that are conventionally raised and mice
that are raised germ-free, so they don’t have any microbes associated with them.

DYANI LEWIS
With all of those functions you would imagine that it would be pretty hard to live without the gut microbes that we have. How do these germ-free mice fair without gut microbes

ROB KNIGHT
Well, it’s interesting they actually live longer than conventionally raised mice, but on the other hand they have very limited reproductive success. So, from an evolutionary standpoint your gut microbiota are definitely increasing your fitness and contributing a lot to your ability to survive and reproduce and outcompete others of the species. It is really fascinating that individual mice that don’t have any microbes seem to live longer, although they do have a lot of deficiencies, so they’re very bad at metabolising food for example, they tend to eat a lot more than a regular mouse while remaining lean. They also have all kinds of morphological defects, so for example, their gut is very different in terms of the cells that make it up and the shape and so forth and both their gut and their immune system are very reduced in function.

DYANI LEWIS
Given how difficult it is to have a germ-free environment, I imagine that a lot of the functions that the microbes perform in our gut are very much a result of having lived with them for so long in evolutionary time.

ROB KNIGHT
That’s exactly right. Particular kinds of mammals seem to have co-evolved with their gut microbiota. In addition to that what you see is very different functions being represented depending on the diet of the animal. So, carnivores and herbivores and omnivores have systematically different gut microbiotas from one another even in conventionally evolved lineages. So, for example when you liken marsupials versus eutherian mammals, the eutherians are the placental mammal’s so like your cow or whatever, whereas the marsupials are the kangaroos and so forth. So, what you see is marsupial herbivores work a fair bit like eutherian herbivores for example. Then, if you look at animals converged on very specialised diets say for example we recently published a paper looking at ant eating mammals in particular, things like aardvarks and penguins and anteaters and so forth. What you see is a substantial convergence where if you have the same diet, you’ll wind up specialising on the same kinds of gut microbes.

DYANI LEWIS
Rob if we focus on humans, how individual is our microbiota. Would I have the same microbial communities as you have for example?

ROB KNIGHT
No and you wouldn’t even have the same microbial communities as your identical twin if you had one. So, even identical twins can be up to about 60 or 70 per cent different in terms of the microbial community’s that they harbour.
What sort of factors are influencing the composition of microbial communities?

A lot of the factors are unknown at this point really, but there have been studies that show that what you eat has an influence, who you live with has an influence and especially whether or not you have a pet, such as a dog for example. Whether you travel to different places seems to have an influence, especially if you're likely to get a GI infection. So, for example people who have travelled to Thailand or to Bangladesh or other Asian countries, especially from the West, often have a systematic signature that then persists for months or years afterwards. Then beyond that things like host genetics, seem to have an effect, this has been especially been demonstrated in mice. Infection with particular pathogens can have an effect and can leave a signature, so there's a lot of different things that are known to have a statistically significant effect as well as the lot of diseases, including obesity, diabetes, colon cancer and so forth. One of the big challenges for the field at the moment is to figure out which of these factors has a large effect and which has a small effect and for example, if you taking antibiotics how long do you have to wait before the effects of those antibiotics disappear and you can get back to the baseline.

This Up Close, I'm Dyani Lewis and in this episode, we're talking about the human microbiota with microbial ecologist Professor Rob Knight. Rob, with so much variation and so many influencing factors how challenging is it to establish a baseline for what constitutes normal or healthy gut eco systems?

It's incredibly challenging precisely because there is so much diversity. So, for example in the Human Microbiome Project we looked at about 250 rigorously screened healthy individuals. Even within that group you could pick two people, where if you picked a bacterial cell out of the first person and one out of the second person, out of the gut, 95 per cent of the time would be different from one another, out of the species level? of the genus level and in some cases even at the phylum level. What that shows is that there's a lot of different ways to be healthy, we also know there's a lot of different ways to be unhealthy. So, you might need populations of thousands to really get a handle on that. This is why in projects like the American Gut Project for example, where we have over six thousand participants already, so while we are doing this we are reaching out to members of the general public who are interested in having their gut microbes sequenced. So, we can really get those large population sizes and just try to define what is out there in the wild in the human population at large as opposed to a typical study which might just look at a few dozen people.

In terms of disease if you start by comparing healthy individuals with people who have a particular condition, let's say obesity, once you've established that there's a difference between these two groups of individuals, how do you get around the
chicken or the egg question to determine whether it's the illness that's influencing the microbes or that the microbes are somehow causing that illness?

ROB KNIGHT
That's a really important question because so frequently what we see is microbial changes that are just a response to a disease especially if there is an inflammatory response or an immune response. So, there's two ways you can go about it really - well there's three ways but one of those you're not really allowed to do so the gold standard would be to infect people with the microbe and see if you cause the disease. But there's obviously fairly substantial ethical issues to doing that, so we don't do that. So, the two options that are left over our what are called prospective longitudinal studies where what you do is you enrol a whole bunch of healthy people before they get sick, but you think that enough of them are going to get sick during the study. You can then track them over time and then try to ask does it change to the microbes come before or after the change in disease state. And then the second thing you can do is you can do mechanistic studies, mostly model animals like mice. What you do is you take a sample of the microbes from a person, say usually from a stool sample and then you can take those microbes and you can put them into a germ free mouse that you've raised without any microbes of its own. Then you can ask, does that mouse or a set of mice you've colonised from the same person respond differently from a set of mice that you colonised from some other person.

DYANI LEWIS
One of the studies that you collaborated on was looking at twins and obesity in twins and using mice can you explain what you did there?

ROB KNIGHT
Sure, so I should clarify that this was collaborative work with Jeff Gordon at Washington University and all of the germ free mouse work went on in Jeff's Lab. What my lab contributed was primarily data analysis and techniques for analysing the data on that project. But, essentially the goal of the project was to try to find out whether the microbial differences that had been observed in lean people versus obese people could be transmitted into mice. Then to see whether you could recapture that by culturing hundreds of different strains of bacteria and then re-constituting the communities from those cultured strains and putting those into mice as well. Where you had twins who were discordant for obesity, so one was lean and the other was obese, in one of those cases it was a pair of monozygotic twins, what we call identical twins typically then in the other three cases they were dizygotic twins so fraternal or non-identical twins. So, basically the experimental design was initially to take the faecal samples from the lean and the obese individual in each twin pair, put them into the mice and then see how much weight the mice gained depending on whose microbiota they got. What happened in every case was that the mouse that got the faecal sample from the obese person gained weight more rapidly and wound up being more adipose, so having more fatty tissue than the mouse that got the microbial community from the lean twin. Then there will also systematic metabolic changes like in the short chain fatty acids that I mentioned earlier. What was really fascinating was the co-housing experiments. So, normally if you take one
of the obese mice that's obese because it got the transplant from the obese twin if you take a germ free mouse with no microbes of its own and you put it in a cage with that obese mouse it will itself gain weight, it will pick up the microbial community. But, part of the paper was to design a community with 39 members which has been based on their predominance from the lean individual rather than the obese individual in the different twin pairs. So, we can take that designed community and then put it into the germ free mouse and then move that mouse into the cage with the obese mouse and it wouldn't gain weight. Essentially we established that we can design a microbial community that would protect a mouse against weight gain that it would otherwise experience by picking out the microbes from the mouse who got the transplant from the obese subject.

DYANI LEWIS
All of this was with mice that were on identical diets wasn't it?

ROB KNIGHT
Yes, that's correct so that's how we knew for sure that the microbes were involved because the mice were all essentially genetically identical and additionally they were all kept on the same diet.

DYANI LEWIS
Rob, there've been some extraordinary headlines lately in the media about the impact of gut microbes on neurological conditions such as autism. How clear is the link between gut microbes and things that are happening far away in the brain?

ROB KNIGHT
Well, in mice those links are very conclusive for a range of different conditions. I think you're talking about Sarki Mazmanian's paper. [unclear] what he showed is that if you stimulate the immune system of pregnant mice using an analogue viral infection using double stranded nucleic acid, what happens is the pups that are born to those mothers tend to show a lot of the same signs that are associated with autism in humans. So, for example very repetitive behaviour, lack of social interaction with other mice and so forth. What was amazing about that paper, they were able to isolate a particular chemical that was produced by the gut microbes and they were able to show that taking that chemical and putting it into normal pups would trigger the same kinds of autistic like behaviour. The other thing they showed was that a particularly beneficial microbe Bacteroides fragilis what they could do is they could inoculate the pups with that beneficial microbe and prevent the autism-like symptoms. So, this was certainly very exciting and then this other work that's being done on mice by different groups that shows for example that you can reduce anxiety using a lactobacillus probiotic that you can reduce the symptoms of the mouse cohort of PTSD by different micro-bacteria and probiotic and so forth. So, in mice there's a lot of evidence that you can change the psychological state by introducing individual microbes. There's also some fascinating work that's been done by a group at McMaster University in Canada showing that you can actually swap the behaviour between two genetically different strains of mice not by changing their genes but by changing their microbial communities and transplanting the microbial
communities between those two different groups of mice. So, in mice there’s a lot of evidence that microbes can change behaviour, in humans there’s a lot less. There has been some work to suggest that autistic children have systematically different gut microbial communities from neuro-typical children but in that case we don’t know whether the microbes are a cause or a side-effect of the autism and especially this is difficult to unravel because autism is often correlated with gastrointestinal symptoms. So, basically this is one of those things where the phenomenon is very clear in mice, it may take a while to figure out whether it applies in humans or if it does to what extent it applies in humans and whether any of the same treatments work or not.

DYANI LEWIS
With all of these really dramatic connections even if they are only in mice at the moment does this bring into question how much we use things like antibiotics and antibacterial agents in our lives?

ROB KNIGHT
Yes, absolutely so especially with antibiotics we should be worried about the emergence of antibiotic resistant strains of pathogens and this is especially true for using antibiotics in livestock as a growth promoting agent rather than to treat animals that are sick which is still a practice that is regrettably prevalent. You know it’s really interesting in American Gut we’ve had a lot of participants contact us and say that they’ve had psychological symptoms either start or vanish when they either started or stopped taking antibiotics. But, there doesn’t seem to be a lot of consistency about what antibiotic and what psychological symptom. So, one thing that’s entirely possible there is that the responses are very individual for each person, but it is only by understanding the complex microbial communities in each individual and how those interact with different drug responses that we’ll be able to figure out what the effects are going to be on different people. One thing that is fascinating there, Dave Relman’s group at Stanford did a fascinating study a few years ago where they gave the same antibiotic to three different people just to see how they’d respond. The first person got back to baseline within a few weeks of taking the antibiotic. The second more or less back to baseline within a few months. And then the third person was still completely different at the end of the study over a year later. So, what was amazing about that was how differently the three people responded to the same drug. What was frustrating about it is that they only had a sample size of three and they all responded differently so we have no basis for figuring out what in general happens when you take the drug. But, you know, there’s been a lot of efforts to search for personalised responses to drugs in the human genome but maybe that’s the wrong place to look because were all 99.9 per cent identical in terms of our human DNA. But, then in terms of our microbes and the genes that they carry two people can be 80 or 90 per cent different as opposed to being 99.9 per cent the same. So, in many ways if you’re interested in individual variability in drug response, in response to diet, response to exercise or all of these other things where there’s huge individual variation maybe it just makes sense where a lot of the variation actually is, which is going to be in your microbial genome rather than in your host genome.
DYANI LEWIS
Is this why some people believe that we should consider ourselves as a super organism composed of ourselves and our genes but also our microbes and their genes?

ROB KNIGHT
Yeah that?is exactly right and as you mentioned at the start of this we?re certainly outnumbered by our microbial cells and web lastly outnumbered in terms of the microbial gene catalogues. We have about 30,000 or so human genes depending on what you count and then the microbial gene catalogue is up in the range of two to 20,000,000. In terms of metabolic capability microbes are certainly doing a lot that we can?t do. Additionally outside of Star Trek it?s really hard to change your own genome whereas each of us has profoundly changed our microbes throughout our lives. For example the difference between what?is in the gut of a newborn infant versus the gut of an adult is comparable to the difference between say the microbial community in a bear versus the microbial community in a gazelle. They?re completely different microbial communities. Each of us has profoundly changed the microbial genomes that we have associated with is throughout our lives and we continue to do that as we take antibiotics, as we take other drugs, as we change our physiological state, as we eat different things and so forth. The potential for those changes to be made in a directed way that improves health is really tremendous. A lot of what the scientific community is doing at the moment is just trying to figure out how those changes are different in different people and how individualised the recommendations about each of those lifestyle choices, dietary choices, drug choices and so on going to be and what extent can we find out and protect the implications of those choices.

DYANI LEWIS
I?m Dyani Lewis and my guest today is micro-biota researcher Professor Rob Knight joining us via Skype from Colorado. We?re talking about our gut bacteria and their impact on our health here on Up Close. Rob how well can the make-up of the microbial community predict whether someone is obese or not?

ROB KNIGHT
Well, obesity is one of the best characterised conditions linked to the microbiome and in that case we can tell whether someone?is lean or obese with at least 90 per cent accuracy based on the microbes that they have in their gut. On the one hand 90 per cent accuracy for obesity might not sound that impressive, as a test for obesity it?is not going to replace your bathroom scales and your mirror any time soon. But, on the other hand if you take all of the human genes that have been linked to obesity by genome-wide association studies you can only tell whether someone?is lean or obese with about 58 per cent accuracy based on all those human genes and so that?is where, really, the microbes might be playing a big role.

DYANI LEWIS
If we do have an unhealthy gut bacterial community can we simply switch in a new one like you would do with the mice?
ROB KNIGHT
Well, remember that the mice are raised germ-free without any microbes of their own and it's a lot easier to colonise the equivalent of an empty field than it is to colonise a thriving ecosystem already. But, people who have especially Clostridium difficile associated disease have had a tremendous amount of success with something called faecal microbiota therapy. Basically what you do is you take a stool sample from one person and you transplant it into another person going through either of the two obvious routes to get it into the gut. Both of those work and at least the published literature suggests that they have a 90 to 95 per cent cure rate. So, there's a tremendous amount of potential for using that type of transplantation to reset your microbiota.

DYANI LEWIS
What about more subtle manipulations like consuming probiotics in yoghurt for example?

ROB KNIGHT
Well, it's important to remember that most of the food associated with probiotics won't colonise your gut. So, we did a paper again with Jeff Gordon's group a few years ago were looking at the effects of probiotic yoghurt. Basically the strains of yoghurt - at least in that particular yoghurt get but I think it's true for most of the ones on the market - don't colonise the gut. So, they're not going to change the species that are present and they're not going to change the genes that are present. Although, one thing that was interesting is that the yoghurt as it was passing through had a substantial effect on the expression of genes of the bacteria that were already in there. The way that probiotics from food are likely to have a positive effect is not so much by colonising your gut but as changing the capabilities of the bacteria that are already in there.

DYANI LEWIS
Is there any way that we could just I guess foster a healthy gut community by consuming the right things using prebiotics as they're known?

ROB KNIGHT
Well, there's certainly a lot of enthusiasm and excitement about prebiotics. The evidence of fibre, especially resistance starch and other fibres that are going to make it through to your large intestine, provide a substrate for beneficial microbes that are going to ferment it into butyrate which is going to feed the cells lining your gut and generally promote gut health, reduce inflammation and so on. That's pretty solid, similarly there's a lot of evidence that in breast milk for example pre-biotic compounds are really helpful for fostering a good microbial community there initially. There's a lot of effort at the moment to isolate those oligosaccharides and introduce them into infant formula so that in cases where breastfeeding doesn't really work out, it's still possible to provide some of the same health benefits. In general though the specific effects of particular foods on bacteria in the microbial community in your gut, it's only starting to be unravelled at this point. So, although conceptually the idea has a lot of appeal, what you should specifically to and how much it varies from
person to person is still very much being worked out at the moment. So what are some of the really burning questions in microbiota research that you'd like to see the research community answering over the next few years?

ROB KNIGHT One of the big ones is how much can your microbiome change over time and what can you do to modify it in a really substantial way. There was a really exciting paper that came out in Nature last week by Peter Turnbaugh’s group at Harvard, which had with an extreme enough diet, say switching to a diet primarily based on meat, you could actually get a substantial change in the microbiome of healthy people, just in the course of a couple of days. Which was really exciting because effects that large and that rapid have been seen before in mice but not yet in humans. Being able to understand the directions that you should change your microbiome in order to improve health, is still a major challenge and being able to understand for different diseases what direction they take your microbiome and what specific foods or specific other lifestyle strategies you should take to move it back towards the direction that improves health is again something really exciting, really important and needs to be characterised a lot better. Then finally understanding the connections between the different levels say between the microbes, the gene’s they express, the proteins that they make and the metabolites that they produce and how those metabolites are able to diffuse through the body and have effects on all kinds of other tissues like the heart, the liver and even the brain, is another area that’s spectacularly exciting. There’s really a lot to do. One thing that’s especially exciting, especially for students entering the field at the moment, is that a lot of the technologies to do these things have only existed from the last two years to the last five years. The vast majority of studies you would like to do are feasible now and haven’t yet been done. So, there’s tremendous scope to really contribute to the field and find out something new and exciting, even from the obvious question that say your grandparents might ask you. One of the things that people in my lab have said that speaks to them about this line of research is that finally - especially compared to other scientific topics that they were studying - they finally have something that they can talk to their families about when they visit. Because everyone eats, everyone has gut microbes and it’s a topic that really touches a lot of people’s lives.

DYANI LEWIS
Perfect dinner table conversation?

ROB KNIGHT
Yeah exactly, you might not necessarily want to discuss it at dinner.

DYANI LEWIS
Rob Knight, thank you for being our guest on Up Close today and telling us all about our microbes.

ROB KNIGHT
Oh great, thanks again Dyani.
Professional Rob Knight is a microbial ecologist in the Department of Chemistry and Biochemistry, the Bio Frontiers Institute and the Howard Hughes Medical Institute at the University of Colorado in Boulder. If you’d like more information or a transcript of this episode head to the Up Close website. Up Close is a production of the University of Melbourne, Australia. Created by Erik Van Bammell and Kelvin Param. This episode was recorded on the 19 December 2013. Producers were Kelvin Param, Erik Van Bammell and myself, Dr Dyani Lewis. Audio engineering by Jeremy Taylor. Until next time, goodbye.

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