398 - The Gut Microbiome

With Steven Bruce and Mr James Kinross

Steven Bruce, 00:09
My guest is a consultant colorectal surgeon, Dr James Kinross, who is also the author of a splendid book called Dark Matter, which is well worth a read, and we'll talk a bit more about that later on. But obviously this evening is largely about the inner recess of the colon as well as the stuff that emerges from it.

I'm just saying about the book Dark Matter. I've read it recently - I finished reading it today. Obviously, I wanted to get it finished before we started the show. And one of the things I love about it is that it's full of lovely, scientific information, lots of long words ending in difficult to pronounce suffixes and things like that. But it's also a very readable book, I mean, I've learned that sex originated in Scotland, for example, and there's a chapter which is entitled "Sex and bugs and oestradiol" and things like that. So you've written it in a very, very approachable, accessible manner.

What about yourself? You're a colorectal surgeon. You're researching, at the moment, how the microbiome causes cancer, which might come as a bit of a surprise to people. I'm surprised, as a consultant surgeon, you've got time to write books apart from anything else.

James Kinross, 01:58
Well, yeah, I mean, first of all, I'm very sorry not to be with you in person today. I'm speaking to you from St Mary's Hospital in Paddington in London, where I'm clinically based. It's salient to this conversation. I'm sure we'll get onto it, because, of course, Alexander Fleming made his antibiotic discovery here, and that has shaped so much of the microbial world. And we'll talk about its implications more broadly later.

Yeah, like all good things in life, the microbiome, came to me by accident, really. Whilst I was training, I did a PhD, and during my PhD, I began to study how microbes change our risk, or change the risk of having a bad operative outcome, how they change your risk of having wound infections. And that was some 20 years ago. And of course, back then, the microbiome was very much a niche subject, and no one really paid it much attention.

And the world has changed quite dramatically in the last 20 years or so. And now, of course, we have a much better understanding of really what the microbiome is and how important is to health more broadly. So I spend my days now not just thinking about how the microbiome defines operative outcomes. I think about why it causes the diseases that I have to operate on in the first place. And I think, like all surgeons all across the world, I've can come to the conclusion after a long, a long period of operating that it would just be much better if people

didn't get these diseases in the first place. And so really, I think the great gift, the great gift of the microbiome, really is in disease prevention,

Steven Bruce, 03:24
And as I sort of intimated in that introduction there, I feel that most people would assume that the microbiome is a good thing, not that it causes diseases. But we'll get on to that, I'm sure. But also, you talk about it as though the microbiome is a single thing. I got the impression from your book that really that's not entirely true, is it?

James Kinross, 03:45
it's definitely not true. And I mean, well, I suppose you better start by defining it. Otherwise we won't have a basis for the conversation. So a microbiome, in its driest interpretation, is a collection of microbes and all of the things that they need to sustain themselves within a niche. And that niche can be really, very, very broad and at its most sort of massive scale, it's a planetary microbiome.

Microbes, it's definitely a prokaryotic planet. The planet's most dominant life forms are single celled organisms. They are bacteria, both by mass and by biodiversity, there's probably about 28 billion tons of bacteria alone underneath the soil, and there's only about 350, 400 million tons of human. So, so we're dwarfed by diversity in biomass, in terms of microbes. But microbiomes also exist in microscopic niches, so they can exist within the individual crypts of our gut. Our gut is, of course, just a long tube that goes from the mouth all the mouth all the way down to the bottom, and we have discrete niches of microbes that exist throughout the gut. And you have microbiomes on your skin, you have them in your lung, you have them in your bladder and your urogenital tract and and they're everywhere. Every single living organ, every single living system, every single living animal, has their own microbiome. So we can think about them in that context.

But I think a microbiome has two other really significant and important parts of its definition which are often not really talked about. The first is, is that to be a true microbiome, you have to have a deep evolutionary partnership between the microbiome and its host. The microbes that live within us, they're not there by accident. They're not there just because we just happen to tolerate each other. Our biology has been shaped by them. We have co evolved with them, and they continue to shape our health. And, it probably goes without saying that microbes will be here long after the human race is long gone. The second thing is, is that the microbiome is dynamic. It's not a constant. It doesn't stay with us in the same structure or function for our whole lives.

Of course, we'll probably talk about this in a bit more detail, but we're not really born sterile, but nonetheless, when we're born, there aren't many microbes within us, and they have to grow. They have to culture into an ecosystem, and then they change with us as we age and as we change. So I think about the microbiome almost really existing in a quantum state. If you look at it, it changes. A microbiome can simultaneously be good for us and bad for us, and we have to have the degree of precision when we talk about it, because of that.

Steven Bruce, 06:11

Thanks for that. When I was preparing for this, this discussion, I find it quite difficult to organize my thoughts, because so many things lead into others. And you just mentioned earlier, we're not sterile when we're born, but a lot of people, I suspect, watching this show, will be thinking, well, one of the very important elements of the microbiome is vaginal, and as the baby is delivered, it picks up the mother's bacteria and so on, which is healthy in developing its own., I suppose leading on from that is the question of, well, Surely they must be getting bacteria from, they must be sharing the microbiome with their mother while they're in utero as well, by one mechanism or another. But what happens to those babies which are delivered by cesarean delivery, for example?

James Kinross, 06:59
Yeah. So I think that there's quite a lot there. And I think it's probably worth unpicking some of what you said, because there's some really important themes within it. So I think the first thing to say is, is that what we're beginning to understand is that, because the microbiome is so dynamic through our ages, how the microbiome is set up in early life, maybe even the impact of the maternal microbiome on us as we're gestating is so important in defining our risk of chronic diseases in later life. Therefore, if there's a problem in the assembly of the microbiome in our very earliest parts of our lives, maybe even the first hundred days, the consequence of that might be very, very long lasting.

Now, traditional science, traditional medicine, teaches something called a sterile womb hypothesis, which basically states, when you're born, you're completely sterile, you have no microbes within you or on you, and then you're colonized through the delivery of the birth canal, and then through breastfeeding, and then through your introduction into the world. But we're beginning to sort of challenge that hypothesis and these sorts of scientific challenges are really, really difficult for many clinicians to grasp because they are so challenging in terms of our understanding of basic science.

So traditional basic sciences says, of course, microbes can't cross the placenta and they don't get into the gestating infant., The first thing to say is that the maternal microbiome can influence the baby's development without needing to do that, because it produces this very large array of small molecules which can happily cross the placenta. So metabolites, that's what we study, or proteins, or other various immunological molecules, and these have a very important role in shaping infant health.

But also, we know from the second trimester that very, very low abundances of these microbes can be detected in an infant gut and, more importantly, their T cells, so that parts of their immune system that you can culture actually seem to already have a memory to these bacteria. And that gives us some evidence, at least, that maybe these microbes are actually abundant, and they're present in very, very low abundances within infants at a much earlier stage than we had thought.

And the significance of that? Well, one of the most important, significant issues with that is that I think about the microbiome as the puppeteer of the immune system. It educates the immune system, both the innate and the adaptive immune system, and if, therefore, the microbiome is not functioning properly, it's not signaling, signaling to the gestating infant properly, it's not assembled in early life. That means your immune system can't be set up.

And if your immune system can't be set up properly, then that leads we think, Well, it's a sort of core mechanism that underpins many of the risks of chronic diseases that we see.

Steven Bruce, 09:44
I was fascinated reading the section about the immune system and its development in the book. Do you mind just running quickly over that? I'm sure many of the people watching will be very familiar with all of that, but I'm one of these people who forgets everything. Almost instantly. So, yeah, I mean, just learning a bit more about antigens, T cells and so on might be quite helpful.

James Kinross, 10:04
Don't worry, that makes two of us. so the immune system, I think, is can seemingly seem overwhelmingly complicated. And I think the point that I'm trying to make in my writing is that we often think about the immune system in the wrong way. We think about it as a defense system, and we purely think about it in the Cold War language through which most of this system was developed and discovered in the sort of 19th and 20th century, but, but actually, it's not, it's it's actually a molecular memory. It's a way of our body remembering whether we've come into contact with a friend or a foe, and it creates, it creates those memories that are actually passed from mother to infant, and they are with us throughout our entire lifetime.

At a cellular level, we can think about our immune system in its most basic sense, in a sort of what we call innate or adaptive. So innate is like being born with basically an antiviral software, both literally and figuratively, within us. So the minute we're born, it's there and it's functioning, and it doesn't need any memory, and it's a point and shoot system, and it will attack anything that comes into our bodies, which we think is going to cause us harm.

The adaptive system has memory, so it has to be educated, and it has to generate an immune response. It has to learn that response. And it works by releasing antibodies into the blood. And there are lots of different types of antibodies that excrete into the blood, and there are lots of different cells within that adaptive immune system. So I think about that as a targeted strike. It's like a precision strike mechanism where we send out antibodies to damage and kill things when we know that they're a threat, and we've got to learn that memory somehow, and the microbiome is important in the setup of both of those systems, and both of those systems cause different types of diseases and have different implications for our health.

Steven Bruce, 11:57
Okay, that's helped me. I hope it's helped some others as well. I've had a question from Hannah, who says, How does this relate to epigenetic mechanisms influencing the baby? And I realize that you're not an obstetrician, but obviously the microbiome spreads a little bit further than just the colon, doesn't it?

James Kinross, 12:13
It does a bit. So, so I'm not a neonatologist, but increasingly through my work, what we've begun to understand is that understanding microbiome interactions and microbiome host interactions in very early life is the key, really, to understanding why younger people get bowel cancer.

And just to deviate before I answer Hannah's question, that's important to me, because we see dramatic changes in the epidemiology of bowel cancer in young people, millennial generations now have a risk of bowel cancer four times that of people born in the 1950s and 60s and 70s, and that rate is climbing, and that has to be understood in the context of the changing epidemiology of other chronic diseases that are seemingly unrelated, but in terms of the science I've just described, it's very related. So, for example, allergies, immunities, inflammatory bowel diseases, rheumatoid arthritis, mental health problems. You know, all of these things are climbing, and they're all happening in younger people. And our hypothesis is, is that part of the reason for that is because we are losing the microbiome. We are we are seeing basically a mass extinction event of the microbiome, and that, of course, is key, because it means our immune system then cannot simply keep up with industrialized world.

So epigenetics, for those of you that listening that aren't too familiar with it, is a science of post translational modification of genes. So you're born with a gene, it has a program function. Of course, that gene can mutate in some way, and that that function will change. But even after that gene is set, its code can be modified by external factors. Some of those things can be in our environment, so it might be toxins or pollutants, but microbes can also change these gene functions.

And bacteria, we're beginning to now understand how bacteria cause epigenetic modifications, and we've got some good examples of that, inflammatory bowel disease being really quite a good example, where we've got some evidence of it. So bugs, yeah, do absolutely cause epigenetic modifications. Some of those things might be in infancy. Some of those things might be during gestation.

The problem is it's super hard to study in human systems, of course, because to study it, you have to do something invasive, and that's really very difficult. So much of this work also comes from animals. So it is my belief. And, we've just picked up on one of those main themes there, which is, I think, a core hypothesis from my work, which is that I do believe that we're experiencing an internal climate crisis. I believe that many of these diseases really need to be considered through the spectrum of climate change. And because the microbiome is a living system, it's a living organ. It's living microbes that are populated within us through our interaction with the environment. It is a literal and figurative connection to the outside world, to the climate around us, to our external world. So when you damage one, you damage the other.,

we could talk about mechanisms through which the microbiome is being damaged internally, but I absolutely believe it to be important. And there are multiple mechanisms through which the microbiome will influence our health, epigenetic modification, just being one,

Steven Bruce, 15:14
are you alone in what you're saying about this, or is this becoming more and more widespread, accepted doctrine in medicine. I mean, I don't mean that in a rude way, but new ideas in medicine have a habit of being dismissed by those who are old and bold, in the profession,

James Kinross, 15:34
there's a very, very long and distinguished record of people being dismissed. I don't think I'm that radical, and I don't think what I'm saying is that heretical, to be honest. And I think there are people out there. There's some very, very good scientists. So Martin Blaser at NYU wrote a really good book called Missing microbes, if you, if you, if you haven't read it.

And there are definitely other people that that hold a similar belief. I think what I'm arguing for is not that we throw the baby out with the bath water. What I'm arguing for is an evolution of scientific theory around how microbes cause disease, and a rethinking of our relationship with them. Because my basic hypothesis is, is that the destruction of our internal ecosystems is a key, is a core driver of these ecosystems and microbes are still very, very important in determining our health, not because we have too many pathogens.

So pathogens are harmful microbes that cause cause a disease. There's probably only about 1500 known pathogens that really cause harm to humans and and less than a few 100 that are capable of causing epidemics or serious, serious outbreaks of disease, but, but actually, it's the loss of key mutualists and symbionts that causes us harm.,

now to take a step back into the history books a little bit. Most of medical thinking, a lot of medical thinking, is indoctrinated in germ theory. So I said to you at the beginning of our conversation that Alexander Fleming discovered antibiotics here right? That was on the back of Louis Pasteur's work and other various giants in the 19th century that worked out that the things that were most likely to kill us in the 19th century, namely, pneumonias, typically bacterial pneumonia, tuberculosis, cholera or infectious diseases were caused by germs and microbes, and we've spent the last few hundred years systematically doing our very, very best to kill all of those pathogens and to wipe them all out.

And what I think is that there's been a bystander effect. We've gone so hard and so fast for these pathogens that we've inadvertently wiped out very large populations of really important mutualists that protect us, that keep us healthy, which are important for developing our immune system, important for our metabolism, important for our growth, important for brain development, important for, our risk of immune developing immune diseases, and what we've been left with is a rising pandemic, a global pandemic of things that now probably don't kill us, but leave us in a very poor state of quality of life.

So actually, the things that are most likely to kill you today are cardiovascular disease. Most people in the world, 16% of us, die of stroke. You're most likely to suffer from diseases related to cardio metabolic diseases, obesity and type two diabetes. You're likely to die of cancer. You're likely to have mental health problems, you're likely to be trapped by these things in very, very expensive healthcare systems with very poor quality of life, and you're probably going to live much, much longer than you did, a few hundred years ago. But microbes are still important in the causation of those diseases. It's just that they're not pathogens. It's just that it's a dysfunctional relationship that we have with our mutualists and our symbionts that live within us. So it's about reframing germ theory into microbiome theory, where conservationism of our critical microbial systems is a valid form of preventative health care and actually something that needs to be promoted both that national policy level as well as at an individual level. And I'm sure we'll get into some of those things as we as we talk.

Steven Bruce, 19:09
Well, yes, and I was struck in your book about the number of both infectious and non infectious chronic diseases that you've associated with to some degree or another, with the microbiome.

We've got a question here from KCW, who says, Good evening. Is there a known cause or hypothesis for what is causing the microbiome crisis, and therefore, how do we avoid it or deal with it in infants?

James Kinross, 19:35
Oh, that's a peach of a question. And I'll do my best. I'll do my best to answer it. So, so I think you have to think about in terms of climate crisis, right? So if you think about the sort of planetary climate crisis, of course, there's not one factor. There's multiple factors that drive it, and our internal climate crisis is just the same. However, having said that, I think there's a couple of really big players that are very, very important.

The first has to be antibiotic misuse. So we consume massive amounts of antibiotics. Globally, we consume about 38 billion daily doses of antibiotics each year. The majority of those antibiotics are not consumed in adults. They're consumed in children, and actually they're consumed in low and middle income countries with rapid growth in China and India, where they're not regulated and they're handed out.

The other problem with antibiotics is that the majority are not used in healthcare. They're used in farming, and they're used as antimicrobial growth products in countries where there isn't effective regulation, or they use in animal husbandry. And for that reason, they're soaked into our soil. They're soaked into our, oceanic systems, they're soaked they're just everywhere. You can't really escape antibiotics now, and that's a huge problem.

The second major driver is polypharmacy. So we don't really think about the medicines that our patients maybe take as being antimicrobial, but many of them are probably well over a quarter of them are and we take a lot of drugs globally. So, we take 4 trillion doses of medicine each year globally, which means that across the planet, half the world's population takes a drug every single day, and many of these drugs are changing the microbiome and having an anti microbial effect.

By the way, many of those drugs, their mechanisms are determined by the microbiome. It's just that we don't think about them in that way. Of course, we are urbanized. You know, 6 billion of us, I think, are going to live in urbanized systems by 2050, and urbanization has a very, very big impact on our microbiome, not just because we live in different social environments and that we're exposed to different pollutants, which also shape and change the microbiome, but our social network changes.

So your microbiome is defined by your family network, the number of people within it, and how many of them you share your food with or you share social interactions with. It's shaped by your social network. I don't mean by your digital social network. I mean by your real world network. So teenagers that have big friend groups have a much more diverse microbiome

than those that do not. So we are we are lonely in the modern world, and that has a big impact on our microbiome.

The fourth thing is diet. So nutrition, diet, of course, is important. It's important both in the manufacture of food, as I've described, because to manufacture the massive amount of meat that we insist on consuming takes a lot of antibiotics, and of course, our reliance on subsistence farming and pesticides, has a big impact on the microbiome, but also the way that we consume food and the type of food that we consume.

So a westernized diet, is classically high in animal fats, low in fibre. We eat a lot of refined sugar, we have a lot of additives in our foods, of course, and ultra processed ingredients. All of these things have a very dramatic effect on a microbiome. Now there are some other factors, so global migration, for example, and various others, but I think those are the main ones, and probably the ones that are most, most actionable.

Steven Bruce, 22:58
Salome had already sent in a question asking whether PPIs affect the microbiome, and obviously, they are implicated in a lot of problems with health, is that through the microbiome as well,

James Kinross, 23:10
So PPI is very interesting because, they were one of the world's most prescribed drugs. Like, we've given trillions of doses of PPIs across the world, and they have a very dramatic effect on the impact, because, of course, if you're changing the pH of the foregut, which is what those drugs do, you're changing environmental conditions in the lumen of the gut, and that changes the microbiology of the hindgut.

So it has a whole systems effect on the gut. And what we know from looking at epidemiological studies of PPIs is that, of course, it changes your risk of other chronic diseases.

But it would be remiss of me to talk about this without bringing up the topic of h pylori. So Helicobacter pylori is a microbe, it's what we call an extremophile, which means that it's adapted to living to very austere, difficult conditions in the in the stomach. It can cope with very, very low pH, and it's very happy there, and it's been in the human gut for tens or probably hundreds of thousands of years.

I perceive h pylori as a commensal but Barry Marshall, who famously won a Nobel Prize for its discovery, really challenged the dogma of all modern medicine and modern surgery, because until that point, we thought gastric ulceration was caused by too much acid, and we used to do these really terrible, awful operations on people to fix their ulcers. That really didn't work very well. And he was able to prove by drinking h pylori that he could cause a gastric ulceration. And then, if he took antibiotics and eradicated it, his h pylori induced ulcer went away.

And then we've, of course, taken that really nice piece of science, massively scaled it globally. And what have we done? We haven't just given patients PPIs. We've mass

eradicated h pylori with huge doses of broad spectrum antibiotics. And of course. This has had a very big impact on the human microbiome.

So now when you look at the epidemiology of h pylori eradication, what you see is actually in people where it's eradicated, their risk of asthma changes, their risk of respiratory disease changes.

Actually, we see quite controversial data on risk of gastric cancer. We know that h pylori is actually classed as a carcinogen, and it is thought to be causally associated with the presence of gastric cancer. But actually, if you don't have it, if you don't have enough of these microbes that are supposed to be there, your risk of other cancers goes up in its place.

So our way of targeting these microbes is incredibly blunt. We don't think about the body as a living ecosystem. That actually requires a nuanced strategy to try and get these bugs in check. We don't think like ecologists. We just think with a sledge hammer. If it doesn't work, we just drop a nuclear bomb in there, try and kill absolutely everything, and then wonder why it doesn't work very well, and we create a whole bunch of other diseases, and you can't understand why unless you have some working knowledge of the microbiome.

Steven Bruce, 26:09
One would like to think that that attitude is changing, and that we have got a greater understanding of the collateral damage that we do with those H bombs.

James Kinross, 26:20
I think it is changing, but it's changing really, really slowly. And I suppose I feel optimistic when I go around the world and I give talks and I go to conferences of my colleagues, and you start to see the microbiome being a theme, and you start to see people wanting to talk about it, but I think clinicians are, in fairness to most clinicians, they're not really armed with the tools for measuring the microbiome or doing anything about it, so they don't really know what to do. They know it's a thing, but they're not either educated in it, in the detail, or they're lacking in evidence based interventions to really drive or change their practice.

So actually, clinicians do what clinicians have always done, which is they go to their toolbox and use the tools they can as best they can to solve the problem, which invariably means handing out antibiotics. So, I think microbiome science has got to catch up a bit, and we've got to give our clinicians tools so that they can really target the microbiome and leverage it in a more in a more meaningful way.

But I don't think we should beat up microbiome scientists too much because, we it's basically like we discovered an entirely new organ about 25 years ago, and we're only just beginning to work out how it actually works. And therefore, it's taking us a bit of time to get to point where we can begin to create and leverage new therapies that really take advantage of it,

Steven Bruce, 27:43
I want to take you back, if I can. You were talking about the large social group, meaning that people would have a more diverse microbiome, and you spent quite a bit of time in the book, talking about how we spread good or bad or other bacteria.

In fact, Valerie sent in an observation earlier on, saying she thought that some New York hospitals now insert a sponge into the vagina when they're doing a cesarean delivery so they can slap the biome all over the newborn.

But also I got to thinking, Well, if you have somebody who has a poor microbiome as a result of eating meat which has been treated with antibiotics. Will that affect your own microbiome? How might that happen? What are the methods of influencing each other, as it were? Long winded question.

James Kinross, 28:35
Well, yeah, okay, so, we're starting to get much better insights into how the microbiome is seeded in the gut, and key events in in the early development of the microbiome, what seems to be much more important than your birth route or how we're delivered, is how premature we are. So irrespective of how you're born, if you're Prem, your microbiome evolves and changes in a very different way than if babies are not premature.

And we have two cohorts of infants that I currently have at Imperial where we've been studying their growth, and one is preterm and one is term. We've been looking at microbiome changes over time. So prematurity is probably a much more important factor, but if you are delivered by cesarean section, yeah, the early stages of your microbiome are very different to if you're born by natural delivery.

And yes, you're right. There are various birthing practices where they will take swabs and smear them over the baby's mouth to helpn colonize.

I think what's probably more important, because I think the problem with these conversations is that quite often women are left feeling guilty about the choices that they've made, and quite often, the decision to have a cesarean section is not a choice. It might be because they have to have a Caesarean.

And I think women should always feel confident they can make the choices that are best for them and best for their baby and and therefore, my advice is, don't worry if you've had a Caesar.

I think probably what's much more important than your birth route is two things. Number one is whether your babies are breastfed. Again, the whole guilt issue still applies. If you can't breastfeed, don't worry. If you haven't breastfed, don't worry. Like there's lots of reasons why that might be a really legitimate choice and just can't do it. But at the same time, what we know is that breast milk, which is a living tissue, by the way, is incredibly important in determining the evolution and growth and stability of the microbiome long term.

And most women in the developed world are unable to follow who guidance and get to six months of breastfeeding, and very few get to the, two years of intermittent breastfeeding oncev their babies and their infants have got on to a mixed diet.

And what we know is that infants who are formula fed have a very different microbiome, with lots more pro inflammatory type microbes that exist within the gut, and those are sustainably different over the duration of their lives.

The second really important thing is, irrespective of how you're feeding your kids microbiome, because it's much, much better for your kid to have formula feed, than no feed and to starve, is not to, misuse antibiotics and damage it in that early life phase and so actually, we need to think much more carefully about how we administer antibiotics and in particular to our young and vulnerable.

Now, two things on that. Number one, I am not anti antibiotics, right? So I have to keep saying this, antibiotics are life saving medicines. They're really important drugs, and we should be using them very judiciously and very, very carefully., Arguably, there's a significant crisis brewing in the antimicrobial resistance side of things. And actually, we're going to run out of these drugs anyway at the moment.

But, if your kid is sick and you're unwell and you've got a pathogen, well then you need the antibiotic, obviously. And that's not what I'm talking about. I'm talking about people who perhaps don't because they've got viral infections, or perhaps we don't have proper proof of microbial infection. So I think you know that those are really important.

The second thing that I would say, or the third thing I would say, so a bit of a long winded answer to your question, is that, actually, we've got really good data for the fact that if you change your microbiome in early life, you have long lasting impacts. And that data comes from epidemiological studies, where we've got historical data sets over many years, but it also comes from prospective longitudinal studies of infants in various parts of the world, so in Finland, for example, but we know that children having macrolide antibiotics in early life, and certainly children having recurrent doses of macrolide antibiotics like erythromycin have increased risk of asthma, obesity, type two diabetes and multiple other chronic diseases that then manifest themselves later in life.

So it's not just about having one hit of antibiotic. It's about the type of antibiotic you have, the number of different doses of antibiotics that you have, and the duration over which you have them.

Steven Bruce, 32:51
Okay, but what about later in life? I think somewhere in your book you say there is you transmit, I think, 80 million different bacteria or something, if you have a decent kiss, or something like that. So how is that going to affect you?

There's a lot about sex in your book, including sex started in Scotland, as I said earlier on, so, go on. Tell us why sex was invented in Scotland

James Kinross, 33:20
So what I'm interested in is a little bit of evolutionary biology and why we have sex.
So microbes, of course, don't., They, prokaryotes, don't need to sexually reproduce. They they do it asexually, and it's very, very efficient to asexually reproduce. Having sex takes all

the time, and it slows you down. You've then got to gestate an infant for nine months. Is really not a very good way of reproducing. Yet we do it.

Steven Bruce, 33:47
I wouldn't say it's not a good way. I think it's an inefficient way. The other way is an efficient way

James Kinross, 33:52
Inefficient exactly. And so why do we do it? One of the theories is that we do it because it effectively allows us to protect ourselves against parasites and gives us more resilience against pathogens that might want to do us harm, and that it also might be a very good way of sharing symbionts and mutualistic microbes that might help protect us.

And, sexual reproduction is a relatively new thing. It was first done in fish and, first discovered in Scotland about 380 million years ago, which is why I think sex was invented in Scotland.

But I also the point that I was also trying to make in my book is that we are thinking around sexual health is almost entirely informed by pathogens. We only think about the harm that can be caused by sexually transmitted diseases, and we don't think about the way that sex allows us to potentiate the spread of healthy microbes that we really need, but also the value that healthy microbes have in our urogenital tract and in our mouths, in protecting us from disease and protecting us from harm.

So the promotion of a healthy urogenital microbiome is actually a part of sexual health. It's an important way to protect our more vulnerable members of the public that really need to have safe sex.

And it's also a very important way to promote fertility. So we know that the microbiome has a very important role in determining recurrent miscarriage rates in women, and we know that actually the vaginal microbiome is unusual in that actually a healthy microbiome typically has high levels of diversity, so large numbers of different types of microbes. But actually the vaginal microbiome is a bit more of a monoculture, and it's predominantly dominated by lactobacilli, and the women that don't have this are much more likely to be infertile.

And actually, in some quite interesting work recently published, you can potentially change their risk of infertility through microbiota transplantation in of the vaginal microbiome. So, the point I'm making is, is that sex is has an evolutionary basis for the sharing of microbes that we really need to help us and maintain our health.

The sexual microbiome should be part of good sexual health practice, and we should promote it. It protects us from pathogens, and helps keep us healthy, but it's also a very important part of healthy reproduction. And we do have a global infertility crisis, right? Fertility rates are dropping in an alarming fashion, and I would argue that the decline in human fertility rates is being driven by the same thing that is climbing, our cancer rates, our obesity rates, and our, at immune mediated diseases, which is that it's a ultimate dysfunction in our immunology.

Steven Bruce, 36:48
Presumably, of course, it is possible to share hostile bacteria or unhelpful bacteria, but I'm guessing from what you're saying that on balance, it's beneficial.

James Kinross, 36:59
Oh, look, 100% I'm saying practice safe sex, and I'm saying that pathogens are bad and we should be killing them and and I'm not, in any shape or form saying or trying to dismiss the harm that pathogens cause us.,

Clearly, we have big global problems still in HIV, for example, we have, new sexually transmitted pathogens that are that are that are problematic. So I'm not saying that that we shouldn't be pursuing pathogens and we should absolutely be be promoting safe sex. I'm just saying that when we conceptualize of sexual health, we just don't think about the protective effect of mutualists that we need to maintain our sexual health.

I'm also saying in that particular chapter, the impact that that microbes have on our sexual behaviors., We've got really good examples of that through many other animals and species, we know that that happens. And the fruit fly, for example, if you give a fruit fly an antibiotic, it's unable to reproduce. It simply can't reproduce, and that's because it needs microbes to create pheromones, to create an attractor.

And then you can give a single strain probiotic, which is a form of lactobacilli, and I think it was lactobacilli reuteri. And then, of course, it switches back on its ability to create pheromones, and it can reproduce.

And in humans, it's the same, because not only do we need those microbes, they influence our scent, they influence our skin health, they influence the way we look and our basic measures of attractiveness, but they also play a very important role in defining how our hormones work. So estrogen, progesterone and testosterone, for example, their bioavailability and effectiveness is influenced by microbes, because microbes create enzymes that influence its bioavailability, and also because they indirectly affect the way that those hormones those hormones work., For example, through cholesterol metabolism, or through liver co metabolism, and various other mechanisms.

And we know that bug hormone interactions are very, very important in influencing things like our mental health. So men with depression, for example, have a microbe that is particularly good at blocking testosterone effect on the brain, and then that drives symptoms of depression. Women have a similar thing that does the same thing in estrogen. So our sexual behaviors are also indirectly influenced by microbes in ways that we don't just think about really in our in our day to day lives.

Steven Bruce, 39:35
Well, going back to your comment about infertility, it sounds to a simpleton like myself that all you have to do is introduce some lactobacilli into the woman who doesn't have any, and that's the problem solved. It's presumably not that simple.

James Kinross, 39:53
I wish, because, of course, it takes two to tango, and the problem is not exclusively that of one sex or one gender., Men have declining fertility rates, and they have problems with sperm motility, etc, and again, the microbiome seems to play an important role in in this process.

So an example of that would be, we know that men who are obese are more likely to be infertile. One of the mechanisms, for example, through which the microbiome is thought to drive that is because it will change in obese people, the way that you break down bile the way you create secondary bile acids in the gut, and that influences the way you absorb vitamin A, and vitamin A is dependent - you need that for spermatogenesis.

So, there are lots of indirect ways through which the microbiome seems to play a key, a key part, in that mechanism, and there are some direct ways. So there is a penile microbiome, there is a testicular microbiome. This is, a very, very new science. We are literally in the foothills of it.

Steven Bruce, 41:02
I was going to say that again, in your book, you comment that this is a very new science. And so although I think the microbiome has been in the press, and people have been learning about it for some time, There's still a lot more to be to be discovered, isn't there?

I've got a question for you from Matthew all about his own health. Matthew says, I've been off work with another flare of ulcerative colitis for a couple of months. I suspect that the heavy meds and prior antibiotics might have played havoc with my gut biome. He's taken Sympruve, and it says here Inulin, I think he means insulin, for a couple of years. Do you think they can do any good? I wonder how the active microbes can pass through the stomach and still be effective.

James Kinross, 42:04
He's definitely taking inulin, which is a prebiotic fibre, which certainly is good for the gut. So first of all, Matthew, very sorry to hear that you're suffering. That sounds miserable. And yes, your antibiotics absolutely would have changed your microbes. And yes, your medicines will have done and depending which medicines you're on, they'll change them variably.

We've had some interesting studies that have been published in the last year or two that have shown that actually, your pre intervention microbiome is sometimes or can be predictive of your treatment response.

Does Sympruve have benefit? For those of you that don't know what Sympruve is, it's a probiotic. It's a drink. It's made by a particular company. It has a very good marketing campaign. It has a handful of probiotic strains, predominantly Lactobacilli and biffs in it, and its marketing material says that it's good because it reaches the sigmoid, because it's a liquid.

So a lot of these, these microbes survive to get to the site of disease, I probably would advocate for taking a probiotic in that case and Sympruve is as good as any other. But

there's some other very good formulations that are out there, and I think Inulin is also very sensible.,

But I think with all of these things, the better thing is also to think really about your diet and your nutritional strategy. So having a a diet, which is, anti inflammatory that is developed with your with your dietitian, is by far the more important thing, because that's going to promote diversity of a microbiome, and that's going to give you a healthier microbiome. So typically, that is something that has to be developed on an individual basis. And it's difficult for me to give you specific advice on that, because I don't know any of the detail of your case, and I rarely advocate for generic changes, but certainly avoiding foods that are going to be high in Ultra processed content or refined sugars is going to be a smart move, because these are going to produce lots of more pro inflammatory microbes that are going to keep you in a slightly unhappy state. And trying to get as many fibres into your diet as possible, I appreciate you're taking inulin, but the more variety of fibres that you can have, that you can tolerate without getting bloated or distended will certainly help.

Steven Bruce, 44:14
Okay, hopefully that's helpful to Matthew you I was going to get on to diet, specifically later on but you talk there about probiotics, not surprisingly, we've had questions about kimchi and various other possibly things such as kombucha, sourdough breads, fermented foods and so on. Have you got anything that you can say about that? Obviously, that is a generic sort of prescription, if you like. Are they good?

James Kinross, 44:39
Yeah. So the first thing that I would say is, a probiotic is, by definition, a live bacteria that has a proven health benefit, right? And we've been taking them for thousands of years, in fermented milk, and they're very well known and very well established, and having them as part of your regular diet and regular intake is a good thing. It improves diversity of your microbes.

So sauerkraut or kimchi, although we don't technically call them probiotics, because by definition, they're not, because there's variations in the particular strains that are found within them, they do have health benefits, and I regularly recommend my patients take them, because it improves the diversity of the gut if taken with a high fibre diet.

So generally they're pretty good, and we probably should consume more of them. We don't take probiotics very well because we're not really taught to take them very well. So what I mean by that is the majority of the strains that come in direct to consumer probiotic products are not actually designed to live in the human gut

So these are microbes that have been found outside of the gut, like in fermenting milk, for example. And therefore, to keep them in the gut, you've got to take them regularly. You've got to take them every day, and if you're trying to have a health benefit, you've got to take them for at least 12 weeks, because if you don't, they won't colonize the gut, they won't grow there, and they won't have the health benefit. So if you're taking them intermittently every other day, and you're not really taking them for a sustained amount of time, they won't have a health benefit.

The second thing is, if you're taking them and you're feeling bloated, you're having pain, you don't feel well, stop taking them, right? I have a lot of people that turn up at my clinic and they're still taking these things, and actually threy're consuming them thinking that they're having a health benefit. They're making you feel unwell. Don't take them. There's absolutely no need. And they're very unlikely to have a health benefit.

Perhaps the other problem that we have is that we're very bad at selectively targeting them, which means that clinicians quite often don't have the information that they really need to give these in a very specific way. So for example, in Matthew's case, giving very particular strains where we know that there is a proven health benefit, and that's probably a failure of education. It's also a failure in the way that probiotic companies engage with clinicians and consumers and how they start to educate them. It has not been done at all well. We have a lot of bad marketing speak that we adopt, like good and bad bacteria. There is no such thing as good and bad bacteria. It's complete nonsense. There are pathogens that cause harm, that cause disease, and there are symbionts. If you treat your symbionts badly enough with the wrong diet or you hit them with antibiotics, they'll cause you harm. All microbes could be harmful under the under the right circumstances. But coming back to the probiotic theme, the other thing that I would say is that we're now getting a next generation of probiotics where we are beginning to discover microbes that have been discovered within the human gut, that are supposed to be in the human gut, and that we consistently see missing in human studies of chronic diseases like obesity, ulcerative colitis, asthma, all the rest of it.

So a good example of that would be Akkermansia muciniphila. So you can now start to see these commercial preparations coming online. If you go onto Amazon, you can buy them again. There's very little trials data to support their use. Quite often the cart is going before the horse, but increasingly, we do try and use them in a more targeted way. And the other thing that I would say is that what we've got coming over the horizon is what I would call next generation probiotics, which are really not going to be probiotics in the traditional sense.

So at the moment, probiotics are technically food stuffs. They're regulated as foods, but the next generation will be regulated as drugs. So these are microbes that are going to be dosed in a very particular way for very specific indications, and that will have a very specific set of toxicities and side effects and side effects and risks, and they will be regulated by the MHRA in the UK or the FDA in the USA. And that's exciting. I think you're finally going to get these products that are going to have a proven efficacy, and that will be easier for to be administered to patients and to consumers alike.

Steven Bruce, 48:38
Can we assume that those will be available over the counter, though, rather than by prescription only,

James Kinross, 48:42
No, they will not be available over the counter. I don't think, because they will have a safety profile that will mean that that's not possible,

Steven Bruce, 48:52

So if we were to look at the various products that you can buy in the supermarket at the moment, those little bottles of yogurt -, Actimel, is that one of them? - which claim to be probiotic. Can we safely assume that the manufacturers are giving them to us in a suitable quantity, that if we take it daily, it will populate our gut flora?

James Kinross, 49:13
So, the regulation around these products, certainly in Europe, has been very stringent for quite some time around making health claims, and we've got lots and lots of studies on probiotics. Well over 16,000 or 17,000 studies have been published.

So there is evidence there. But actually, what we often lack with these products is mechanisms and really established evidence for very specific, proven health benefits at scale, where you can say, yep, that one individual strain is having a specific health benefit, and here is some really strong proof for it.

So most of the products that you buy will sidestep making health claims, and they'll try and sell you a wellness product as a bypass around that. So it'll be a wellness product, and that's convenient, because then they don't have to make any health claims. Yeah. So just be wary of that.

The other thing is, is that a lot of these products have very, very high levels of refined sugars in them, or they have lots of sweeteners or artificial products to make them more palatable, which is why, quite often I give all of my patients kefir, because it's cheap as chips. Some of these things are very, very expensive, and they are often bought on subscription models like Symprove which is fabulously expensive. You know, it could be 70 quid a bottle or 70 quid for a subscription. Whereas, actually, kimchi is two quid a bottle and it's cheap and it probably does the same thing that's got less sugar in it.

So, when you're buying these things, just be aware of those issues. The second thing is, is that if you're going to take one generally, unless you're taking very specific strains for very specific functions. What you want is multi strains, as many different strains as you possibly can get, and in high doses, which are typically described as something called colony forming units. And a billion colony forming units sounds like an awful lot of bugs. But actually, when you've got 100 trillion bacteria in your gut, it's really not very many at all. Right? It's a tiny drop in the ocean. And so, high doses will have anywhere from five to 9 billion colony forming units, or even more. And so you want to try and get something with a reasonable dose with reasonable numbers of strains in there.

You're right. Many of these microbes will be killed off in the foregut and won't make it. But actually, with modern preparations, they do reach the hindgut, and there's evidence there. Certainly in my day to day practice, I measure the microbiome, and I will often sequence the microbiome to target my probiotic therapy, and I will measure it after I've started it. And actually you can see these things getting through. So we do know that they get to the gut,

But, the overarching advice here is make sure, even if you're taking a probiotic, you've got to have a good diet, because those bugs have got to be fed. They're living things. They if they're going to be in your gut, they also need to sustain themselves. So if you're not making

lifestyle, nutritional dietary changes around it, it's not a panacea, it's not a magic bullet. It's not suddenly going to make all of your problems better.

Steven Bruce, 52:01
Julia has asked one regarding probiotics. She's heard that if one person takes them, then everyone in the family should take them to make sure they're effective. Is that something that has any truth behind it?

James Kinross, 52:14
I'm not sure about that, but, maybe Julie's privy to some evidence that I'm not aware of.

What I would say to you is that, of course, family members' microbiome very much align, because, of course, they live in the same environment. They eat the same foods. You have physical contact with your family members. And for that reason, when we're doing microbiome analyses or we're doing faecal transplant studies, we go to family members because they're going to have the most aligned microbiome that there is.

And we also know that, individual homes have their own microbiomes. In fact, when you move house, you take your home's microbiome with you, and in studies done in Fiji, you can identify individual people based on sequencing their microbes from their gut and then comparing it to the microbiome of the house that you've also swabbed.

So there is some some truth in the fact that microbiomes are aligned and that it would make common sense if you're if you're trying to have a health benefit, that all taking the probiotic is potentially beneficial. But ultimately, if you're taking it for a health related reason, for example, you've got IBS, then actually, just the person who's got the problem needs to drink it, and that should be enough.

Steven Bruce, 53:31
Okay, you mentioned just a few minutes ago that you test the microbiome in your patients as a matter of course, and we've got a number of people have asked if there is a simple diagnostic method to assess, not necessarily test it specifically, but assess whether a patient has an imbalance in their microbiome, but I guess a problem of any sort in their in their biome.

James Kinross, 53:56
This is probably the most challenging area, really, in all the microbiome practice, because direct to consumer testing of the microbiome has basically been the Wild West, and the quality of products sold to consumers has been really poor, really inconsistent, really overwhelming, really confusing, and a lot of the companies that are selling these products are basically just trying to flog supplements and giving really very poor advice and very poor quality data. So I typically do not recommend consumer testing at all of the microbiome.

And part of the problem that we've got in microbiome science is that we don't have any professional agreement about the best way to analyze it and to measure it, and we lack standards for really doing that. So you can take the same sample, you can send it to five different companies for, sequencing, and you'll get five different answers. Therefore, it's not

reproducible. It's not particularly helpful. Now, the caveat to that is that the way that most microbiome direct to consumer tests work is they're doing something called 16S Sequencing. So the 16S ribosome within bacteria is a sort of short, reproducible segment of of, DNA. You know, it's a few 100 kilopascies long. And actually, it's relatively discrete for a microbe.

One of the benefits is it's cheap and it's easy to do because you're not sequencing massive amounts of DNA. But one of the problems with it is that to work out which bug it is, you then go to a database, and you plug in that little bit of DNA into the database, and the database gives you a read that doesn't really give you anything that's very specific, because what you really want to know is, what is the strain that I'm dealing with? What is the absolute specifics of that microbe that I'm interested in studying?, Quite often, if you're lucky, it will get you down to family or class.

So it doesn't really tell you very much, because, for example, if you take E coli, a very common bug in the gut, there might be 2000 different species of E coli. E coli can be a pathogen. It can cause enterohaemorragic colitis, a life threatening illness. There was an outbreak on salads, was it this year? And it caused deaths. It was really, really damaging.

On the other hand, it's a probiotic. We give it to patients as a therapy. So the specifics and the precision of what you're measuring is extremely important. You've really got to have that depth of read, and that's what we took. That's the phrase we use depths of read, or that precision of read.

Now microbiome sequencing is changing. It's becoming much, much more affordable, and we can do much, much longer reads of DNA, and we can now get down to that precision. So I use what we call long read sequencing technology to look at bacteria in my clinical practice, and I use a particular product. If you're interested, I can send your members a link, but I use, gut id.com.

Now the problem, the second problem, is learning how to interpret the data set, because it's a bit like whole genome sequencing. If I give you a whole genome sequence data set, it's kind of overwhelming, and what we're trying to do is to turn that information, which is quite complex into something that's actionable and simple to understand and actually is robust and repeatable and relevant. And there are a number of different measures those tests give you, they give you measures of diversity and ecology, but they will also give you specific measures of perhaps probiotic strains or missing probiotic strains or over representation of pathogens.

The bit where it gets a bit grey is when they start making associations to other disease states. So most of those data sets come from, association studies in humans, and you have to really take that data with a bit of a pinch of salt, because, of course, association does not imply causation. That's an entirely different thing. So, I think, a lot of those data sets really need to be interpreted by people that are either at least trained in trying to understand them, or have some sort of education understanding the microbiome data that you get. Otherwise, you end up in a position where those data sets are overwhelming. You're either giving generic information or you're not. You're just creating more confusion.

A lot of the, consumer test reports are also completely unwieldy and completely unreadable. Like Zoe's is pages and pages and pages of nonsense. You know, In Vivo is 90 pages of data. We've looked at all of these reports, and it's just, it's unintelligible, it's impenetrable.

So you really need something that's simple, that's actionable, that gives you the patient specific access insights that you really need.

Two other quite quick things on the microbiome. The best time to test the microbiome is when you're healthy, because the microbiome varies so much between individuals. What you really want to know is what your baseline microbiome is, so that when you get sick, you know very specifically what your microbiome is and where you want to get back to. So testing them as part of a wellness and health screen is a really good idea, and I definitely do that.

The second thing is that, because the microbiome is dynamic, and I told you about that before, it should be deployed longitudinally. So where it's very helpful is if you're going to make nutritional dietary changes, or you're going to make drug changes, you're going to change your lifestyle factor, you can then work out whether or not those things are actually targeting specific bits of the microbiome. And it's very, very helpful, when you're with patients, trying to explain to them that the effect that they're having is working. It's just that they may not be seeing that, the direct health benefits of it.

And the final thing to say on microbiome testing is that, of course, these tests only measure what they're supposed to measure. They don't measure a lot of the microbiome, which is also very important. So for example, some of these tests don't measure fungi, they don't measure viruses, they don't measure parasites, they don't measure eukaryotes. And so, they have obvious limitations, like they're not necessarily telling you about what these microbes are doing. They're just telling you who is there. So it does require some some careful use, but I do believe that it has a use in routine clinical care when used appropriately.

Steven Bruce, 59:55
Okay, so I'm glad that you said what you did there, because I was thinking I had no idea where you would start with testing, given that the microbiome is different in everybody anyway. How on earth do you know what it is you're looking for that's unusual, unless you're just looking for a specific. But you have answered the question to some degree.

When do you think it will be important for us to say to our patients, you might consider going to get a test. And yes, I'd appreciate getting that link from you if I can, because I will send it out by email to everyone who's watching.

James Kinross, 1:00:27
I think all of your viewers, medical professionals will have a sort of diagnostic algorithm, maybe, that they will go to and they were using their standard practice, and it's about deciding for the specific condition that you're treating, where that microbiome testing is going to fit into that algorithm.

So the first thing says that a microbiome test is not diagnostic. So if you're trying to diagnose a specific pathology, or you're trying to identify a very specific clinical problem, at the moment, microbiome testing cannot be used in that way. I think we're getting to that moment, and there are some areas where that's coming, and I can talk about some of those areas in a second, but what you're really doing is using it as a measure to get an understanding of gut microbial health, and it's and it's basic microbial diversity, and

Increasingly, I use it to explain symptoms and symptomology, or I use it to explain or to target therapy, particularly nutrition and dietary interventions, where I find it particularly helpful. I find it very, very helpful in managing patients with chronic gut dysfunction and chronic gut pain, typically patients with SIBO (Small intestinal bacterial overgrowth) and too many IBS type symptoms. It can be extremely helpful. And it's very, very helpful in targeting those interventions,

Steven Bruce, 1:01:48
Okay, lots of questions coming in about the various products that people can take. PIP says, kefir, kimchi, spirulina, make me seriously ill, violent vomiting. Any suggestions on what she might take instead. And, well, there were other questions as well on a similar theme.

James Kinross, 1:02:06
Well, I mean, if they make you violently ill, 100% do not take them. As I said, it's a hard question to answer, because the question is, well, why are they making you sick? And that would be exactly the time that I would be sequencing a microbiome, because I would want to know the mechanisms for your vomiting.

And I wouldn't just be saying to you, Hey, go and take this other off the shelf product, because it's probably going to make you vomit too, and there'll be a reason for it.

I have to say, if you've ever tried to, drink kefir, it is like drinking cold cat sick. It's gross. It probably does make most of your audience, vomit.

But, that would be the perfect example where actually testing would be very helpful. And actually what you really want to be doing something in a targeted way, like, if we're saying that the microbiome is important for health, we really, really should be measuring it, and we really should be doing things in a much more selective way. And my other really strong piece of advice is work with a dietitian. I'm sure there'll be dietitians listening to this. But, in my in my clinical practice, the dietitian is just so important, and what I have to do is sit down with them and look at the microbiome data together and go, Okay, look, this is the particular problem we're solving. We think, this could be a particular target that we really need to address. What do we think together could be a good strategy for doing it.

Steven Bruce, 1:03:23
Okay, given your cold, cat sick analogy, is this the appropriate time to talk about faecal microbiota transplants, because perhaps that's something people can do at home as well.

James Kinross, 1:03:32

Please don't do that at home. The second thing you need to take away from this is that don't take a home faecal transplant. It's really not good. You'd be amazed. There's some crazy people out there that doing that. There are YouTube channels that you can go to that will teach you how to put a poo in a Magimix - just don't do it.

I think that point actually raises that. I mean, it's an interesting point, which is that, I'm an absolute microbiome evangelist, obviously, and I believe it to be fundamentally important in determining human health. But the problem with microbiome science is that there are lots of unknowns in it, because it is a new science, and because modern medicine has lots of gaps within it where we don't have therapies that either work effectively or we don't understand mechanisms.

The microbiome can become a convenient sort of filler for that, and it can become anything that you want it to be. And there are lots of people misrepresenting microbiome science or misrepresenting microbiome targeted therapeutics online, and a lot of vulnerable people come to my clinic who have been failed by modern medicine and are in pain and are suffering and are desperate.

And there are people out there that are absolutely desperate enough to go home and try a faecal transplant, because their disease is just so awful.

So, I think part of the battle that we have in microbiome science is really always coming back to the data, always coming back to the evidence, really trying to prove causation and really trying to prove that these interventions are safe and reproducible.

So faecal transplant, just to extend my answer, and please interrupt if I'm talking too much, but, faecal transplant is as gross as you think it is. And it is literally taking the faeces of someone that's healthy and well and transplanting it into someone that isn't and there is a process through which we do that you'll be relieved to hear.

In many ways, we treat these donors very much like any other transplant donor, which means that we have to very carefully screen them to make sure that they are healthy and that they don't carry pathogens within the gut, and that actually, what we're going to transplant is as safe as we can possibly make it. We typically transplant faeces in one of several ways.

We either try and process it under anaerobic conditions, because many of the microbes in the gut actually find oxygen very toxic. You can't just poo in a pot and stick it in a magimix. Actually, you have to process it in a low oxygen environment. Then we either turn it into a slurry, so we mix it with a bit of saline, and that goes down a tube into the gastric stomach, called a nasal gastric tube, or sometimes it goes through an enema, or sometimes it goes via colonoscopy. And increasingly, we're developing that technology into something called a crapsule or a capsule, which is a lyophilized frozen, freeze dried sample, which comes in a digestible capsule made of cellulose, which you can take as a tablet.

And, of course, the route through which you give the faecal transplant will have different clinical effects and different side effects and risks with it. And those things are constantly

evolving. Now, faecal transplants been used for 1000s of years. The Chinese famously did it as yellow soup to treat traveller's diarrhoea 2000 years ago, and it came back into modern use around the 1950s when Bern Eisman was doing it to treat a pathogen in the gut called Clostridium difficile in the US. And then the Dutch did a big study of this in the late 90s, early 2000s where actually it was much, much more effective than antibiotics in the treatment of Clostridium difficile, and now in the UK, NICE approved faecal transplant as a first line treatment for patients who've got recurrent Clostridium difficile.

But there's two things. Number one is that faecal transplant has been used, really, as an experimental tool for studying the microbiome and for beginning to understand how it works and why it's so important in human health care, but also we've got, now, I think it's about 410 - 420 trials globally looking at faecal transplant to treat numerous different chronic disease states, everything from depression and anxiety and addiction through to inflammatory bowel disease through to Cancer. And it's not just used as a treatment. It's used as an adjunct to treatment. So we use it to modify how drugs work, like chemotherapeutic treatments, like immunotherapy. So it's been used now very, very widely throughout the world,

Steven Bruce, 1:07:55
But not to be done at home, in the magimix. I think I remember you saying that one of the one of the difficulties is that you don't have any way of measuring who is going to be a successful donor, because the mechanisms of action are not properly known

James Kinross, 1:08:12
So there's this phenomenon within the FMT (Faecal Microbiota Transplant) world of super donors, there are some people that just produce very effective faeces that cures all diseases, and these people become very valuable.

In studies, there is serious debate about whether or not that really exists and whether that's actually a real phenomenon, because it might just be that at the host microbiome is as important a determinant of what we call engraftment. So actually, these microbial systems can stay within the host and grow and culture within the host as the donor itself. And actually, what we're very bad at, is it matching donors and recipients.

The other thing is, is that you're right. We don't really know how faecal transplant works. It might be that you're making a wholesale change to the ecosystem, and actually, by correcting diversity and in removing toxins from the gut, it has an effect. We know, for example, that is how we're able to prevent graft versus host disease in patients having bone marrow transplants for leukemias, for example, we know that change in diversity is very, very effective, but also there's probably something in the way that it interacts with the immune system, there's something in the way it changes gut brain interactions. And don't forget, there's this sort of dark matter in the microbiome. There's all these phage and viruses that we don't really understand and we haven't really properly mapped. And actually, sometimes you can, filter out all of the microbes, just give the faecal water, and that's also very efficacious. So again, we're beginning to get much better at targeting FMT and feeding these microbes once they've been transplanted.

Steven Bruce, 1:09:52

Just out of curiosity, when you carry out an FMT a faecal transplant, what quantity of faeces are you transplanting from one donor to a recipient?

James Kinross, 1:10:03
So it depends how you're dosing it, and in what route you're dosing it. So it could be anywhere from 30 grams, which would be in a capsule, to around 60 to 90 grams, if in a slurry. So it can vary a little bit. It's also, there's also there's also questions about frequency of dosing, and so how often you give these doses? And that really varies depending on the disease that you're treating and the trial that you're in. So for c difficile, quite often it will get better with one or possibly two doses. If you're trying to treat conditions like obesity or diabetes or liver problems, it can be many more doses.

Steven Bruce, 1:10:40
John has said, are things like colonic irrigation helpful in any way to boosting the microbiome?

James Kinross, 1:10:50
No, they're pretty damaging. So, so generally, like, we don't advocate for that, because there's a risk of colonic perforation and bowel injury. But you'll have a mass cull of your microbiome, so you'll have a 40,000 fold reduction in your microbiome. The counter argument to what I've just told you is that many patients with IBS, for example, will have it, and they'll feel much, much better, and they'll feel much better because, actually, they've done exactly that. They've just killed all these microbes out of their gut. The problem is that they grow back, and what grows back might not be the same as what was there in the first place. I mean, if you're fit and you're healthy and you're well, it might be, but if you've got, an underlying condition of the gut, it might not be. And that can be part of the challenge.

Steven Bruce, 1:11:36
Do you know statistically, how many colonic irrigations do go wrong? How many perforations, for example, there might be?

James Kinross, 1:11:43
Do you know what? I don't know the answer that question. I'm slightly embarrassed that I don't. And I think the problem is, is that it's probably quite hard to measure, because we probably don't know the total number of actual irrigations that are done each year, because they're not recorded. But the data on attendances, I'm sure, is probably there.

Steven Bruce, 1:12:03
Sarah says, Do we know why some people feel unwell taking fermented foods and drinks? Does it mean they have enough probiotics, things similar to the question you had earlier on about somebody being sick?

James Kinross, 1:12:13
Well, I mean, it's a very interesting question. There are several mechanisms through which that that might happen. It might happen, because, if you're drinking, lots of these live bacteria, of course, these microbes are very, very bioactive. They're going to start metabolizing a lot of the fibres that are in the fermented food that you're eating or whatever

else is sloshing around your gut. And they will produce lots of, gas that so there might be a mechanical distension of the gut that might cause nausea, vomiting or bloating, they will produce lots of bioactive small molecules that will do that, that will not just affect the gut, that will affect the brain, and can centrally influence your risk of feeling nauseous or vomiting. And we know that also happens. So it can be a mechanical effect, or it can be a centrally mediated chemical effect.

Steven Bruce, 1:13:00
What I would like to just touch on is, we've talked you've talked very briefly about food. There is a lot more in your book, Dark Matter.
What about the preparation of food? How does that affect the absorption of the stuff that we want, and I'm including things like the materials we cook in. And there's a great film, isn't there, called Dark Waters, very similar to your own title, about the mis-selling of Teflon in the early days.

James Kinross, 1:13:36
I think the thing that I'd say, before we get into the cooking food, is that I think that food delivery apps really should be classed as carcinogens. You know, they really are terrible. And they do a couple of things which are really problematic. First of all, of course, they change eating behaviors so that we're much more likely to eat ultra processed foods or fast foods or junk foods, and if you read the Uber Eats annual food survey data, it's inherently depressing, and they trap some of our most vulnerable people in that cycle. That's a huge problem with it.

The second thing is, of course, it dissociates us from our responsibility about choosing the ingredients that we have for our food. And of course, it changes the social nature of food preparation, food cooking, which is actually should be a social event, like, sharing food is not just good for our mental health. It's not just good for us, all aspects of our health. It's important also for our microbiome. But, yeah, cooking food has a big impact.

Obviously, when you cook food, you heat it, you denature the proteins, your denature those starches, your denature those carbohydrates. And of course, that changes the food matrix. So you know the physical, chemical properties of that food and how microbes are able to interact with them, and that will have a very big impact on how those microbes will benefit. At your gut, and that can be very, very variable.

So, what you obviously need is a combination of raw food, because sometimes, actually you don't want a lot of microbial co metabolism, and sometimes you want lots, in which case, you can cook your food, and then they'll be able to break it down more accessibly.

Steven Bruce, 1:15:17
Hannah's asked about your thoughts on people having to take antibiotics post splenectomy, and also on teenagers being offered long term antibiotics for acne, which I know is something you specifically covered in your book, and you've got your own teenager now.

James Kinross, 1:15:34
Yeah, I have, I have my own teenager with acne. So, God love him.

I spend a lot of my time treating people, in fact I had a patient this week online, who'd been on Lymecycline (an antibiotic for acne) for three months, who turned up in my clinic wanting to know why they suddenly had diarrhoea and altered bowel habit. And I really struggle with it.

I mean, I think the first thing to say is, is that acne is a terrible condition, and we shouldn't belittle it. You know, it's deforming and it really destroys people's lives. And I fully understand that people need treatment for it and that this should be taken seriously.

I think the microbiome is a great opportunity, though, to change the way we think about acne, because, of course, the skin microbiome plays a very important role in explaining why we get acne, but so does the gut microbiome, and actually, it presents us with new targets through which we can treat it, and I think you're going to see that come through. And I'm really excited about that. I think that's going to be like a major growth area in terms of skin health.

Splenectomy, different ball game. Your risk of having Haemophilus Influenza and dying from an encapsulated microbe that causes sepsis probably outweighs the benefit of having a penicillin, and it's typically a penicillin that we give, and penicillin disrupts the microbiome in less dramatic ways than a macrolide.

But of course, over a lifetime of having it, it's going to have an impact, and it's a risk benefit situation where you you're going to have to just make the call, and the better half of that equation.

But of course, then thinking about your gut health is going to be very, very important.

Just as a side note, what we know is that the microbiome plays a very big role in influencing how vaccines work. So, many of these splenectomy patients obviously need to be vaccinated. It's very important. And having a diverse microbiome that is that is optimized and healthy will have a big impact on the efficacy of those of those vaccines, which is why, part of the reason why things like influenza vaccines work very different in Europe than they do in Africa,

Steven Bruce, 1:17:33
By which you mean a more diverse microbiome means a better working vaccine?

James Kinross, 1:17:38
no, not necessarily, in Africa they're less effective. And we think one of the reasons they're less effective is that actually the sub Saharan, rural African microbiome, is more diverse. It's probably more likely to have things like parasites in there, to have, eukaryotes in there. And actually it's just a bit more resilient. It's a bit it's a bit tougher than our slightly wimpy Western European microbiome bathed in hamburger fat? So, so actually, it was a counterintuitive observation.

Steven Bruce, 1:18:14

Well, look, you've, you've confessed to being a MAMIL, a middle aged man in lycra, yes, and fond of your bicycle. What's the effect of exercise on the microbiome?

James Kinross, 1:18:26
Well, I mean, I probably don't need to tell anyone listening to this exercise is a good thing, and of course, it improves every aspect of our health, and many of those health benefits have got absolutely nothing to do with the microbiome at all. But what we do know is that if you put a mouse on a wheel and you study its microbiome as it exercises, its microbiome will absolutely change. It will adapt to the exercise. And of course, the reasons for that are multifactorial. As it adapts to increase energy expenditure and aerobic demand. So the microbiome, is certainly modified by exercise.

But it's also true that elite athletes and people who are very fit and have that aerobic tolerance also have discretely different microbiomes, and that actually you can modify exercise tolerance through faecal transplantation. And actually, faecal transplantation is a drug of abuse in some sports like professional cycling, not only does it, perhaps improve your tolerance to endurance events, but also it's quite good at hiding the metabolism of drugs which perhaps you shouldn't be taking. So we do find it misused in some sports.

Interestingly, there was a study done in athletes competing in the Boston Marathon, and when they looked at these endurance runners, they had this one very specific microbe that they found in very high abundance, a single strain, and they were able to then transplant that single strain into mice, into mouse models. And what they found is that actually that single strain changed the way that those athletes metabolize lactate and, of course, lactate is one of those metabolites that limits the aerobic tolerance of your muscles. It's a product of anaerobic metabolism, obviously. So, we are beginning to get down to mechanisms through which those things happen, is the point I'm trying to make. And yeah, good exercise, good for your microbiome

Steven Bruce, 1:20:16
It must make the job of the drug testing bodies quite difficult, actually, because there's an obvious pharmaceutical product on the one hand, and then there's a perfectly normal human waste product on the other that they could be testing for.

I made a couple of notes earlier on, when you were talking about the effect of drugs, and it occurred to me to wonder about the effect of recreational drugs in particular. Let's take a simple one. Let's take someone who's smoking weed. Does that have a detrimental effect on the microbiome?

James Kinross, 1:20:50
Well, I mean, smoking, full stop, does and smoking changes the lung microbiome. It has a really big impact on the lung microbiome, and there's a lung gut axis and the gut will influence the toxicity of smoking by changing the immune response to it. And we know that smokers, for example, have very different risks of things like inflammatory bowel disease and diverticulitis and numerous other gut disorders. So there's absolutely link there, and it definitively changes it. In fact, different brands of cigarettes have their own microbiomes, and you can tell which brand of cigarette smoking simply by sequencing out the bugs.

Steven Bruce, 1:21:28
to be honest, I think there's an easier way of telling

James Kinross, 1:21:31
Well, at the moment, everything's white label, so it's quite difficult to tell!

It changes the microbiome because, again, there's a co evolutionary basis for it. So fungi, for example, which are big determinant, actually that make up about 1% of the gut microbiome.

You know, they produce lots of, very bioactive molecules. psilocybin, for example, is used as a drug of abuse. But it's also used as recreational drug. And of course, bugs and fungi have completely co evolved together, so it stands to reason that they've got enzymatic functions for changing how those drugs work and how the side effects and toxicities you feel of those drugs in opiates.

I use opiates in my job. I'm a surgeon. Opiates will change the microbiome, but also the microbiome will influence how effective those drugs are treating pain and also their risk of toxicity and side effect, which is why faecal transplant is being used as a treatment for drug addiction, and even the most simple drugs that we take, like paracetamol, the most studied drug of all time, the most used drug. Its efficacy and toxicity is modified by the microbiome, because the microbiome has lots of Clostridia in it. Clostridia soaks up sulphur, and your liver needs sulphur to metabolize paracetamol through the glutathione reductase pathway to to excrete it. And of course, if it doesn't have enough sulphur, it can't do that, and therefore you're more likely to have toxic side effects. And we can predict that by measuring, the byproducts of these microbial metabolites in urine.

So gut bug drug interactions, whether they're recreational or pharmacological, are hugely important, massively misunderstood and not at all well understood, particularly by clinicians administering drugs. I talked about polypharmacy earlier on in our in our conversation, for elderly people who have a less resilient microbiome, with less ability to co metabolize these drugs, their risk of toxicity and side effect is greatly changed by the microbiome. Therefore, nutrition, diet and promoting gut health becomes a key component of that treatment, not just to make them healthy more broadly, but to help them metabolize their drugs more safely. And actually treating and preventing polypharmacy is something that we should probably all be doing more generally in our practice.

Steven Bruce, 1:23:55
Yes, we've actually had a private GP on the show talking specifically about that in the past, and I've tried to get him back, but I think we must have scared him off, because he's been a bit shy about coming back in the studio.

Last question. It was the other comment that I noted down earlier on, and it's been raised by Jonna and several others. You mentioned. Zoe. Zoe is obviously a very popular product discipline, whatever one would like to call it these days and Tim Spector has also been mentioned here.

The audience is interested in hearing your thoughts. Is it just a money making machine, or is there some value in it? Even if their research is indecipherable.

James Kinross, 1:24:32
I always get into trouble when I talk about this. I have to be careful. So, we really need Zoe to work in many ways, because microbiome science needs a company like Zoe to really improve patient health or consumer health. And I do really believe that the fundamental basis of what they're doing is probably right. And actually that idea was stolen from some Israeli scientists who published a paper in 2015 that showed that actually, if you apply machine learning to microbiome data sets, when you have a very good idea of the dietary intervention, that you can predict glycemic index, and it works really, very, very well.

My problem with Zoe? Well, I've got multiple problems with Zoe. The slight problem is that they're selling a wellness product, and to me, that just doesn't sit well. It's not a wellness product at all. It's a medical device that measures your blood sugar. And what it's doing is it's basically fetishizing glucose measurement in healthy people that really don't need it.

And what they're doing is very plainly trying to create very, very large microbiome foundational data sets and to close and lock those things down, protect them, so that no one else can access them, and they're going to generate money that way. And to me, I have a slight problem with that.

I have a problem with the fact that there are potential harms in doing this, because I think if you are prone to eating disorders, you're prone to fad diets. Actually, it's a gateway drug for those things, and we have no data, really, on its safety. And it's also, it's a solution for the middle classes. If you're rich enough to spend 400 quid on these kits, and then to keep spending on these very expensive ongoing subscription costs, well, that's great, but actually the people that really need this are vulnerable and can't afford those things. \

And what we really know about the microbiome, the true value of the microbiome is that, it's a tool of prevention, right? And actually, we know how to prevent chronic diseases through better Nutrition and Dietary regulation. And the value of the microbiome is it explains why those things work.

So I don't need Zoe. What I need is really effective food policy that says that actually we can get fibre into kids, we can get fibre into our most vulnerable people. We can make it affordable, we can make it accessible, and that actually prevents harmful nutrition and diet, and does that in an equitable way, which is for the benefit of all.

I think if I'd been running Zoe, I would have called it a medical product, because that's what it is. And I would be trialing it in diabetic populations and populations that really need it.

But I'm sure it would be very effective. And I think it becomes very problematic when you start selling gut shots and products in M and S, which are really not based on any scientific evidence at all.

And I think the reports are problematic that, they just not clinical reports, and you've got data sets that are not clinically actionable. And I really get angry when I've got patients with metastatic bowel cancer turning up in my clinic going, well, I've taken the Zoe app and it's doing them harm but they think it's doing them good.

So, before we even get into the fact they're marketing their own homework I think it's problematic, but at the same time, I want it to work. It's not that they're bad people doing bad things. I want their product to work. I just think we need to have a slightly more honest conversation about what it really is.