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2017 Colloquium
Exploring the latest developments with regards to the microbiome and translating the findings into clinical practice

The Role of Microbes in Human Health and Disease
Dr. Brett Finlay

Microbes make up the vast majority of life on earth. In the late nineteenth century, Robert Koch and Louis Pasteur demonstrated that microbes caused disease. Pasteur showed that if you killed the microbes, you killed the disease. Ever since, there's been a microbe-killing program (hygiene) going on. This program has been effective and the rate of infectious disease has dropped. But there is another side to the killing program. Today, rates for Crohn's disease, multiple sclerosis, Alzheimer's, and Type 1 diabetes have soared.

Microbes are key for normal health, but they are also factors in disease. Allergies, asthma, COPD, colon cancer, MS, obesity, RA, ulcerative colitis, autism—all are associated with microbes. But what is the relationship? Can we influence this relationship?

We get our first dose of microbes from our mother at birth (it makes a difference if we are breast-fed or if we were born by Caesarian). Then we get new microbes when solid foods are introduced to our diet as babies. Once we are teenagers, we develop our adult microbiome. That microbiome stays pretty constant throughout our adult lives. After age 65, our microbiome declines dramatically (which leads to the question: can we influence healthy aging by changing or supporting the microbiome in older age?)

The role of fecal transplants
Fecal Microbial Transplants (FMTs) came into effect to combat C. difficile infections in hospitals. Antibiotics don't work on C. difficile; there is just a 25 percent cure rate. But fecal transplants have led to a 95 percent cure rate for this illness. So fecal transplants hold much promise, though the science is still quite crude. It is still debatable whether they work for other diseases such as IBD.

Discussion
Q: How long does the effect of a fecal transplant last?
A: The gut microbiome changes, but can then go back. It really depends. Often one or a couple FMTs are sufficient, for other diseases, it requires multiple transplants.

Q: Does a single dose of antibiotics (pre- or post-surgery) set off a chain reaction? When do people see the effects of antibiotic use?

A: Even single-dose antibiotics can be harmful. Don't use them unless you have to, but if you do take them, consider probiotics afterwards. We really must stop using antibiotics unnecessarily.

Q: Most animals we eat are given antibiotics. How harmful is that?
A: We don't actually get much in the way of antibiotics in the meat we eat. But there are a lot of adverse effects in agriculture more generally and this causes increases in antibiotic resistance.

Q: If you play cards with someone and you get their microbiome, what should you do if they have a bad microbiome?
A: The jury is still out on the communicability of the microbiome. But you definitely want it to be diverse. Perhaps the solution is to play cards with many different people, not the same ones over and over!

Neuroplasticity
Dr. Norman Doidge

Traumatic brain injury (TBI) is the greatest cause of combined death and disability in people under 60. The current treatment for it in traditional medicine is "rest and restore." Those who have had a TBI are told they have an 80 percent chance of recovery, but the 20% who do not recover become disabled and have an increased risk of dementia. (And many people have had multiple TBIs.)

Neuroplasticity is the property of the brain that allows it to change its structure or function in response to mental experience. (The mainstream model of the brain has been that it is like a hardwired machine and can't change. This idea is now shown to be incorrect.) So you can use your mind to deal with extraordinary problems.

Three factors allow a brain to improve:

1) Learned non-use (the tendency of circuits which are not used due to damage or disease to turn off. But we now know these can often be turned on by neurostimulation).
2) The "noisy brain" and dysrhythmias. Often when 90% of function is lost in a person, it is not because 90% of brain cells are dead. Rather some are firing at irregular rates producing "junk signals." We now know how to resynchronize the brain and improve the firing rates.
3) The poorly synchronized brain cannot modulate itself. But we can also use neurostimulation to modulate the brain.

There is an important gut-brain link. For instance, there are frequently gut-brain problems that develop in traumatic brain injury and autism, and that predispose us to dementia. The same diet – one which is low in toxins and which doesn't promote inflammation – is used in all three. For instance, it is similar to the one proposed by Dale Bredesen which has been shown to reverse cases of Alzheimer's disease.

Discussion

Q: How excited are you by the Bredesen Diet?
A: I am excited by a program that has already stopped or reversed the progress of Alzheimer's disease in 200 people. There's been a small study of ten of these cases, including brain scans, showing regrowth of brains that had shrunk. There's not yet been a large clinical trial for the Bredesen Program, in part because it is a very complicated intervention, which involves diet, supplements, exercise, and hormone replacement in certain cases, and is not about using a single magic bullet or pill. He's also explained major mysteries in the illness, which we've been told over and over are based on the buildup of amyloid plaque in the brain. That isn't quite correct. And it's wrong in important ways. We know that there are plenty of people who die in their 80's with lots of amyloid plaque in their brains who don't have Alzheimer's. That's because the plaque is a response to something—it is a defence that tries to protect the brain from invading organisms. Amyloid is not just garbage or a waste product. It protects the brain from invasion.

Interestingly The Bredesen Protocol indicates that those with the Alzheimer's ApoE4 gene are most likely to be helped by the Protocol. In Alzheimer's, the brain shrinks because an "anti-plastic" switch is flipped, and the brain starts removing its own connections and cells. We need this kind of programmed "cell suicide" to clean out old cells, or connections, when we bring in new ones. The brain doesn't like to carry the "dead weight" of unused circuits, it's a waste of energy and so, for reasons of economic efficiency, it gets rid of these cells and circuits. But in Alzheimer's, this process has gone awry and the brain goes from being pro-neuro plastic to anti-growth. (This might be a case of learned non-use at the cellular level). And we know that three things flip the switch from pro-neuroplastic towards shrinkage: inflammation (and that can be caused by diet); toxins; and a lack of proper nutrients and hormones. These are three things that functional medicine has paid a lot of attention to and which, if addressed (along with exercise), can lower and in some cases reverse Alzheimer's.

Q: Is there a limit to neuroplasticity?
A: Well—we do die. There is a limit to all biological processes, but we've been using a bad model of the brain that says there is no plasticity at all, and now that we know that is wrong, we are just beginning to explore the extent to which plasticity can help us. So, in that sense, we do not know what the limits of plasticity are, which is not to say that it has no limits. And there are a lot of different therapies that can direct our plasticity to help the brain model itself in a positive way. But in everyday terms, if you want to have a healthy brain, you *must stay active* both mentally and physically. In terms of lifespan, we are plastic until the day we die. There is serious development that can take place in middle and old age.

Treating Illness with Fecal Microbial Transplants
Jeremy Burton

Each person's microbiome is unique. How do we manipulate the microbiome for patient benefit? We can kill off members of the microbiome with antibiotics and antimicrobial

solutions. But we can also promote elements of it through diet, probiotics, fermented foods, and prebiotics. And we can also replace it.

Fecal Microbial Transplant (FMT)
How does FMT work? We are not sure how or why, but it does in cases of recurrent *Clostridium difficile* infection and in other experimental studies where certain host properties are transferred with the FMT. Could we also recondition someone's microbiome? Consider as an example, kidney stones, which in fact have an unlikely link to the gut microbiome. Treating them is expensive, there is high morbidity, they are painful, and many people are affected. Can we restore the necessary *Oxalobacter formigenes* bacteria in someone's feces to break down both dietary and secreted oxalate from metabolism which are responsible for most kidney stones? Yes. It takes a couple of days, but it can be done by taking stool from affected people, putting it in our gut model in the lab and giving it huge amounts of oxalate, which wouldn't be possible in humans. We now need to try it out and test it on people as an alternative to using a FMT from another donor to rejuvenate these bacterial populations.

It is clear that the microbiome is likely to be involved in numerous aspects of cancer. That is why the International Cancer Microbiome Consortium has been established by Imperial College London with the aim of creating a consensus on microbiome-induced carcinogenesis and to define key questions for the exploration and exploitation of the microbiome for cancer prevention, diagnosis and therapy. As there are links emerging with the microbiome and cancer, we will likely need methods to change the microbiome for health benefits. At present, this is very challenging and we only have very crude tools with which to do it at the moment. But the advances thus far have been encouraging and this area is likely to rapidly develop.

Discussion
Q: Is the microbiome always changing?
A: If you maintain a certain diet and lifestyle, the microbiome is resilient and stable. However, at certain times, some people's microbiome are affected by antibiotics, lifestyle and their own genetics which can have health implications.

Q: Are there problems with [fecal] transplants versus reengineering people's own feces?
A: Are we carrying over a phenotype that we might not think is desirable? Absolutely. We must be careful with this in these transplants. Finding FMT donors for applications beyond recurrent *Clostridium difficile* infection is tough. Only about 1 person in 50 makes it though the screening process with our own rigorous criteria—and it is an expensive process. It cost us about $15,000 to properly screen enough potential donors to get a single individual who was suitable. This was because our extended screen not only covered aspects of infectious diseases, but also other diseases previously thought to be non-transmissible, such as metabolic conditions.