Transcript of Cerebrum Podcast: Gut Feelings on Parkinson’s and Depression

Guest: Ted Dinan, M.D., Ph.D., is professor of psychiatry and a principal investigator in the APC Microbiome Institute at University College Cork in Ireland. He was previously chair of clinical neurosciences and professor of psychological medicine at St. Bartholomew’s Hospital in London. Prior to that, he was a senior lecturer in psychiatry at Trinity College Dublin. Dinan has worked in research laboratories on both sides of the Atlantic and has a Ph.D. in pharmacology from the University of London. He is a fellow of the Royal Colleges of Physicians and Psychiatrists and a Fellow of the American College of Physicians. In 1995, Dinan was awarded the Melvin Ramsey Prize for research into the biology of stress. His current research is funded by Science Foundation Ireland, the Health Research Board and European Union FP7. He has published over 400 papers and numerous books on pharmacology and neurobiology and is on the editorial boards of several journals.

Host: Bill Glovin serves as editor of Cerebrum and the Cerebrum Anthology: Emerging Issues in Brain Science. He is also executive editor of the Dana Press and Brain in the News. Prior to joining the Dana Foundation, Mr. Glovin was senior editor of Rutgers Magazine and editor of Rutgers Focus. He has served as managing editor of New Jersey Success, editor of New Jersey Business magazine, and as a staff writer at The Record newspaper in Hackensack, NJ. Mr. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

BILL GLOVIN: You may have heard references to the microbiome, the gut-brain axis, or microbiota. However, or whatever it’s labeled, the bacteria and all the other gross stuff inside our stomachs has been increasingly linked to the brain and our overall health, and is one of the most important frontiers in the neuroscience field.

Hi, I'm Bill Glovin, Editor of Cerebrum, and welcome to this month's Cerebrum Podcast on SoundCloud. On the phone with us today, all the way from the APC Microbiome Institute at beautiful University College Cork in Cork, Ireland, is Ted Dinan, co-author of our latest Cerebrum article, “Gut Feelings, Depression, and Parkinson’s.”

Dr. Dinan is both an M.D. and a Ph.D. and a professor of psychiatry. He was previously chair of clinical neurosciences and Professor of Psychological Medicine at St Bartholomew's Hospital in London. He has won the Melvin Ramsay Prize for research into the biology of stress, and has published over 400 papers and numerous books on pharmacology and neurobiology.

In reviewing Dr. Dinan's article, co-authored by his colleague, John Cryan, one of my advisors, Bruce McEwen at Rockefeller University, called it a fascinating read by two pioneers. While the article focuses on a recently discovered link between
microbiota, depression and Parkinson's, we branched out a bit to generally discuss issues surrounding what some have called the second genome.

Welcome, Dr. Dinan.

There are hundreds of thousands of species living inside of you, most in your stomach. I guess, we all have about three pounds of bacteria in our bodies.

TED DINAN: That's correct.

BILL GLOVIN: Does that sound about right?

TED DINAN: Yeah. That's the current estimate that we do have about two to three kilos, or two to three pounds of bacteria in the adult intestine. Most of these bacteria are in the large intestine. We obviously have bacteria in the upper parts of the gastrointestinal tract as well, but most of the bacteria are actually concentrated in the large bowel.

BILL GLOVIN: How old is the field, and how does a neuroscientist find their way to gut bacteria?

TED DINAN: Indeed, the field is a relatively new one. It really is within the last decade that it has taken off. I've been involved in research on the brain-gut axis now for quite a long period of time; goes back, in fact, to the late 1980s, early 1990s, when I collaborated with one or two gastroenterologists at Trinity College in Dublin, where I was on the faculty at the time. I just became interested and quite fascinated by the interaction between the brain and the gut, but it's really only within the last decade, and I suppose even more specifically within the last five or six years, that the role of the bacteria within the gut has really developed as a potentially important communication route to the brain and a way of influencing the brain.

BILL GLOVIN: How did you and your co-author John meet up and decide to collaborate?

TED DINAN: I had returned to Cork about 12 or 13 years ago now and I had been out of Cork, I had been to medical school here but left over 20 years ago and came back to Cork as head of the Department of Psychiatry, and microbiology at Cork is very strong. There are a number of people there who were leaders in the field of microbiology, so I began collaborating with them as somebody who really knew very little about microbiology, but I know about behavior and I know about brain biology, so we began to collaborate and it was a fairly fruitful collaboration. Then John Cryan returned to Cork about two years later, or three years later, and he and I were friends and we began to collaborate together. We were on a brain-gut kind of microbiota research grouping of about 45 people within the ACP Microbiome Institute. John is very much in neuropharmacology background, brain biology. My background is similar as well, but of course, I'm a clinician, so I do work with patients as well. Between the two of us, we run a
translational research group looking at both pre-clinically at the pet problems and into patients and healthy volunteers.

BILL GLOVIN: What are some of the ways that gut bacteria affect our health both in a negative and a positive way?

TED DINAN: Well, I suppose the biggest initial indication that gut bacteria could have an influence on health was the work of Marshall in Australia showing that Helicobacter Pylori could cause peptic ulcers and that was bacteria that is, and still is, very common, especially in third world countries and it was more common in the western world up to maybe three decades ago and when he demonstrated that, that bacteria, which was present in the gut of many individuals, could cause peptic ulcers, that was a very important breakthrough. In my opinion, it was one of the most important medical advances of the twentieth century, certainly the most important medical advance in the second half of the twentieth century.

But it's really only within the last decade that we're beginning to explore the positive benefits of bacteria and those benefits are probably related to all organs in the body, but obviously, as a psychiatrist, I'm particularly interested in the brain and what is clear is that bacteria do produce molecules that the brain and other organs in the body definitely require, so for example many listeners will be familiar with serotonin because it's the neurotransmitter that iconic drugs like Prozac act upon. Serotonin is produced from the amino acid tryptophan. Now, bacteria in the intestine can produce tryptophan, but they also produce things like short-chain fatty acids and short-chain fatty acids that are an important energy source and are important for many organs within the body, so we still haven't got a full appreciation of all of the molecules that are produced by bacteria that are essential for the brain and it's an ever increasing list of molecules.

BILL GLOVIN: Your gut bacteria could affect, well, obviously your mood, but also how much stress you feel.

TED DINAN: Indeed. And that's something that we've kind of very much focused in on in our research group. We've been demonstrating that for example, depressed patients, they have an altered microbiota, they have an altered set of bacteria, but we've been also trying to use bacteria to actually improve anxiety levels, to improve stress levels in healthy subjects. Recently, we published a paper showing that a specific bifidobacteria longum, which is a probiotic bacteria, or classified as a probiotic bacteria (in a study that was placebo controlled, so the subject either got placebo, or the bifidobacteria longum, we showed that it) reduced anxiety levels and it wasn't just a subjective feeling of reduced anxiety, we also showed that cortisol, which is the main stress hormone in men, their cortisol levels were reduced when subjects ingested the bifidobacteria longum, so unquestionably, bacteria can be used to influence our mental processes.
BILL GLOVIN: What tipped you and John off to the idea that there was a link between gut bacteria and Parkinson's and depression?

TED DINAN: Well, I suppose my interests would have been fundamentally an interest in depression to begin with and because I do clinics for very large numbers of patients with depression, and the people I see with depression are very severe forms of depression, often rather difficult to treat, they would have failed to respond to antidepressants and to cognitive behavior therapy, so I with a large cohort of such patients, we decided it would be a good idea to profile the microbiota in patients with depression and what we essentially found was that the microbiota was altered in such individuals that they had a less rich, a less diverse, microbiota. But to our amazement and surprise, in the second study we decided that we would give animals, we would transplant the microbiota from either a depressed patient, or from a healthy subject into rats. What we found was very clear, was that when rats had microbiota from healthy subjects, their behavior was entirely normal. But when they received a transplant of a microbiota from a depressed patient, their behavior altered. They seemed to have a depressed type behavior pattern. Their inflammatory molecules increased in the blood stream and tryptophan, which we've mentioned already as the precursor of serotonin, tryptophan levels or metabolism altered in those animals who were given the transplant from a depressed patient.

So that's how we really went down the route in depression, where obviously trying to develop either bacteria, which we call psychobiotics, are cocktails of bacteria to try to treat depression.

We are, as you say, interested in Parkinson's disease and we have one or two studies kind of running in that particular area and some of the research in Parkinson's disease published of late, is also very intriguing because it does suggest that the microbiota is altered and I suppose, until very recently people felt that they understood the biology of Parkinson's disease and Parkinson's disease is clearly a very debilitating disorder, it was referred to as Parkinson, described by James Parkinson as the shaking palsy. We thought until relatively recently we knew what the cause of it was, that it was the death of dopamine cells in the substantia nigra, which is a selective area of the brain and that those cells were dying because of the build-up of alpha-synuclein. Now, the more recent studies looking at the gut would suggest that some, if not a significant proportion of that alpha-synuclein, which kills the dopamine cells actually originates in the intestine.

There's an intriguing paper published about a year, 18 months ago now, from a Scandinavian group and it looked at people who had a vagotomy, which is when the vagus nerve is cut, for treating peptic ulcer disease, now that was a treatment for peptic ulcer disease before the 1970s, when effective treatments came along, namely the H2 Antagonist, Histamine 2 Antagonists, so prior to that, if somebody had severe peptic ulcer disease, the surgeon would snip the vagus nerve. It did help people, obviously, it wouldn't have been around as a treatment for decades if it wasn't at least partially effective, but the
Scandinavian group decided to look at people who had vagotomies back in the 1950s and the 1960s and probably the early 70s as well and looked at their rate of Parkinson's disease and what they found was that the levels of Parkinson's disease after a full vagotomy were significantly decreased. So, people who have had a full vagotomy have had less Parkinson's disease than the rest of the population.

Which raises the intriguing possibility that something in the gut was contributing to the formation, or the genesis of Parkinson's disease. What the more recent data merging would indicate is that alpha-synuclein produced by microbes in the gut may track up the vagus nerve and into the brain, so those individuals who would have had a vagotomy, where the vagus nerve were severed, of course would not have that pathway, so they would be less inclined to develop Parkinson's disease.

BILL GLOVIN:
Really interesting. You write that gut bacteria depends on us for their nourishment. How early does this gut bacteria form and are there ways we can make sure an infant develops so that he or she can use it to their advantage?

TED DINAN:
Indeed. The reality is that the initial microbiota we develop is dependent entirely on the way in which we were born. If we were born out of our mom's vagina, we form a microbiota largely from the lactobacilli bacteria in our mother's vagina, because we ingest those bacteria as we're being delivered. If we're being delivered by caesarian section, the microbiota formed is largely developed from microbes on the skin of the doctor, or the skin of the nurse and maybe bacteria in the operating room, in other words, bacteria from the environment. Now, over the first three years, there's a convergence so that after a year, there's certainly movement toward convergence, which is complete by years two to three and I think this is certainly of relevance because we know that caesarian section leads to increased levels of asthma and we know that it increases levels of allergies in general and this seems to be related to the microbiota.

Given the fact that caesarian section levels are increasing very dramatically globally, I mean if one takes New York, the levels are around 55 percent, the World Health Organization suggests we should have rates of around 11 or 12 percent, I think our rates here in Cork are around 35 percent, so they're not as high as New York, but they are very high. If you look at areas in parts of China where there had been a one child policy, or very high rates of caesarian section, Brazil has very high rates of caesarian section as well, so there would seem to be health implications. One of our big research interests here—and we have a big European grant looking at this—is what are the long-term mental health implications of the mode of delivery. We know that there are increased allergies with caesarian section, we know there are increased asthma rates, but what are the mental health implications and we're trying to explore that right now.

The other issue raised there was the issue of microbes and how they're fed. Of course microbes are fed by us, so our diet determines to an extent our
microbiota. I mean, there are certain microbes that like carbohydrates, there are certain microbes that like fat, so if we take in a lot of fat, we’re going to clearly facilitate those microbes that like metabolizing fat. If we take in a lot of protein, we’re going to facilitate microbes that like metabolizing protein. So, the microbiota we develop was initially determined by how we’re born, is subsequently determined by our diet. And there’s no doubt about it that a diet of junk food leads to a very bad microbiota and that diversity is established by a good diet.

I mean we talk about Mediterranean diets, which tend to be healthy diets with lots of fruits and vegetables and fish and that leads to diversity in the microbiota, whereas fast food, burgers, chips, whatever, it tends to lead to less diversity and of course, one of the really important issues that has come to light in recent years, is that if we want to live and grow old in a healthy way and clearly we all want to grow old, but we want to do so in a healthy manner, but what is clear is, growing old in a healthy manner requires maintaining diversity and what you find is, that if elderly people lose diversity in the microbiota, frailty follows very rapidly. Really, it is essential in elderly people to maintain diversity.

Right now, there are no obvious medical foods that we can take to bring about diversity, although there are many companies trying to develop such foods, the only thing one can give in terms of advice to people would be to have a diverse diet and to exercise. There’s no doubt about it, that exercise through a variety of mechanisms as well does maintain diversity in the microbiota.

BILL GLOVIN: Do you recommend a vegan diet?

TED DINAN: I wouldn’t recommend a vegan diet. I do think that, there are some people who clearly do, I do believe that a very broad spectrum Mediterranean type diet with plenty of fruit, veg, nuts, fish, I think that type of diet does induce an optimal microbiota. Now maybe a vegan diet to some extent does as well, but for most people, I think a Mediterranean diet is at least a feasible diet and it’s a diverse diet and a palatable diet. I think it tends to promote a really healthy microbiota.

BILL GLOVIN: Yeah, well I guess a lot of people claim that a diet with meat, especially red meat, means that the meat has been injected with antibiotics and all kinds of chemicals and that could have an effect.

TED DINAN: Oh, absolutely. I mean there are two problems with meat, really. One is that particularly, in the US, you have a lot of antibiotics and there are more levels of antibiotics in the food chain than we would have in Europe and, of course, if you take in antibiotics in the food, be it in meat, or in any other food, it’s likely to kill bacteria in your intestine because after all, they’re antibiotics you’re ingesting. But the second thing about red meat, apart from any potential antibiotics in the red meat, is the fact that red meat, when it’s ingested, leads to the production of the molecule called TMAO, by bacteria in the intestine, so the actual bacteria in the intestine produce this substance called TMAO. And TMAO has been
shown to be profoundly cardio toxic, so actually red meat has a terrible impact potentially on the cardiovascular system, largely because of its impact on the microbiota. Interestingly enough, if animals are germ free and have no microbiota, you do not see the production of TMAO, so TMAO is produced by microbes in the intestine in response to the ingestion of red meat and leads to potentially to cardiovascular disease. It certainly is cardio toxic.

BILL GLOVIN: What's your feeling about antibiotics in general, especially in young people or infants?

TED DINAN: I think that there's far too much use of antibiotics, very frequently for viral bacterial infections and the long-term health consequences are not good. I mean we know that if a baby in the first year of life has two or more courses of antibiotics that the risk of obesity later on in life is dramatically increased. Obviously, the older we become, the less dramatic the impact of antibiotics, but even there, when we knock out our microbiota with an antibiotic, it takes several months for the microbiota to reestablish itself in the way it was pre-antibiotic treatment.

BILL GLOVIN: Can you explain the role of probiotics?

TED DINAN: Yes, now the term probiotic is one that the regulators dislike enormously. I mean the FDA used the term live-bio-therapeutic and in Europe here, FSA, which is our regulatory authority, hated the term as well. Probiotics are bacteria that are supposedly health benefiting. Most of the probiotics that have been studied have either been bifidobacteria, or lactobacilli, and most of them are tourists in our intestine. By that I mean, when we ingest them, they go in our mouth and out our anus and they do not colonize, so they do not grow inside in us.

There's a very occasional scenario where they might, but in general, they are tourists. So even when they're having a very beneficial effect and there's good evidence that, for instance, certain types of bifidobacteria are effective in treating irritable bowel syndrome and when people take these bifidobacteria, they have to take them on a continuous basis because these bacteria are not colonizing the gut, they're just simply, as I say, passing through the system, but having a positive benefit when they do pass through the system. Now, more and more probiotics—and I use the term very loosely—are being tested and, of course, people are also using polybiotics, which are combinations of probiotics. We and others have been working with prebiotics and these are, prebiotics are non-digestible, or indigestible molecules that are metabolized by the bacteria in our intestine and promote the growth of good bacteria, so there are molecules that we take them in, like FOS and GOS, and they're found in various vegetables for instance, and they're ingested by us and metabolized by bacteria in our intestine and they promote the growth of good bacteria like bifidobacteria, particularly, that the growth of bifidobacteria is promoted by prebiotics.

BILL GLOVIN: Now you can buy probiotics in pill form in any drug store-
TED DINAN: Yes.

BILL GLOVIN: ... in the United States-

TED DINAN: Yes.

BILL GLOVIN: ... is that something you would recommend?

TED DINAN: The problem in going into a health food store and buying, let's say bifidobacteria off the shelf, is that some of these bifidobacteria do not survive, let's say, the acid in the stomach, so they don't really get into the intestine at all. Some of them have been tested and studied, so what I would suggest to any listener who is interested in taking a probiotic, to kind of do a little bit of research and to make sure that at least preliminary research has been done on the putative probiotic because some of these probiotics have absolutely no science whatsoever behind them.

BILL GLOVIN: Have there been any studies done using human beings, or is most everything done with rodents?

TED DINAN: Well a lot of the, I suppose more fundamental studies have been done on rodents, but there are an increasing number of studies that have been conducted in healthy subjects. I mean, we've published I think two placebo-controlled trials now of probiotics in healthy subjects. What there is at the moment is a paucity of studies in patients, let's say patients with anxiety or depression, or Parkinson's disease or whatever, but there are an increasing number of studies being conducted and published on healthy subjects with probiotics.

BILL GLOVIN: Is there anything that I've left out that you think is important to add?

TED DINAN: I think you've covered most of the key issues there. Yeah, I think you've covered most of the key things though.

BILL GLOVIN: Okay, well that's great then.

TED DINAN: Great.

BILL GLOVIN: So I want to thank you again for your-

TED DINAN: My pleasure Bill.

BILL GLOVIN: ... great article. One of our advisors, Bruce McEwen, said that the article was a fascinating read and written by two pioneers.

TED DINAN: Oh, thank you. I'll be meeting Bruce; actually, he and I are doing a plenary at the ISP Anemia thing in Zurich, I think in September, so I'll be meeting him. He's
somebody, I've only met him a few times, but he is somebody I'm very fond of, he's a lovely, lovely person.

BILL GLOVIN: Oh, so you didn't pay him to say that then.

TED DINAN: No, I didn't.

BILL GLOVIN: Oh, that's good.

TED DINAN: I will say, I think his work on glucocorticoid receptors is worthy of a Nobel Prize, I really do. I think it's some of the most important work that has been conducted on glucocorticoids ever.

BILL GLOVIN: Well, okay, thank John for me as well-

TED DINAN: I will indeed Bill, I will indeed.

BILL GLOVIN: ... I appreciate it and if I'm ever in Cork-

TED DINAN: Oh please, absolutely.

BILL GLOVIN: ... I will stop by and buy you a pint, at least one pint.

TED DINAN: Absolutely Bill.

BILL GLOVIN: Maybe two.

TED DINAN: Take care Bill, lovely to talk to you.

BILL GLOVIN: Bye-bye.

TED DINAN: Bye Bill, bye.

BILL GLOVIN: And that's our Cerebrum Podcast for this month. Thanks again to Ted Dinan and John Cryan for their article, “Gut Feelings on Parkinson's and Depression.” And thank you to the listener. To access the article and all Cerebrum content, go to dana.org\cerebrum\archives.

This podcast was brought to you by the Dana Foundation, a private philanthropic organization committed to advancing brain research and educating the public.

Again, thanks for listening. I'm Editor Bill Glovin, see you next time.