



## **Dr. Rogers Prize – Transcript of the 2019 Colloquium**

### **Speaker 1: The Microbiome at the Beginning of Life** *—Dr. Alessio Fasano*

The idea of the impact of the microbiome comes from the hygiene hypothesis. The timeline is too short to blame genetic mutation as an explanation for the explosion of epidemic proportions of auto-immune conditions.

Consider China, for instance. Changes there have happened in only 10 years—they've moved from rural to urban (Western) lifestyle in that time. And they've had food allergies rise from 0% to 5% or so in just a decade. We're seeing epidemics of cancer (prostate, thyroid, etc.). Those rates are not justifiable on the basis of genetics alone. Consider autism. The rate of autism used to be 1 in 5,000. Now it is 1 in 58. The conclusion we must draw is that we have radically changed our lifestyle and our environment to adapt to these changes.

We always used to follow the paradigm: one gene, one protein. But changes are happening too quickly for this to be fully true now. Environment must play a part. The intestinal barrier is not working anymore and that is causing much of the problem.

There are 5 targets by which we can change our clinical outcomes:

- 1) Genetic editing (not a pursuable target at this time)
- 2) Change our environment (not do-able)
- 3) Put a brake on the immune system (immunosuppressant) (doesn't address the cause). All the treatments we have for autoimmune diseases address the symptoms, but not the cause. Finally, we can go after
- 4) the microbiome, or
- 5) gut permeability

These last two are something we can work with.

If we look at the anatomy of the gut (the battlefield where friends and enemies need to be properly handled), we can see that we are protected/divided from the world by a single layer of cells in the gut. They

are the barriers that keep out the foes and let in the friends (and sometimes the foes).

There are four types of immune cells:

- a) epithelial cells
- b) dendritic cells
- c) B-cells
- d) T-cells (these are the heavy weaponry). They can go anywhere in the body and create inflammation. These have set the stage for the immune problems we are seeing now.

The walls of the single layer of cells in the gut are like doors—they open and shut. There is a problem when they stay open. The molecule that opens and closes the doors is zonulin and is a trigger for many chronic inflammatory diseases, including aging, cancer, autoimmune diseases, etc.

What makes the excessive production of zonulin?

- 1) Gluten. The body cannot digest gluten. Gluten leads to the gut microbiome going off balance (dysbiosis).
- 2) The gut microbiome, which is very complex. Ninety-five percent of gut microorganisms live in harmony with us. Five percent are pathogens. The 95% win—they enable us to salvage extra energy from food. They produce vitamins that the body has no other way of getting. The 95% fight against adverse invaders, but if there are events that change its composition (dysbiosis) zonulin is released and the cascade of events leading to inflammation is activated.

There is a misconception about probiotics. Probiotics are not a simple answer to addressing problems in the gut. How you keep your gut healthy is a balance—and personalized to you—between your genes and your microbiome. One size does not fit all. The microbiome must be personalized.

The “engraftment” of a proper microbiome is critical to health and comes through breast milk—through the mother, yes, but also possibly through the father at the point of conception. The microbiome in the first year of life is chaotic. At the end of the first year, it becomes more stable. If the body develops its microbiome properly, we’re in good health. If it doesn’t, we develop problems.

In the last three to four decades we have had a radical departure from the past 2 million years of immuno-evolution. We take too many antibiotics, for one thing.

Of all the factors affecting the development of the microbiome, the one with the most impact is food. Diversification is key. What is the right food? There are “good” anti-inflammatory foods and “bad” pro-inflammatory food. But it is much more complicated than that. The number one cause of death worldwide is inappropriate nutrition. Among the problematic diets are those

high in sodium and low in fruit, nuts, seeds, veggies, etc. All these latter items feed the microbiome. So what should we eat? There is no one diet for everyone. But your diet should include lots of fruits, vegetables, nuts, tubers, fish and only limited amount of meat. The Mediterranean diet pyramid seems to be best. At the bottom of the pyramid, the firm base, is healthy lifestyle, including eating together, being physically active, laughing a lot, and sleeping well.

At the moment, we cannot establish if an imbalanced microbiome causes inflammation or vice versa (who is the chicken and who is the egg?).

We need to follow individual microbiomes over time to see the changes in microbiome functions. We need to do this to determine why, for example, people develop celiac disease. Preliminary data shows that we can tell when people take a wrong turn in their microbiome composition and function and we can see how that affects their future health. In the near future we'll be able to ask: what kinds of genes are affected by what changes in the microbiome?

## **Speaker 2: Treating Auto-Immune Diseases with Microbes** **—Dr. Jeremy Burton**

The microbiome is everything that can be found in the fecal sample, i.e., bacteria, viruses, DNA, etc. The relationship between them and us is important

What is a normal, healthy person? A survey of a thousand people in China aged 3 to over 100 discovered that super healthy people maintain a lot of diversity even when they are elderly, though there is no one "healthy" microbiome. (Diversity may be a contributor to their great health or may be a result of it.) Dysbiosis [an imbalance in the organisms in the gut] is caused by many things.

### ***Autoimmune diseases***

In the case of auto-immune diseases, the immune system is over-reacting to itself—or under-reacting. Bacteria may start the disease, but the host finishes it. Would we get autoimmune conditions anyway, no matter what we do, and can we do anything about it? The microbiome might be a driver, a passenger, or both.

Microbiota analysis is not predictive and not correlative.

How do we change a microbiome?

- Change it through diet
- Replace it with new bacterial types (eg FMT)
- Kill it off with antibiotics

### ***Probiotics***

In the real world, probiotics is a business. Most probiotics are derived from dairy industry isolates or are “domesticated” intestinal isolates, originating from mixed populations, but then grown individually. They rarely colonise—if at all. They do seem to have some benefit against certain conditions, our research showed an effect on heart failure (at least in one study on rats). And probiotics are safe. It is just fine to go ahead and experiment with them if you are relatively healthy.

### ***Fecal material transplants***

Enemas of fecal matter [transplanted from a healthy individual to a sick patient] are used to treat recurrent *C. difficile* by replacing one microbiota with another. We need to keep using this method for treating *C. difficile* until we know exactly what microbes we need to counteract the infection. In time we may be able to use just a few microbe in the faecal mixture.

We conducted a study to see if a fecal matter transplant (FMT) would help fix fatty liver disease. We found that there was no improvement in insulin resistance or hepatic fat. But there was some improvement in intestinal permeability and lowering cholesterol.

### ***Multiple Sclerosis***

MS damages the myelin around the nerve. There is no cure for this inflammatory disease. There is thought to be a link with the gut microbiome. So, does an FMT help early-onset MS patients? In one study, this was tested and the FMT was given by enema. The change in the microbiome was cumulative (i.e., it took six transplants). The transplant was safe and tolerated. Seventy percent had changes to their microbiomes. It is still not clear (yet) if the FMT helped the MS. (The study is still on-going.)

### ***FMT and melanoma***

In the case of melanoma, FMT does seem to be changing the immune system to get the “check point inhibitors” to work better.

## **Speaker 3: Micronutrients, Mental Health, and Mechanisms** **—Dr. Bonnie Kaplan**

To make a brain work optimally, you need to give it all the micronutrients it needs. Suboptimal nutrition is just one cause of mental health problems. There are others, but here we will focus on nutrition.

A couple of years ago, the results of the 2004 Canadian Community Health Survey were analyzed for dietary intake across Canada and across all age groups. It found that 48% of the dietary intake of Canadians comes from ultra-processed foods, which by definition contain negligible nutrients.

In a study of suboptimal nutrition from 1950, 36 normal healthy men were put on 6 months of nutrient deprivation and 50% of caloric and nutrient

intake. The men displayed all the symptoms of depression, anxiety, and some of ADHD.

In 1960, the prevalence of mental health problems was 3 in 10,000. Now it is 2,000 in 10,000. That is an increase of .03% to over 20%—an epidemic!

There is a distinction between acute and chronic use of psychiatric medications to treat mental illness. It is valid to use medications to treat acute symptoms, but research shows that long-term use is problematic. In the Netherlands, a randomized trial found that people who had had a first episode psychosis and who were weaned off their medications did better than those who lived on them long-term.

### ***What do micronutrients do to the brain?***

The role of micronutrients should be taught in elementary school, but it is not taught at any level now. Enzymes enable chemicals to transform from A to B. But minerals and vitamins are cofactors that enable the enzymes to do their work. There are 50 genetic mutations associated with physical health where people don't have enough (or need more) vitamins and micronutrients to stimulate the enzymatic process. Although such mutations have not yet been identified for brain health, they likely exist. We need all 15 minerals and 15 vitamins (and probably at least 1200 phytonutrients) to survive. These should not just be examined in isolation (1 at a time).

In mitochondrial function, the way to think about the production of ATP is micronutrients in/ATP out. ATP is the energy molecule and it is critical. Almost all, if not all, micronutrients have a role in mitochondrial function. Therefore, we must be eating a broad spectrum of foods to ensure we get all the micronutrients we need. The mental health of many people has improved significantly with an improved diet. A better diet costs a lot less than many processed foods (or drugs).

When people are given broad-spectrum micronutrients, it has been shown that they've had a reduction in stress after earthquakes, floods, and massacres (following the earthquakes in Christchurch, New Zealand, and following the floods in Calgary, for instance). Dosing people with micronutrients is a safe and cheap method for helping people in times of distress. Unfortunately, following the fires in Fort McMurray in 2016, the government declined the offer of micronutrient treatment and the result was heightened affective disorders, heightened anxiety disorders, and a slight elevation in substance abuse disorders among the affected population.

While some people don't respond to micronutrient treatments—it isn't a magic bullet—in the case of one boy with psychosis, it was shown that not only were micronutrients effective in eliminating his hallucinations and delusions, but also a health economist showed that the cost of the nutrient therapy over six months was less than 2 percent of the cost of conventional drug therapy during the previous six months.

If you want to know more or have questions, contact me at [Kaplan@ucalgary.ca](mailto:Kaplan@ucalgary.ca). You can join my e-mail updates list and receive links to various lectures on nutrition and mental health. And you can find out more about the two donor-advised charitable funds I manage which support young scientists wanting to study the nutritional treatment of mental health disorders.

## Panel Discussion

*Q: What does a healthy diet look like to each of you?*

**Bonnie Kaplan:** Eat mostly plant-based foods, less red meat, more complex carbohydrates—the Mediterranean diet. Note that Round-Up (glyphosate) sequesters dietary minerals making them less available to us. Glyphosate is impoverishing our food. We should be eating organic.

**Alessio Fasano:** I only eat what I cook. I cook for taste, but I avoid red meat. You should eat everything. I do short fasting. I eat lots of fruits and veggies and fish. I cook from scratch and grow my own veggies. I also have lots of good wine—it has good anti-inflammatory properties. And I also no longer use the car—I walk everywhere.

*Q: Is there a role for intermittent fasting?*

**AF:** There is growing evidence that there maybe so. That's akin to the way we used to live when food was not so prevalent. Some microbes need your body to fast. So fasting could be beneficial, though there is no magic bullet.

*Q: Bruce Ames [a respected American biochemist whose research focuses on cancer and aging] came out against organic veggies because when he went to check out a problem at a celery farm, the cultivars selected had been selected for disease tolerance and he found that pesticides emulate the naturally occurring disease fighting agents in plants. He concluded that organic farming involves selecting cultivars that have high concentrations of pesticides. Also, organic is more expensive, so people will eat fewer vegetables. So most people benefit from mass-produced veggies.*

**BK:** I received 40 soil samples from Harvey Dann [owner of Alert Agri Distributors] and when I assessed them I found that their micronutrient levels were very low—whether organic or not.

**JB:** Chemicals are useful, but we need to use them carefully.

**AF:** There is an element of scamming in products labelled “organic.” Healthy and organic are two different things.

**Q:** *What is the validity of publicly-offered fecal testing?*

**JB:** It is not reliable and is a waste of money. We don't know how the testing agencies collect the data. And anyway, what is "healthy"?

**Q:** *[I am part of a program that] feeds 100,000 people a week in India. We are teaching kids what "healthy food" is. About organic: The essential nutrients in fruits and vegetables have decreased since 1965. Even organic fruits and vegetables are not as healthy now as we'd like. How do you explain that to the person on the street or the therapist? How do we share this information with those who make decisions?*

**BK:** I try to convince mental health clinics to educate and talk about nutrition. Our emergency rooms are flooded with kids in mental health crisis. They can't see a psychiatrist for months. It would be so easy to introduce nutrition and micronutrient counselling.

**AF:** My colleagues are focused on the *quantity* of nutrition over the *quality*. You must be patient. The *quality* of nutrition is a lifestyle issue. We should teach hygiene and nutrition in school.

**JB:** We sequenced the human genome, but it came as a shock that we didn't understand about the microbiome and *its* genes. I think we're going to see a time when people will start to feed their microbiome.

**Q:** *What about Vitamin D? It is an essential nutrient and it is a problem [getting enough of it] with people staying indoors so much. Autism is highest in Sweden where there's little sunlight. It is particularly prevalent among Somalis who cover up and get even less sunlight.*

**AF:** [Lack of] Vitamin D is linked to specific problems. But it is part of a whole range of vitamins that matter. We make a mistake in assuming autism is a heterogeneous disease with one cause and one cure. We likely can't generalize. Clearly there is a group of individuals who would benefit from Vitamin D [therapy], but it won't necessarily solve the problem. But clearly it would be worth trying this in the Somali community.

**Q :** *Abram Hoffer changed the way I looked at medicine. When I grew up, everything was organic. How much research do we need to do to show that good soil is critical and the earth contains all sorts of micronutrients that we need? How much of your research is getting to the general population—and to the companies making our food? We need co-operation amongst food producers.*

**JB:** Everything we do should have a translatable end. Science must serve medicine. That is the philosophy of my lab. Science is funded in a certain way—the funding model determines the type of scientists we've produced.

**BK:** If we don't influence the policy-makers, we can have no impact. But we are making inroads. It takes a long time to implement political change. There is an opening up of people's minds and perceptions, but we need a teenage activist to push for change.

*Q: Is there any research on the changes in the microbiome after vaccination?*

**AF:** No. The metagenomic component of the microbiome isn't affected by vaccination.

*Q: Where does the microbiome work move into hospitals and into physicians' offices?*

**AF:** We're at the same place with the microbiome as we were when penicillin was discovered. We need to do more homework so we can use this tool effectively. We're not there yet. We must be careful about playing these cards.

**JB:** FMTs have come to prominence because of *C. difficile* problems with a poor prognosis. It is worth it to take a risk with the seriously ill. Will it become cosmetic so people will be demanding it just to be younger? We have to be very cautious.

*Q: Can you comment on probiotic supplements?*

**AF:** Probiotic supplements can be used prophylactically for kids who are having to have a lot of antibiotics and perhaps infants who might be at risk for necrotizing fasciitis. Probiotics are considered a food additive, not therapeutic (to avoid FDA scrutiny). There is no legislation covering their therapeutic use.

**JB:** There is not enough information on probiotics [to give a clear recommendation]. But that's not to say they don't help. People need to do their homework if they want to use a probiotic supplement. But they are unlikely to hurt.

*Q: Is there any zonulin testing available?*



**AF:** There is growing use of zonulin as a biomarker for several diseases. It is a cumbersome test to do. But gut permeability is only one of the five pillars necessary for disease to occur. It has to be kept in context.

*Q: Thirty percent of pregnant women have streptococcus and right now they're treated with massive doses of antibiotics and this has an effect on babies. Should we be very specific about the antibiotic strain?*

**AF:** Yes, we should be very specific (customize) the antibiotics we give. And we should use a mix of probiotics as we'll have more chance of them working.

## **About the Dr. Rogers Prize**

Founded in 2007, the Dr. Rogers Prize for Excellence in Complementary and Alternative Medicine is a \$250,000 biennial prize highlighting the important contributions of complementary and alternative medicine to health care.

The Dr. Rogers Prize recognizes those who embody the same level of vision, leadership and integrity as that of the late Dr. Roger Hayward Rogers. Among the first physicians to provide non-traditional therapies for cancer patients, Dr. Rogers was appointed to the Order of British Columbia in 2001 in recognition of his groundbreaking work.

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