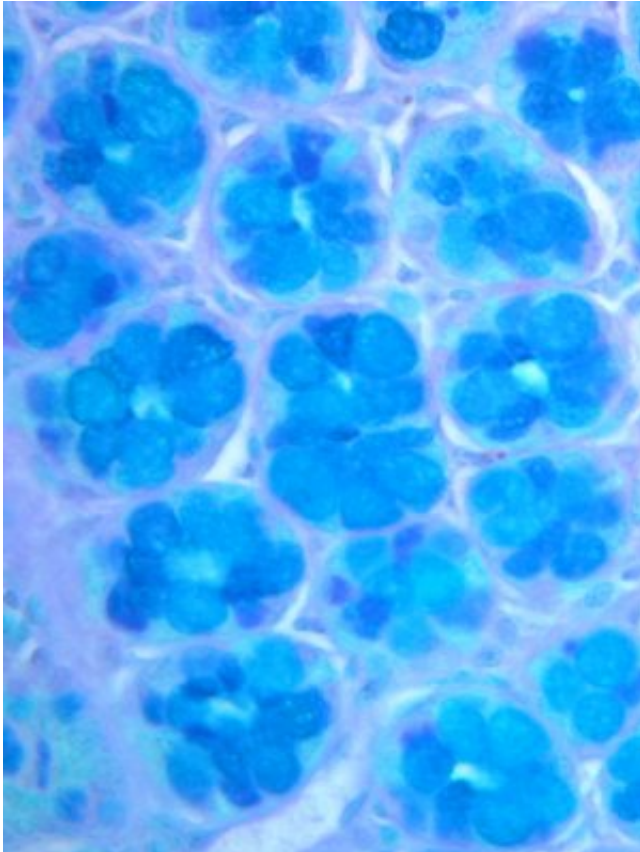


Why gut bacteria are essential for a healthy immune system

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The intestinal cells of the colon is covered by a protective mucus layer, which some bacteria use as food. Under the microscope, this mucus layer look like small flowers.

Most people are aware of how important it is for our well-being to have a healthy gut, which depends on a healthy gut microbiota. In fact, few things disturb our daily routines, social events or even travel experiences as the worry, pain and embarrassment of a malfunctioning intestinal system.

We even have sayings that describe how the gut can affect us: We often use our "gut feeling" to make difficult decisions, and when we are nervous of a job interview or a big examination, we have

"butterflies" in our stomachs and may need to make a sudden dash to the bathroom.

Researchers are increasingly discovering and recognizing that other organ systems are influenced by the gut environment, and these links are gaining attention as possible factors in a number of diseases, such as depression and lung disease.

We may only just be beginning to discover the many ways in which a healthy or unhealthy gut can impact our lives, but we already know a lot about the important little bacteria, namely about how they impact our immune system.

1. Bacteria teach our immune system how to behave

The immune system is the main link between our [gut bacteria](#) and their influence on our health and disease. And we now know that this education begins even before we are born.

It was previously assumed that the prenatal environment in the womb was free from bacteria, but thanks to increasingly sophisticated analytical methods, we now know that bacteria are already present in the placenta. We are born with a naïve immune system and are at first protected by antibodies from our mother. However, the immune cells need to be educated further in order to learn how to protect the body from harm when the maternal antibodies are gone. This education is essential for our future health.

Bacteria educate our immune system from the moment we are born

We also know how important bacteria are for maintaining a normal immune system from experiments with germ free laboratory mice born without any bacteria at all.

These mice have an immature immune system lacking important types of immune cells. But when they are provided with even a restricted bacterial flora, the immune system matures and develops more diverse cells. These experiments have provided extensive knowledge on the function of the immune system, and of the effects of single bacteria or specific groups of bacteria.

Research conducted in both animals and humans has helped us to understand the early life factors of disease development. For example, we know that children born from caesarean section have a higher risk of developing certain diseases – some studies show as much as 20 percent higher risk of type 1 diabetes, asthma, and an increased risk of obesity, compared to vaginally born children.

This is probably due to the cleaner method of delivery, which delays the colonisation of gut bacteria and the education of the immune system. It is also known that extensive treatment with certain antibiotics at a young age increases the risk of allergy and asthma. The hygiene hypothesis has led the way to this line of thinking, but other factors such as antibiotics use of the mother and pre-term planning of caesarean sections with immature maternal milk may also influence these increased risks of disease.

2. Gut bacteria maintain a balanced immune system

Throughout life, we are constantly exposed to new things in our gut, nose and lungs, via our food and environment, such as food additives, pollen in the air or non-pathogenic microorganisms in dust or dirt. But thankfully, most people have healthy immune systems that handle all of these invading objects with ease.

If it didn't, it would elicit an inflammatory response every time you tried a new food or visited a new country with different types of trees. This would be a highly ineffective and unnecessary use of energy.

The essential task of the immune system is to maintain a balance between reaction and tolerance. It is essential that this tolerance, called oral tolerance, is established. And a diverse gut flora

established in early life with many types of bacteria, fungi, and other microorganisms, is crucial for this, as it teaches the cells of the immune system that not everything is bad.

Since balance of bacteria in our gut influences the balance of our immune system, an unbalanced bacterial flora with for instance too many opportunistic pathogens can shift the immune system to an increased inflammatory state with a so-called "leaky gut". This inflammatory state may then affect other body systems and increase the risk of obesity, type 1 and type 2 diabetes and even depression.

3. Bad gut bacteria can lead to disease

Most bacteria are beneficial, but some are responsible for the progression of disease.

It is perhaps common sense that gut bacteria play a significant role in diseases directly related to the gut, such as inflammatory bowel diseases. This has been studied for years and today, treatments are available to correct skewed bacterial compositions and aid recovery of beneficial bacteria via faecal transplantation in some colitis patients. Most people are also familiar with the use of over-the-counter probiotics especially during exotic vacations.

Bacteria are survivors in the best Darwinian style, and they will to some extent adjust to the environment they are in. This is, for instance why resistance to antibiotics occurs. This also means that if [good bacteria](#) are removed due to for example diet or medication, some of the opportunistic commensals, or pathogens, will immediately move in and try to fill the gap.

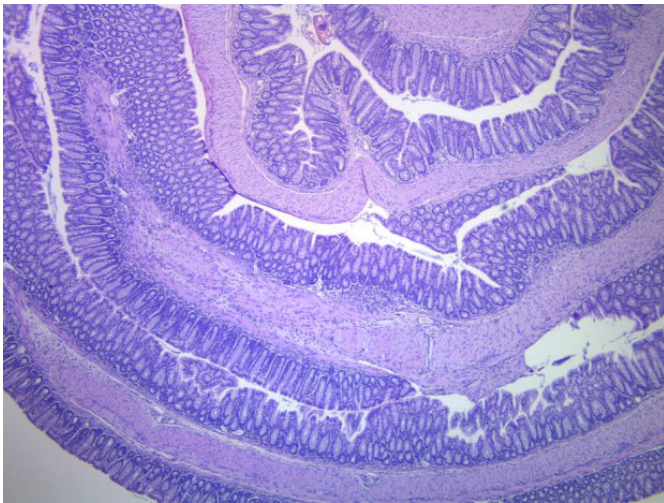
A diverse gut flora is the healthiest

It is not so easy to permanently change an established gut flora, good or bad. Once disturbed, the flora will return to normal within a short time frame, just like when you return home after a vacation and eat your usual diet.

But an imbalanced gut is able to loop in a bad cycle, whereby harmful functions are reinforced. In laboratory mice, researchers have shown that a

certain bacterial composition is associated with type 1 diabetes and obesity – in fact, researchers were able to transfer obesity to lean mice by transplantation of the gut microbiota.

Such skewed microbiotas all have one thing in common: a lack of diversity. A diverse microbiota is more likely to bounce back from unhealthy fluctuations in diet and withstand outside intruders, and this means a much more tolerant and well-regulated immune system.



The colon, here seen from within, contains more than 10,000,000,000,000 cells per gram of intestinal content and between 300 to 1000 different bacterial species.

Gut bacteria could lead to personalised Microbiota Transfer Therapy

So how can we use all of this knowledge in the future?

We know that presence or absence of bacteria is important in the development of several diseases. We also know that it is rarely just one or two bacterial strains that make a difference, but more likely a whole group of certain bacteria influencing other bacteria.

This is all very challenging to study in humans—especially in complicated scenarios,

where these skewed bacterial communities cause trouble elsewhere in the body.

Until now, scientists have focused on understanding the presence or absence of certain bacteria, but what really interests us today, is what these bacteria produce and what signals they send to the rest of the body. Luckily we now have advanced tools at our fingertips to figure this out.

Systems biology with whole genomic, whole proteomic, and whole metabolomics analyses are revealing new details about these bacteria and might even lead to personalised diagnosis and treatment. For instance, it is likely that in the near future, the examination of patients will include a full assessment of the microbiota or its products just like a routine blood sample, leading to precise interventions in diet or administration of bacteria.

Let your kids get dirty

In addition, these methods help explain other mechanisms in the body related to bacteria. For example, a 2017 Nature paper showed that some of the beneficial effects of the type 2-diabetes medicine "Metformin" that enhance insulin sensitivity in type 2 diabetic patients, are due to its effect on gut microbiota and their products. In particular due to the promotion of the good bacteria *Akkermansia Muciniphila*.

Using these methods, we can establish clearer cause and effect relationships between bacteria and outcomes, which have previously been difficult. In other words, we are a step closer to tracking down exactly which part of the [gut microbiome](#) is different in a disease state, improve it with diet, medicine or bacterial transplants, and follow the change in bacterial products and messengers.

Researchers will probably soon be able to buy their laboratory mice with a "diabetes – or obesity" inducing gut microbiota or even with a humanized microbiota. This could improve our disease models and make them more effective. It might even help us understand what circumstances are necessary to really permanently change a person's gut microbiota to the better.

Research in nanotechnology is producing new ways of delivering medicine, vaccinations, and bacteria to the body. Imagine a nano-sized container with a specific bacterial mix meant for the distant part of the gut, designed to protect the bacteria and only open when they meet the appropriate "key" at the right location, for instance an enzyme or a specific pH value.

Clinical studies of microbiota transfer therapy in humans are already taking place and probiotic use is increasing (autism spectrum disorder improved with faecal therapy) and there is no doubt that new and more specialized probiotics will be presented in the near future (for example, the NxtGenProbio project is expected to yield interesting results).

Personalised bacterial "diagnosis" and treatment would certainly be a valuable tool for health professionals, but it is unlikely to become a commonly used tool any time soon since there are still many unknown factors and risks. For instance, should a faecal "donation" come from your own gut, or from a different part of the intestines? How do we prevent transfer of bad bacteria along with the good ones? Are family members more compatible donors compared to a standard foreign donor?

Until then: Let your kids get dirty with a good conscience... you are priming their [gut flora](#) into being balanced and healthy.

The many axes of gut bacteria

Signals run along axes from the gut to other parts of our bodies via neurons, hormones, and perhaps most importantly via the immune system. We call these "axes" and they help describe the connection between gut bacteria and disease else-where in the body.

1. The gut-brain axis

The most studied axis so far is the connection between gut and brain, since it is documented and well-known among health professionals that patients suffering from inflammatory bowel diseases often also suffer from depression.

The gut is able to alter the brain chemistry via

neuronal pathways and through messengers of the immune system, called cytokines – and these messengers depend on the state of the gut microbiota.

Stress is a good example: stress changes the gut microbiota, and the signals running to the brain may impact how we behave. For instance, early life stress changes the gut microbiota of monkeys, and rat pups which are stressed by separating them from their mothers prematurely. Their gut microbiota is disturbed as a result, and they have increased levels of stress hormone and a different immune response.

2. The gut-liver axis

Another axis is the gut-liver axis, which is studied widely in liver research, since 70% of the blood flow to the liver is directly flowing from the gut.

Gut [bacteria](#) are a vital source of fat components and of circulating antigens, and may impact the risk of fatty liver disease.

3. The gut-lung and gut-kidney axes

The gut-lung axis is of interest in respiratory disease research, where the [gut microbiota](#) influences both asthma, COPD, pneumonia and even development of cancer.

Scientists have also proposed a gut-kidney axis where the bad toxic products of a diseased kidney affect the microbiota and a bad microbiota increase the amount of toxins released as a disease mechanism in chronic kidney disease.

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