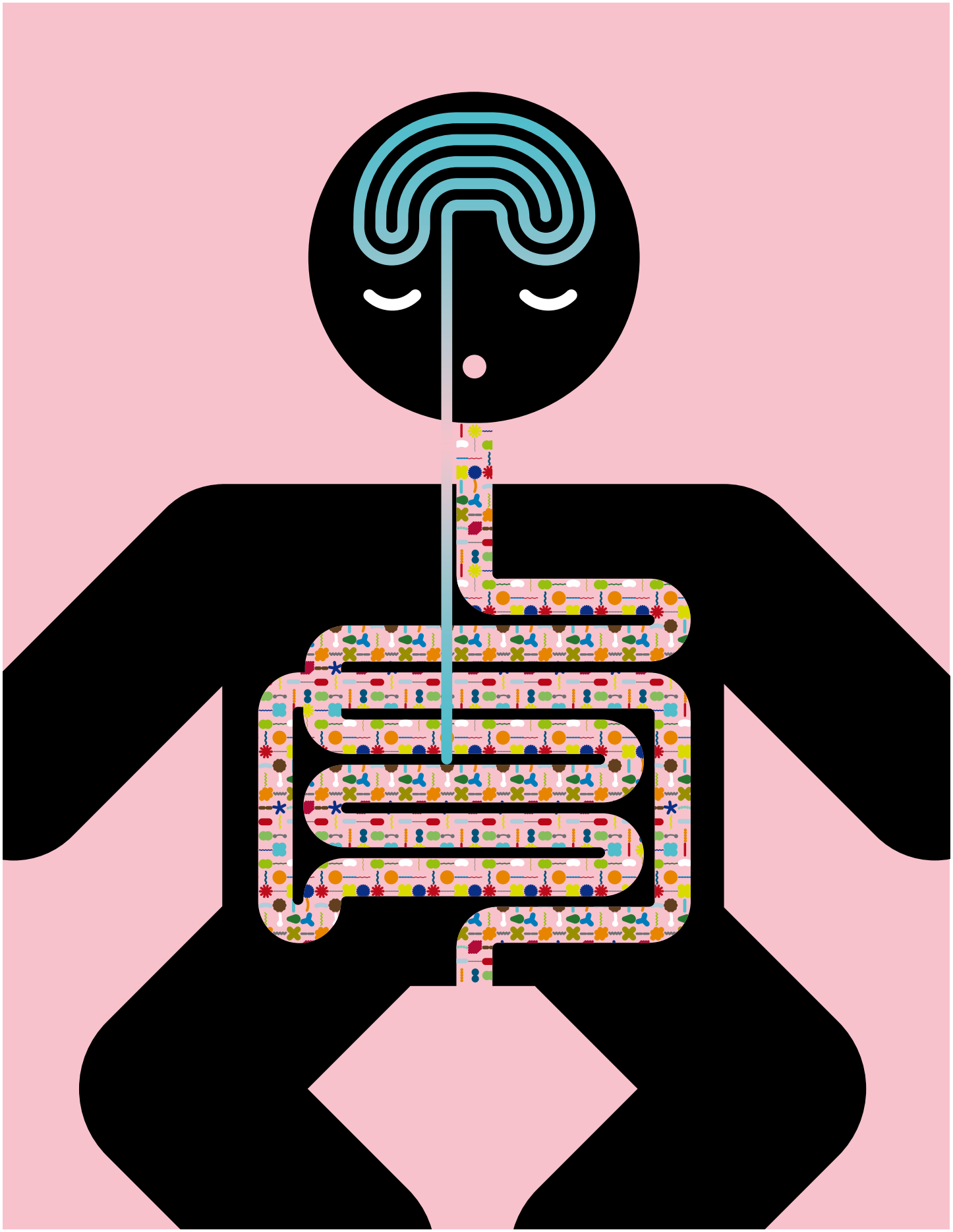


You are what you host: your gut flora

There are more bacteria in our intestines than cells in the human body. They play a role in determining how slim, healthy and resilient we are – and even how we behave. This holds great potential for medical science, says Professor Willem de Vos. 'A microbiological approach can sometimes work better than medicine.'

TEXT NIENKE BEINTEMA **ILLUSTRATIONS** JENNY VAN DRIEL

Physiologically speaking, birth is one of the most abrupt events of your life. From a completely sterile, protective environment, you are suddenly thrown into a cold world bursting with bacteria. The switch to pulmonary respiration comes as quite a shock, but there is another change afoot that is at least as significant. Within minutes the first bacteria start to enter the body. Certain species nestle in the intestines where they start a process that will last for months, maybe years: the development of your own unique gut flora – nowadays known among the experts as gut microbiota. It is a veritable ecosystem in there with different species of bacteria fighting, competing, or even helping each other, and between them producing an assortment of chemical substances.

'The influence this process has on the host is far greater than anyone could have imagined,' says Jan Knol, director of Gut Biology and Microbiology at Danone Research. In April 2012 he was made professor (by special appointment) of the Intestinal Microbiology of Early Life in the Microbiology chair group at Wageningen University. He gave his inaugural lecture on 30 May. 'The gut microbiota help us to digest food and resist diseases,' Knol explains, 'but in recent years it has become clear that their influence stretches far further. Intestinal bacteria turn out to play a role in conditions such as allergies and asthma, as well as diabetes and obesity. There are even indications that they influence our behaviour.'

The complexity of our intestinal ecosystem beggars belief. Each of us is carrying around at least 100 quintillion bacteria in our intestines. Ten times as many as the total number of cells in our body. About one thousand different types have been recorded so far, and the average person's gut contains roughly a hundred of >

> ‘Intestinal bacteria have a far greater influence than anyone could ever have imagined’

them. Together, these bacteria weigh about one and a half kilos and contain 150 times more genes than we do. Scientists are hard at work trying to map this so-called ‘meta genome’. As a result, more and more is becoming known about this dynamic system. ‘The Wageningen Microbiology chair group has been a world leader in the field of gut microbiota for years,’ claims Knol, whose chair is funded by his employer. ‘At Danone we apply that knowledge in order to develop baby and medical foods. So for me this is the perfect collaboration.’

FAT BECAUSE OF BACTERIA

The Microbiology research group has a long tradition of researching gut intestinal bacteria. Some of the most remarkable discoveries in the field in recent years have been made in the Wageningen lab, which is led by Professor Willem de Vos. ‘In early 2011, for instance, our article on enterotypes was published in the journal *Nature*,’ says de Vos. ‘Enterotypes are the three main groups into which we classify gut microbiota. Every human has a specific combination of bacteria, but we can identify three general categories. Apparently our intestines can only support a limited number of stable ecosystems.’

Further research revealed the existence of certain sub-enterotypes, and showed that some of these correlate with a heightened risk of diseases of affluence such as obesity and diabetes. The next question, of course, is which is the cause and which the result. After all, the host’s state of health could be causing certain microbiota to appear in the gut. Or a person’s health and the composition of their intestinal bacteria could be influenced by the same underlying factor. De Vos: ‘But by now we know from research on mice that the gut microbiota certainly can be the cause of certain diseases. If you feed sterile mice, which have no intestinal bacteria of their own, the microbiota of a fat mouse they gain more weight than if you give them bacteria from a thin mouse.’

FLUSHING WITH FAECES

These findings were published in *Nature* by American colleagues in 2006, but De Vos and his colleagues, including some at the Amsterdam Medical Centre (AMC) have since convincingly proven that the same principle applies to humans. In January of this year, they published their findings in the influential New England Journal of Medicine. Some people suffer from chronic bowel infections caused by the bacterium *Clostridium difficile*, the professor explains. They are often elderly, or suffer from a weakened immune system. Such infections are accompanied by severe stomach pain and bloody diarrhoea, and in some cases they can even be fatal. The standard treatment is successive courses of antibiotics. ‘We looked into what happened if, instead, you first cleanse the intestines and then flush them with diluted faeces from a healthy donor,’ says De Vos. ‘The patient essentially receives new intestinal bacteria. Of the people who received this treatment, 95 percent were cured, while only 30 percent of those in the antibiotics group recovered. The difference was so great that the medical ethics committee stopped the experiment prematurely because it was deemed unethical to deny the control group a faecal transplant.’

Together with their AMC colleagues, the Wageningen researchers carried out a similar experiment with people suffering from metabolic syndrome: a combination of obesity, high blood pressure, and heightened cholesterol levels. These people are less sensitive to insulin, which often leads to their developing diabetes. ‘If you give these people a stool transplant using the intestinal bacteria of a slim donor,’ says De Vos, ‘their sensitivity to insulin returns to normal levels. Of course, this is a fantastic discovery. Such cases show that a microbiological approach can sometimes work better than medicine.’

The microbiologists now want to further explore these results. For instance, they want to know exactly which bacteria are responsible for the efficacy of such treatments, how you can optimize the treatment, and whether it can be used to combat other diseases. ‘We mustn’t over-interpret this,’ De Vos warns. ‘I’m not saying that it will help cure every disease. But it is clear that gut microbiota influence our health in all sorts of ways.’

BACTERIA IN BREAST MILK

The ‘transplant experiments’ in Wageningen are shedding more and more light on the functions of gut flora amongst adults, but very little is known about the intestinal bacteria of babies and small children, says professor by special appointment Jan Knol. ‘For instance, we don’t yet know how exactly the intestines are colonized. One thing we do know is that newborn babies pick up a lot of their mothers’ bacteria during birth,’ he explains. ‘In the last few years we have discovered that bacteria in breast milk also play a role, but we don’t yet know quite how they end up there.’ It is clear, though, that the events of this early stage of life have a long-term influence: ‘The symbiosis with the intestinal bacteria develops in the first few months of life. The

INTESTINAL BACTERIA AS AN ECOSYSTEM

Human intestinal bacteria form an extensive, complex and dynamic ecosystem made up of a selection of the c. 1000 identified species, with a different mix of species for every individual.

Number of bacteria in intestines:

100 quintillion

(for comparison: there are 10 quintillion cells in the human body)

Together, these intestinal bacteria weigh

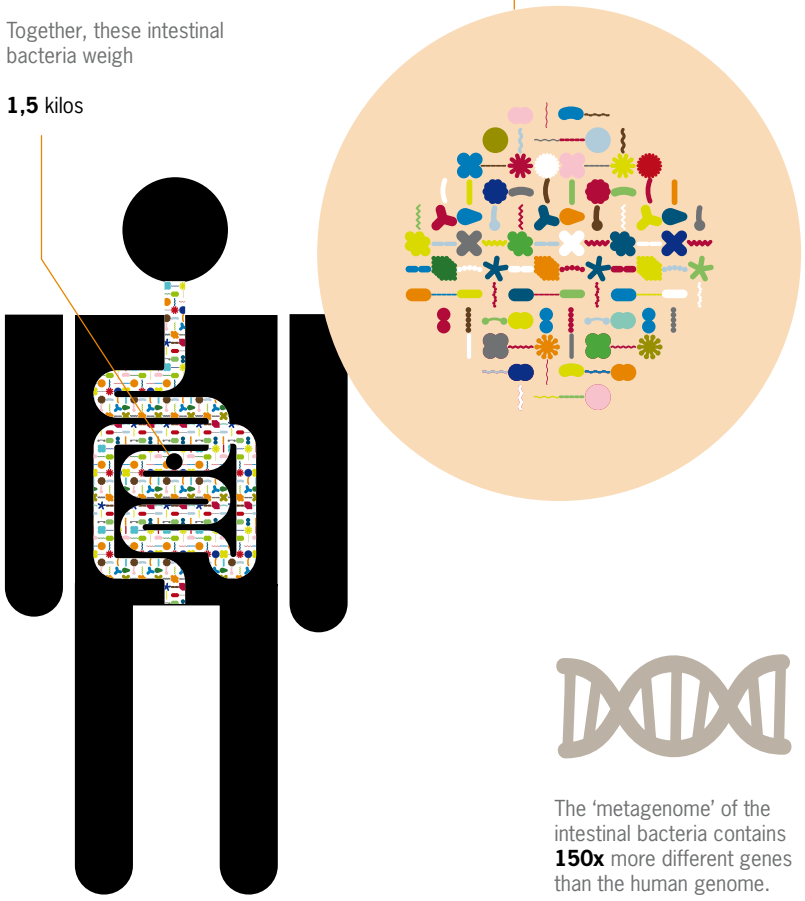
1,5 kilos

Number of species of bacteria in the human intestines:

c. **100** species

This is a sample of the c. 1000 identified species

The composition of the gut flora varies from person to person, but can be divided into a few main types with specific characteristics.



The 'metagenome' of the intestinal bacteria contains **150x** more different genes than the human genome.

immune system needs to mature and we now know that the gut microbiota play an important role in that process.'

It makes a difference, the professor explains, whether babies are born naturally or by Caesarean. Only in the former case does the baby come into immediate contact with the mother's gut and vaginal bacteria, which, it is now clear, are beneficial to the baby. In the case of a Caesarean section, other bacteria are first to reach the baby's stomach, including potentially damaging bacteria from the hospital environment. In any case, babies born by C-section tend to have a different set of intestinal bacteria in their first few months than babies who have a natural birth. 'We don't yet know what the consequences might be for the immune system, the metabolism, and even the brain,' says Knol. 'That's the kind of thing we want to research.' The percentage of Caesarean sections is on the rise worldwide, he says. 'In some countries it is over 50 percent. Besides, antibiotics are increasingly being given to children in their first year. We know that antibiotics can cause long term disturbances of gut microbiota amongst adults, but we don't yet know their influence on the colonization of the intestines during the first year of life. That's another thing we want to research in Wageningen.'

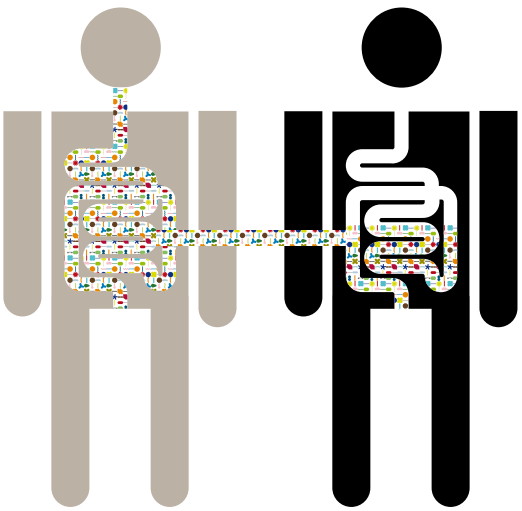
TREATMENT OF BABIES

Knol has no trouble naming a number of potential applications for such knowledge. For instance, medical baby food containing proteins that are beneficial for certain types of intestinal bacteria. Perhaps even procedures for administering certain bacteria directly to babies' intestines. Very positive results have already been >

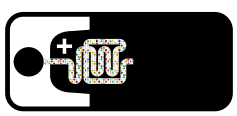
RESTORING HEALTH WITH NEW GUT BACTERIA

The composition of the intestinal ecosystem, made up of 'good' and 'bad' bacteria which collaborate or compete with each other, appears to have an impact on human health, weight and even behaviour. These aspects can be influenced by adjusting the gut bacteria using a faecal transplant.

Replacing gut bacteria



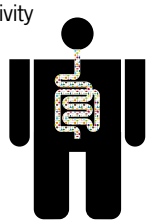
Recovery from *Clostridium difficile* intestinal infection



Following treatment with antibiotics 30% recovery.

Following transplant of intestinal bacteria from healthy person 95% recovery.

Restoration of insulin sensitivity



People with a reduced sensitivity to insulin suffer from overweight, high blood pressure and raised cholesterol levels.

Following transplant of intestinal bacteria from slim donor, insulin sensitivity returns to normal.

Less anxious

Mice that do not dare cross a bridge will do so after a transplant of intestinal bacteria from bold mice.

achieved by adding so-called prebiotic fibre to baby formula, according to Knol. This is dietary fibre such as oligosaccharide, which stimulates the growth of certain types of 'good' intestinal bacteria. 'But if we want to develop a medical application, we first need to understand how the development of gut microbiota progresses in healthy babies,' he adds.

'To achieve this, we want to do research into the differences in intestinal bacteria between healthy babies and, for example, premature babies, babies with infantile colic, and babies with allergies or metabolic disorders. We want to track groups of children over several years in order to see whether the ones who develop obesity already have different microbiota in the first weeks of their life. I suspect they do. I expect to find that there's a window of time within which your intestinal bacteria start to develop in a positive – or less positive – direction.' Knol emphasizes that he doesn't just want to describe how the intestinal bacteria differ between those different groups of children. He wants to research how and why certain bacteria have an effect on our health. 'Which metabolic transformations do these bacteria facilitate?' he wonders. 'Which molecules do they have on their surface, and how do they communicate with the host's immune system? We want to understand these systems at the level of molecules and the transmission of signals. Only once you have that knowledge can you start to look into potential applications.'

MICE LESS TIMID

Willem de Vos too would like to understand these underlying mechanisms. He works on them not only in Wageningen but also in Helsinki, where he leads another research

> ‘How is it possible for these bacteria to influence our behaviour?’

team. ‘To me, one of the most intriguing questions is: how is it possible that these bacteria influence our behaviour?’ Very interesting experiments have been carried out, he says, in which researchers were able to change the behaviour of mice by giving them different gut microbiota. For example, mice that were initially too scared to cross a bridge across a bowl of water were willing to cross the water after receiving a faecal transplant containing bacteria from ‘brave’ mice. And mice that were administered certain probiotic bacteria became less sensitive to fear and depression. How it is possible for the intestines to influence the brain has not yet been clarified. It is clear, however, that the vagus nerve, a long nerve which extends from the brain into the entire body including the intestine, plays a role. ‘So there is a concrete brain-gut-axis,’ says De Vos, ‘but how bacteria are able to send signals to the nerve ends is still a mystery.’

COMMUNICATION MYSTERY

A recent discovery has brought us one step closer to a solution to this ‘communication mystery’. De Vos and his colleagues were the first to notice that the lactic acid bacterium *Lactobacillus rhamnosus* has small protrusions on its surface with which it can latch on to things – the intestinal wall, for instance. ‘These protrusions consist of chains of proteins,’ explains De Vos, ‘including a special mucus-binding protein with which the bacteria can latch on to our intestinal wall very firmly. In the lab we saw that these protrusions are able to interact with the receptors on the outside of the intestinal wall cells which play a role in the immune system. In this way it’s possible to imagine them influencing certain immune reactions.’

The outside world often wants to know immediately when this research is going to lead to treatments, according to De Vos. ‘But that’s still a long way off,’ he says. ‘We scientists are already very happy with the progress we’ve made so far, but it’s still just the tip of the iceberg. We are now targeting a couple of beneficial bacteria, such as Akkermansia, but there are still hundreds that we’ve never looked at.’ ■

Info: www.wageningenur.nl/obesity

THE MAGIC BACTERIUM AKKERMANSIA

Roughly half of all intestinal bacteria live off the food in the intestines. The other half eat the mucus that is produced by the intestinal walls. One of these is *Akkermansia muciniphila*, a bacterium that was discovered ten years ago in Wageningen. It was named after Anton Akkermans, former leader of the Molecular Ecology team in Willem de Vos’s Microbiology chair group. ‘This bacterium is a very dominant presence,’ says De Vos. ‘It covers the intestinal wall and produces certain fatty acids which benefit us as well as other bacteria.’ Akkermansia soon proved to be something of a wonder bacterium. It is more prevalent in the intestines of slim people than in those of overweight people. Animal experiments proved that this was a causal relationship. If you feed mice a fat-rich diet they get fat and develop all sorts of infections in their intestines. If you feed them Akkermansia bacteria along with the fatty diet, they become less fat than the mice on just the high-fat diet and their blood shows fewer indicators of infection. Their intestinal wall also functions as a better barrier, which is beneficial for the immune system. ‘These mice stayed healthy despite their fatty diet,’ summarizes De Vos. ‘It’s almost like magic.’

PHOTO MURIEL DERRIEN