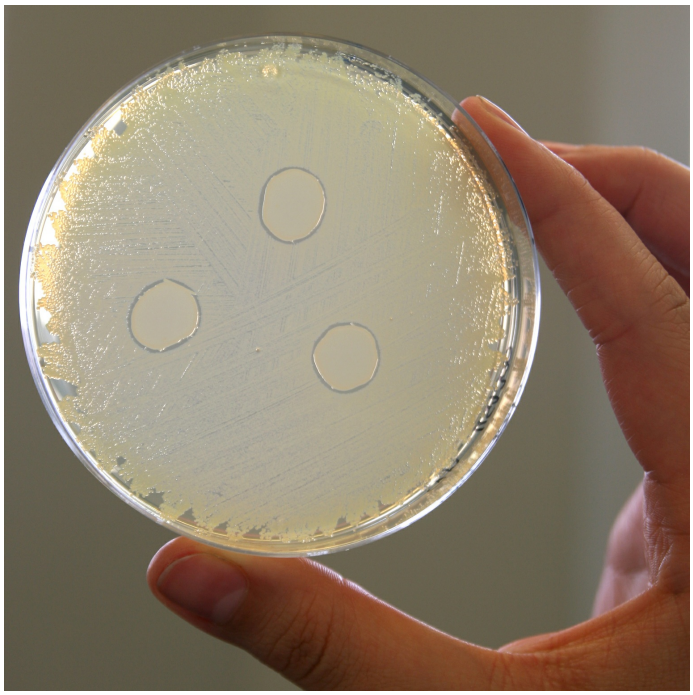
Microbiome: human health is closely connected with our microbial communities

People have 1.3 times more microorganisms than body cells. This microbial community influences how we digest our food, how active our immune system is, as well as whether we tend to be more anxious or curious. A number of diseases have also been shown to be associated with a disturbed microbiome. Researchers still have a long way to go before the knowledge acquired can be used for developing therapies.

The most recent estimate is that about 38 trillion (10^{12}) microorganisms live in and on human individuals[1]. These include bacteria, viruses - especially bacteriophages that infest bacteria - fungi, archaea and unicellular organisms. Researchers call this microbial community a human microbiota or microbiome. In some cases, the term "microbiome" is understood as the entire genome of all microbes that live in or on us, through which individual bacterial species can be identified without requiring long cultivation times[2]. In recent years, faster and cheaper DNA and RNA sequencing methods have led to a boom in microbiome research.



The nasal bacterium Staphylococcus lugdunensis produces an antibiotic called lugdunin, which kills Staphylococcus aureus (MRSA), a pathogen that is resistant to numerous antibiotics.
© Helmine Braitmaier

Most of the microorganisms in and on humans live in the human gut. The mucous membranes in the mouth, nose, lungs, vagina and skin are also colonised by a relatively large number of microbes. The human brain is also thought to host a bacterial community, but final proof has not yet been provided[3]. Most microorganisms are harmless to humans and some are even beneficial. The dense bacterial lawn on the intestinal mucosa and skin, as well as the antimicrobial substances released by the microorganisms, make it difficult for foreign, potentially pathogenic germs to settle on the intestinal mucosa/skin. Bacteria have colonised the colon as humans have evolved and helped us digest some of the fibres that we cannot otherwise utilise. Amongst other things, short-chain fatty acids produced from the microbial fermentation of fibre are one of the beneficial effects of the gut microbiome; short-chain fatty acids serve as an additional source of energy, modulate the reading of genes and can also trigger a sense of satiety in the brain.

The intestinal dwellers also produce neurotransmitters and communicate with the brain via the bloodstream and the nervous system or can be influenced by the brain. Intestinal bacteria can even influence our mood and social behaviour through the gut-brain axis. The microbial subtenants help our immune system to mature and master the delicate balance between inflammation and tolerance of harmless microbes, nutritional components and endogenous tissue by suppressing excessive immune reactions[4].

Every human individual has his or her own microbial fingerprint

Apart from a few microbial species that are common to everyone, the composition of the human microbiome differs considerably from individual to individual. This means that everyone has his or her own "microbial fingerprint". At the time of birth, or perhaps earlier, the decision is made as to which microorganisms colonise the baby first[5]. In the case of natural

births, the baby encounters the mother's vaginal microbial inhabitants as it passes through the birth canal. Children born by Caesarean section are mainly colonised with microorganisms from the mother's skin and are more likely to suffer from asthma, allergies or obesity. It is assumed that they lack the specific microorganisms needed to help them form a normal immune system during the critical time frame[6].

The biodiversity of the microbiome of infant intestines increases rapidly with breastfeeding. After shifting from milk to solid food in the first year of life, the composition of the intestinal dwellers massively changes, gradually stabilising once the child is 2 to 3 years old[7]. Older people have a different, less diverse microbiome than younger adults. It depends to some extent on the genetic composition of each individual as to which microbes prevail and survive their interaction with the immune system. The cleanliness of the environment in which a child grows up also affects which microorganisms a child comes into contact with. In adults, the gut microbiome changes much less dramatically as a result of environmental influences than during childhood. The only exception to this are major disruptions caused by antibiotics or extreme dietary changes.

Medication and nutrition shape our microbiome

The problem with antibiotics is that besides destroying pathogens, they also destroy good bacteria in the body. Although the intestinal flora recovers within 6 to 12 months of short-term antibiotic use, some bacterial species can disappear forever[8]. Children who have been exposed to antibiotics during early infancy suffer more frequently from asthma and obesity as they grow older. In addition, their gut bacteria also accumulate antibiotic resistance genes, which in the worst case can be transmitted to pathogens, rendering antibiotics ineffective[9]. It is increasingly believed that even non-antibiotics can destroy the intestinal flora. Researchers from Heidelberg have shown that more than 25% of over 1,000 drugs tested - including proton pump inhibitors prescribed for heartburn and gastritis, and several antipsychotics - inhibit the growth of gut bacteria[10].

The food we eat, and which our bacterial subtenants also feed on, probably has the biggest influence on the growth of gut bacteria[7]. For example, ethnic groups in South America and Africa such as the Hazda hunters and gatherers in northern Tanzania who live a traditional way of life and eat high-fibre diets, have a different, more diverse range of bacteria in their stool than people from industrial nations, where increasing numbers of processed foods are rich in simple sugars, animal fats and proteins.

While Stone Age humans still benefited from the increased energy yield of gut bacteria, the excessive range of foods, and hence calories, in our affluent society favour obesity. Normal-weight mice have been shown to have more body fat than mice with germ-free guts. If mice are fed a western diet with a high fat and sugar content, the microbiome of the mice will shift to that of good food recyclers. This is also the case with obese people.

Are intestinal bacteria responsible for lifestyle diseases?

However, as the result of a shift to a western diet, some gut bacteria originally required for digesting complex plant carbohydrates have been lost along with a number of useful genes. Scientists believe that this bacterial impoverishment is one of the reasons why lifestyle diseases are proliferating in industrial countries. In fact, intestinal dysfunction, dysbiosis, is not only observed in obesity and related diseases such as type 2 diabetes mellitus and cardiovascular disease.

Food, antibiotics or other environmental factors that cause some bacteria to disappear from the gut or the proportions of different groups of bacteria to change might also result in the reduction in intestinal barrier function, thus facilitating translocation of harmful microbial substances and toxins to the bloodstream. An imbalance in gut bacteria might negatively affect the communication with the immune system and the brain as well as all the processes in the body in which the microbiome is involved.

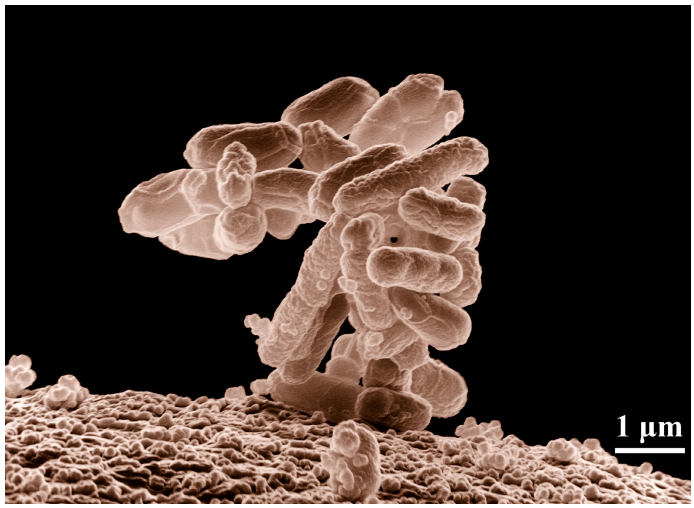
There is also evidence that a disturbed gut microbiome plays a role in chronic inflammatory bowel diseases such as Crohn's disease and ulcerative colitis where the immune system attacks its own gut bacteria. The microbiome is also altered in allergic asthma, multiple sclerosis, colon cancer, as well as in brain diseases such as depression, autism, schizophrenia and Parkinson's. Whether the disturbed gut flora is the cause of these diseases or arises as a result of disease has not yet been determined beyond doubt. Much of what is thus far known about the effect of the microbiome comes from animal experiments and has yet to be confirmed in humans.

Nevertheless, companies are already offering individual analyses of intestinal flora, including individual nutrition plans. Books have been written about microbiome diets. Live bacteria or yeasts and indigestible carbohydrates such as chicory inulin, apple pectin or oligofructose, which are said to promote the growth of beneficial bacteria in the gut, are sold as probiotics and prebiotics. They are added to dietary supplements, yoghurts and baby milk to boost the intestinal flora and strengthen the immune system. Pro- and prebiotic medicines in capsule and droplet form are aimed, amongst other things, at regenerating the intestinal flora in people suffering from obesity or intestinal problems. Pro- and prebiotics are now used in creams to restore the balance of the skin flora in people with acne or atopic dermatitis, slow down skin ageing or relieve vaginal dryness.

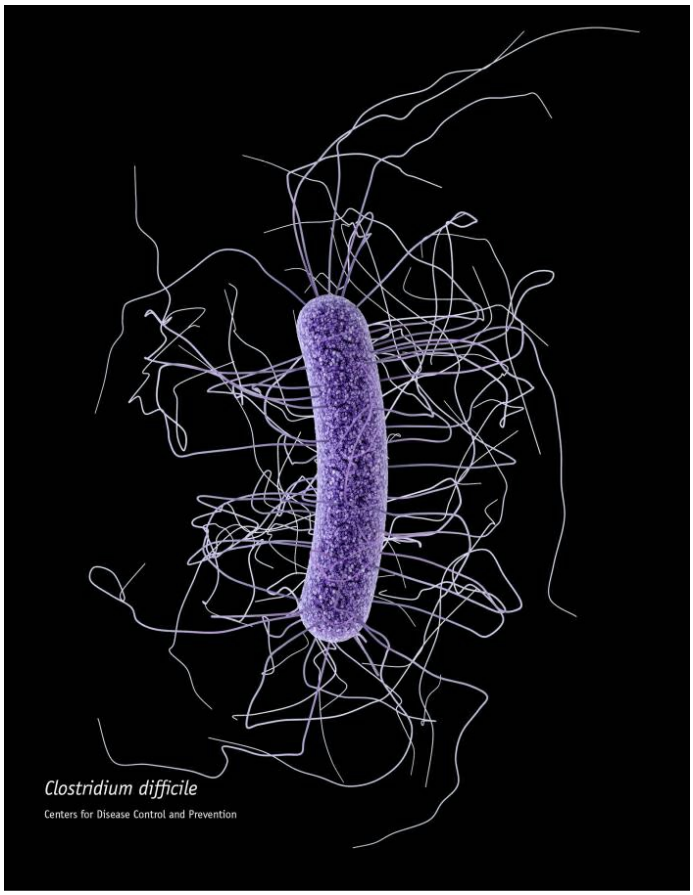
Probiotics – not always useful

The German Consumer Centre writes on its website: "There is no evidence that foods with specific bacterial cultures have a positive effect on health"[11]. Insufficient data is available to recommend using typically highly concentrated pre- and probiotic drugs for treating or preventing diseases. However, clinical studies have found that certain probiotics might be suitable for treating infectious diarrhoea and protecting against antibiotic-related diarrhoea or respiratory tract infections[12]. Positive results have also been obtained for irritable bowel syndrome and ulcerative colitis.

However, such studies are often small, with variations in the methods used to obtain data and sometimes contradictory results. It is also unclear which microbial strains are most effective in which doses for which disease. Whether and how long probiotics can survive in the intestinal microbial gut also seems to depend on individual intestinal flora[13]. According to Deutsche Apotheker Zeitung, doubts have recently been expressed as to whether probiotics are always harmless[14]. Very few investigations into this issue have been carried out.



Escherichia coli is the best-known and most examined intestinal bacterium. Some strains are useful probiotics, while others can cause severe diarrhoea. CC license: PD-US, photo by Eric Erbe (for details see https://commons.wikimedia.org/wiki/ File:E_coli_at_10000x.jpg)



In 1958, one of the first faecal transplants in a person suffering from Clostridium difficile infection took place. This treatment has since been used with great success. License: CDC/James Archer, CC BY-SA 4.0 (for details see https://commons.wikimedia.org/wiki/ File:Clostridium_difficile_CDC.jpg)

Other researchers have been focusing on faecal therapy to improve the intestinal microbiome. This form of treatment dates back to the 4th century. The doctor transfers a bloated stool sample from healthy donors directly into the colon of the recipient via an enema or probe. Another option is to swallow capsules filled with faecal matter. Transferring a complete microbial ecosystem rather than a single microorganism to the patient sounds logical. After all, intestine dwellers mutually influence one another and often cooperate in metabolic pathways.

Stool transplants are now recommended for recurrent infections with Clostridium difficile in cases where a patient no longer responds to standard therapy[15]. If Clostridium bacteria proliferate excessively, they can cause severe diarrhoea. This usually happens when the patients have previously taken antibiotics over a long period, thus decimating other gut bacteria. In over 90 percent of these patients, symptoms improve with faecal microbiome transfer (FMT), a method that is not yet standardised. For other diseases such as inflammatory bowel disease, metabolic syndrome, cancer and autism, not enough data are yet available to recommend faecal transplants. However, there have been indications that the success of the therapy depends on "super donors" who have a particularly advantageous microbiome composition in their stool[4].

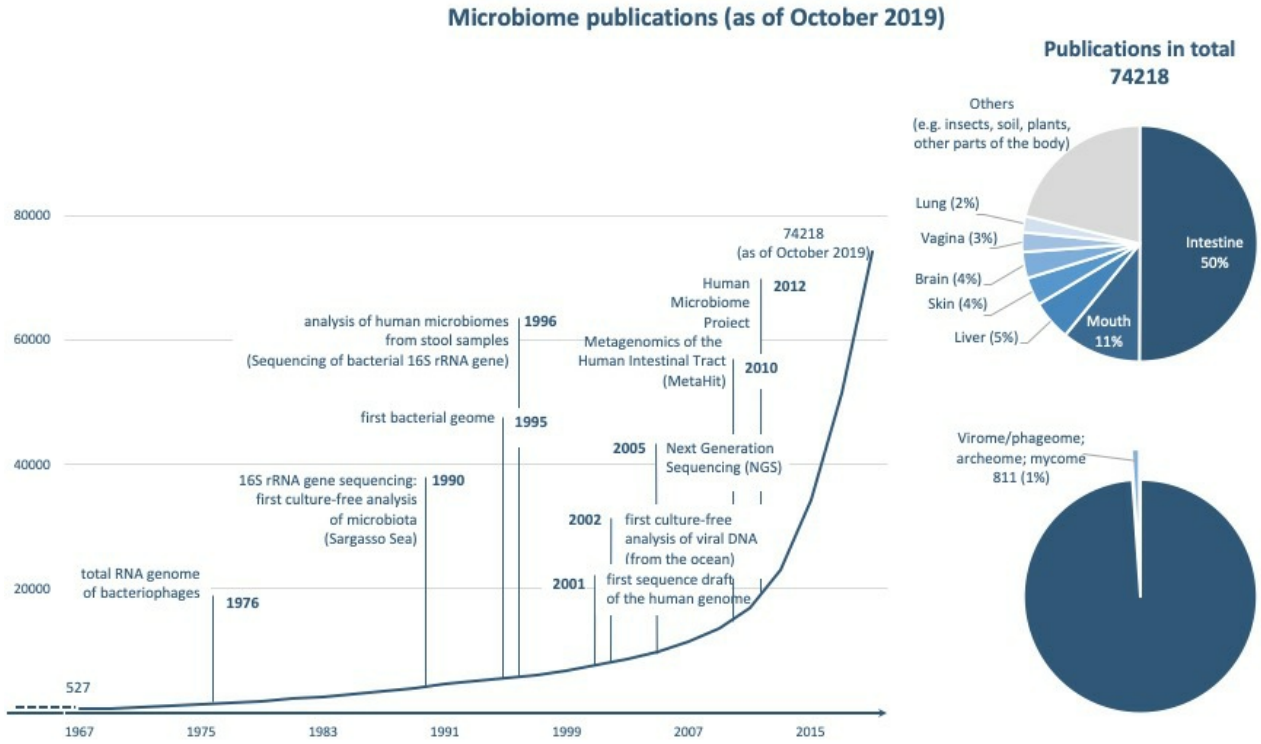
Faecal transplants: a residual risk remains

There is still no consensus among scientists as to what an ideal donor or a healthy microbiome is. This is because the microbiome varies greatly from person to person and also changes dynamically within an individual. "The transmission of known and unknown pathogens is just as conceivable as the activation of unwanted signalling pathways in a patient's body, which over the long term could lead to autoimmune diseases or tumour formation," comments André Gessner, microbiologist at the Institute of Microbiology and Hygiene at the University of Regensburg[16].

Very recently, in June 2019, the US Food and Drug Administration (FDA) issued a warning after stool transplants caused two patients to be infected with antibiotic-resistant bacteria. One of the patients died[17]. In Germany, stool donors and the stool have to undergo a thorough examination before they can be used for faecal transplantation. They are tested, amongst other things, for the presence of multiresistant pathogens. So far, faecal transplants seem to have caused just a few mild side effects. Examinations need to be carried out to see whether they are also effective and safe in the long term. In 2015, a Germany-wide central online registry was established at the University Hospital in Jena for doctors to enter patient and donor data[18].

However, there is the possibility that only metabolic products rather than living microorganisms are needed. The microorganisms form metabolic products to compensate for an imbalance of the microbiome and to positively influence diseases. Nisar Malek, medical director of the new M3 (malignoma, metabolome, microbiome) Institute for Microbiome and Cancer Research in Tübingen, foresees an increasing trend towards "prokaryotic pharmacology", i.e. the search for therapeutically active substances within the microbiome[19]. However, as Malek points out, although the dominant human gut bacteria are known, 80 percent of all metabolites found in humans, including those of the gut microbiome, are still unknown.

Cataloguing is followed by the detection of functions



Data collection using the PubMed medical literature database (www.ncbi.nlm.nih.gov/pubmed/) using the terms "microbiome", "microbiota" or "microflora"

In 2008, a number of significant major projects such as the American Human Microbiome Project[20] and the European MetaHIT[21] project, which also involved the European Molecular Biology Laboratory (EMBL) in Heidelberg, began to study the microbiome of different body regions. In addition to animal experiments, including germ-free mice, modern multi-omic approaches are currently being used to elucidate the function of trillions of microorganisms within the human microbiome. Multi-omic approaches involve linking the information of all microbial gene snippets in a sample (metagenomics) with the data of associated gene transcripts (metatranscriptomics), proteins (metaproteomics) and metabolites (metabolomics). Recently, researchers from the Human Microbiome follow-up project used this approach to decipher the role of the microbiome in premature infants, and in the development of type 2 diabetes mellitus and inflammatory bowel disease[22].

The human intestinal microbiome has long been the focus of research because it is the largest in numbers of bacteria. However, other human microbial communities are now being investigated to an increasing extent. Researchers from Tübingen, for example, are studying the nasal and skin microbiomes in an Excellence Cluster that was launched in 2019 aimed at finding ways to prevent dangerous infectious agents from colonising the nose and skin[23].

However, non-bacterial members of the microbiome still remain largely unexplored. The realm of viruses in humans (virome) has been particularly difficult to detect with existing sequencing methods. There is a long way to go before the complex network interconnections within the microbiome and between microbiome and humans are fully understood and the dream of microbiome-based therapy becomes reality.

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Dossier

06-Dec-2019
Dr. Helmine Braitmaier

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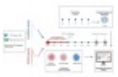

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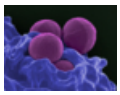

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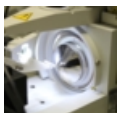

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Further reading

Nature Perspective – The Integrative Human Microbiome Project

Nature Review – You are what you eat: diet, health and the gut microbiota