

The Amazing Human Microbiome

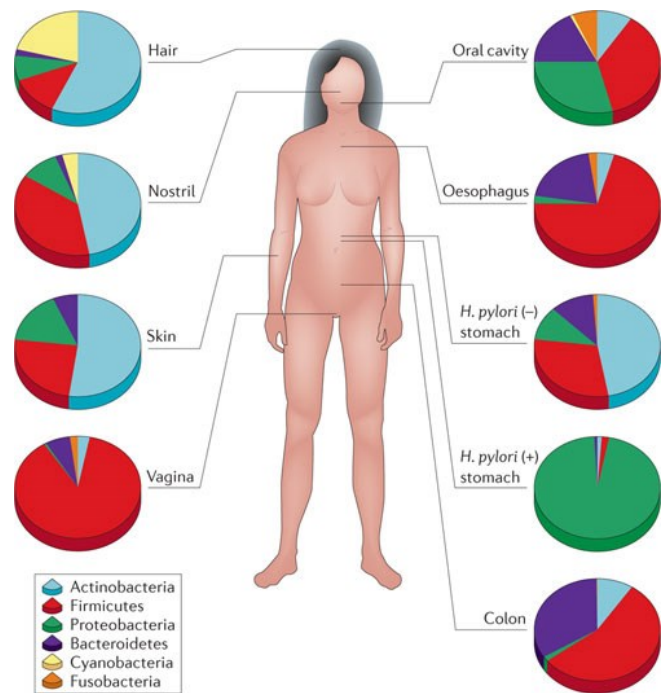
Ann Fullick MA (Cantab) FSB

As a human being, you may well think that you are made up of human cells. But scientists have discovered that in healthy people, microbial cells outnumber human cells by about 10:1 – although they only make up between 1-3% of the body mass. It appears that the human body is a rich and varied ecosystem for microorganisms, and that those microorganisms carry out some important, if not vital, functions in the body. We may even be able to manipulate those microorganisms to cure some very nasty diseases.

For many years our understanding of the microorganisms which live in and on our bodies (our microflora) has been limited to the ones we can culture in the laboratory – and about 80% of our microflora hasn't yet been persuaded to grow outside the human body. But in the last few years techniques in DNA sequencing and genome analysis have improved enormously, becoming not only fast and accurate but also relatively cheap. Projects such as the Human Microbiome Project (HMP) in the US and the Metagenomics of the Human Intestinal Tract (metaHIT) project in Europe have been set up to identify all of the microorganisms that intimately share our lives, and to learn more about their role in both health and disease.

Investigating the human microbiome

The first time the human genome was sequenced, it took years of work by scientists in several different countries. Now, in specialised centres, the genome of a bacterium can be sequenced in less than 24 hours, and a human genome in a few days. Computers can compare and analyse data from thousands of samples in minutes. The HMP was set up by the National Institute of Health in the US to analyse genetic material from all of the bacteria, fungi and archaea living in and on the human body, based on samples from over 200 people. The HMP compared the 16S ribosomal RNA from the microorganisms in a process known as metagenomic sequencing (see fig 2). Scientists have discovered that around 10,000 different types of organisms call the human body home, and that we provide an environment as rich and biodiverse as any rainforest to our microscopic partners.



Nature Reviews | Genetics

Fig 1: Not only do different types of microorganisms colonise different areas of the body, but where and how we live has an impact on our microbiome.

Used with permission from Macmillan Publishers Ltd: Nature Reviews Genetics, The human microbiome: at the interface of health and disease. Copyright 2012.

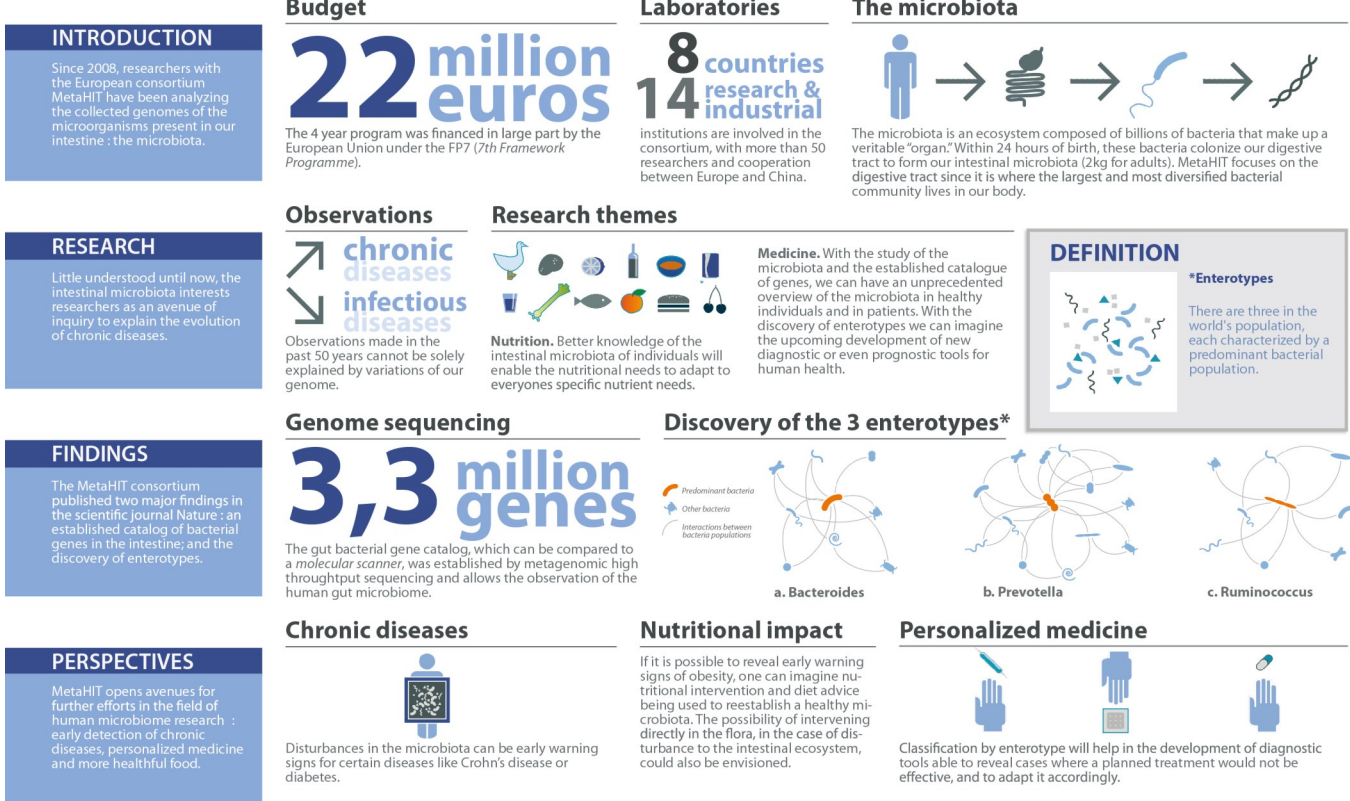


Fig 2: A summary of the MetaHIT project .

Image courtesy of MetaHIT website.

In Europe, the Metagenomics of the Human Intestinal Tract (metaHIT) project focuses on the 10 trillion bacterial cells of the human intestines – they can weigh up to 2kg! These bacteria produce enzymes which help us to digest our food, synthesise vitamins and amino acids which we need and work with the immune system, helping it to distinguish pathogens from useful microorganisms. The Wellcome Trust Sanger Institute in the UK is part of this project, along with scientists from many other European countries – and China.

These and other projects aim to develop a set of reference genome sequences for the human microbiome and to throw light on the relationship between changes in the microbiome and disease.

These projects also help in driving the development of ever faster and more efficient sequencing techniques and computational analysis of the data generated. Some of the health problems that are being investigated alongside the work on the human microbiome include:

- 1) The vaginal microbiome during pregnancy and its potential link to premature birth
- 2) Changes in the microbiome during viral infections or stressful situations which may trigger type 2 diabetes in individuals who are already showing signs of prediabetes
- 3) The role of the gut microbiomes in diseases such as irritable bowel syndrome, Crohn's disease, ulcerative colitis and type 2 diabetes.

The human microbiome, health and disease

Many people only think of bacteria in terms of disease. Even people who know how important they are in the cycling of nutrients through ecosystems are not always aware of how important microorganisms are in the human body. However the evidence from projects such as HMP and MetaHIT confirms what scientists have suspected for a long time - that the microorganisms on our skin and in our digestive system are needed for our health and wellbeing. Some scientists describe the gut flora as functioning like an extra organ.

We are just beginning to understand some of the complex ways in which our inherited genome interacts with the genome of our microbiome. Alterations in the gut microbiome have been found in 25 different diseases so far. The strongest links are with the gut conditions Crohn's disease, irritable bowel syndrome and ulcerative colitis, but there also seem to be strong links with type 2 diabetes.

Evidence is mounting that changes in the gut bacteria are also linked to autoimmune diseases, which can have a devastating effect on individuals, obesity (see below) and severe malnutrition.

Obesity and the microbiome

Many of the gut bacteria have enzymes which can digest compounds in our food which human enzymes cannot tackle – including plant derived pectin and arabinose. It has been estimated that up to 10% of the calories made available to our (human) cells from our food are the result of microbial activity in the gut rather than human digestive enzymes!

Levels of obesity are increasing rapidly in many countries, bringing a range of associated health problems from heart disease and high blood pressure to type 2 diabetes and ulcerated legs. We used to think that obesity was simply the result of eating too much and not doing enough exercise – and those two factors do play an enormous part in the problem.

However, evidence is building that not only your own genetic makeup, but also the balance of bacteria in your gut may affect your risk of becoming obese. The evidence in mice is quite clear. If a lean mouse is given microorganisms from the gut of an obese mouse, it too will become obese. People are not mice – but evidence from a number of studies suggests a similar mechanism may be involved in human obesity. One European team examined the bacteria in the faeces of a group of healthy Danish volunteers, some of whom were obese and some were lean. The people who were obese tended to have a relatively low level of genetic diversity in their microbiome.

Prokaryotic cells, eukaryotic cells and antibiotics

Human cells are in the minority in the human body – but they take up most of the space. They are eukaryotic cells, having a membrane-bound nucleus containing the genetic material (DNA) , membrane-bound organelles and a cell surface membrane. They are relatively big at 1-10µm in diameter.

The bacteria which make up the majority of the microflora of the body are prokaryotes. They are small – typically around 0.02 - 0.2 µm – with the genetic material forming a single circular chromosome called the nucleoid – there is no nuclear membrane. They have simple cell membranes and a cell wall which has a complex structure and always contains peptidoglycans. They don't have membrane bound organelles.

The archaea are also prokaryotes, although we know less about them in the body. But not all of the microflora are prokaryotes – fungal cells, like human cells, are eukaryotic.

Antibiotics are chemicals which stop the growth of bacteria or destroy them. They often interact with the unique structures of bacterial cell walls, which is why they affect the bacteria but not the human cells around them in the body. Bacteria are becoming resistant to many of the most commonly used antibiotics by a process of mutation and natural selection.

What's more, obese patients with low levels of diversity in their microbiome were much more likely to gain weight significantly over a nine year period than any of the others in the study. It isn't simple though – some obese people had high biodiversity...

It seems that it isn't just a case of the diversity of your microbiome. The balance between different types of bacteria (especially the firmicutes and bacteroidetes) also seems to be important. These uncertainties show the early stage of all this research.

The microbiome and type 2 diabetes

We already know that obesity is linked to type 2 diabetes, and as it appears that the gut microbiome may be linked to obesity, a link between the microbiome and diabetes is already emerging. But some evidence suggests the link may be even more direct. Studies in Beijing and Sweden looked at metagenomic linkage groups from people with and without type 2 diabetes. They both found that there are a number of differences in the microbiomes of people with type 2 diabetes which affected carbohydrate metabolism, fatty acid metabolism and the balance of bacteria. There are even changes in the microbiome which could affect the sensitivity of people to insulin. Are the changes in the microbiome the cause of type 2 diabetes or an effect? At the moment it is impossible to tell, but both groups of researchers think that at the very least, the gut flora could become an important diagnostic tool for predicting who will develop type 2 diabetes – and may turn out to be a way of preventing or reversing the condition.

Can bacteria save babies?

In More Economically Developed Countries (MEDCs), early or preterm labour is a leading cause of infant death. It also seems to have a longer term impact on the infants that survive – for example, the risk of a preterm baby developing asthma by the age of 6 is up to 4 times higher than for babies born at term.



The human microbiome projects have shown that the microflora of the vagina are very important for reproductive health. The Lactobacilli present in a healthy vagina help to maintain an acid environment, which in turn defends the body against pathogenic bacteria. If the balance of bacteria is upset, women suffer from low grade vaginosis – it doesn't make them ill and gives no symptoms, but it means they – and any foetus they are carrying – are more vulnerable to infections. And that in turn can lead to premature birth and the death of the baby. The balance of bacteria in the vagina can be changed by many factors including smoking, stress, diet and the number of sexual partners a woman has. Awareness of the importance of the vaginal microbiome could help prevent babies dying because they are born too early.

Microbiomes and brains

So far the clearest links between the microflora of the gut and disease is the link with bowel problems. Perhaps more surprisingly there is a growing body of evidence suggesting that problems in the intestinal microbiome may be linked to the neurological and behavioural problems experienced by people with autism spectrum disorders, Parkinson's disease and Alzheimer's. At the moment scientists are becoming increasingly aware of differences in the microbiome in people with these conditions. Again what is still unclear is whether the changes cause the problems or are a symptom of disease. If they do cause the problems, can manipulating the bacteria growing in the digestive system affect the symptoms? At the very least it looks as if the contents of the faeces may yield some useful diagnostic tests!

Microbial medicine

Antibiotics have saved millions of lives since they were developed for general use in the 1940s. However most antibiotics knock out part of your healthy microbiome when they re destroying the pathogenic bacteria which have caused disease. The effects of this can be seen in the gut for months afterwards – and sometimes they can cause serious illness and may be fatal.

For example, *Clostridium difficile* (*C. Difficile*) is a bacterium which lives in the guts of about 5% of the human population, and in healthy people it causes no problems at all because its numbers are limited by the healthy microorganisms around it. But if the healthy gut microbiome is destroyed by antibiotic treatments for other infectious diseases, the numbers of *C. difficile* increase rapidly. The bacteria produce two toxins which in turn damage the lining of the intestines causing severe diarrhoea, bleeding and even death, which can happen very rapidly indeed. *C. difficile* also forms spores which can last for months outside the body, so it is easily spread from one sick person to another by skin contact or even objects such as bedding or a book. It is resistant to most antibiotics – the only treatment that sometimes works is vancomycin, a powerful antibiotic normally only used when all others have failed. In a mind-blowing experiment in the Netherlands, a team of researchers took 3 groups of patients all with recurrent *C. difficile* infections. In the initial experiment, 13 people were given vancomycin for 14 days. A second group of 13 patients were given vancomycin and also bowel lavage (washing out the colon).

Treatment	% of patients fully recovered
Vancomycin only	31
Vancomycin and bowel lavage	23
Vancomycin, bowel lavage and faecal transplant	94

The third group of 16 was given just four days of vancomycin and bowel lavage followed by an infusion of faeces from a donor down a nasogastric tube. In other words, a solution of poo from a healthy person was fed into the infected guts! After 13 of this group recovered completely, the other three were given a second treatment from another donor and 2 more recovered. The overall results were astonishing.

The study size was very small – but only because the trial was halted. The success of the faecal transfusion was so marked it became unethical not to give it to all the patients affected by repeated *C. difficile* infections.

In the US this treatment is rapidly gaining ground. Scientists and doctors are trying to identify the key microorganisms which out-compete *C. difficile* and culture something which looks and sounds more scientific that faeces to do the job.



Fig 3: The contents of these tubes may not look or smell very pleasant , but they can save lives.

Photo by Jeffrey Thompson / Minnesota Public Radio News. © 2012 Minnesota Public Radio. Used with permission. All rights reserved.

An Australian doctor, Professor Tom Borody, not only treats *C. difficile* patients with faecal transplants on a regular basis, he believes the same treatment is effective for patients with inflammatory bowel diseases such as Crohn's disease and ulcerative colitis – both chronic and painful conditions of the colon. Not everyone is convinced – this is an area of science and medicine which is very new – but in Australia a nationwide trial of faecal transplants as a treatment for colitis is about to start.

The future is....microbial?

Around the world, millions of pounds are being poured into research into the human microbiome. It encompasses so many areas of biology, including cell and microbiology, biochemistry, genomics and genome sequencing, physiology, anatomy, pathology and medicine. Many scientists believe that our new-found knowledge of the massive ecosystem of bacteria, fungi and archaea which make the human body their home, and the interactions between our cells and genome with those of our microbial passengers, will herald the beginning of a completely new and successful model of human health and disease.

Further reading

www.metahit.eu: The website of the MetaHIT project

www.hmpdacc.org: The website of the Human Microbiome Project

www.sanger.ac.uk/about/engagement/yourgenome.html: Website of the Wellcome Trust Sanger Institute, who have made the UK contribution to MetaHIT and are very involved in the various human genome projects, which has clear and vibrant explanations of genome sequencing and work on the human genome

mosaicscience.com/story/medicine's-dirty-secret: Fascinating article by the Wellcome Trust on faecal transplants, with case histories and a very accessible journalistic style

www.ncbi.nlm.nih.gov/pmc/articles/PMC3564498/: Highly readable paper on the link between the gut biome and autism which gives a thorough explanation of the work so far on the microbiome

www.abc.net.au/news/2014-03-18/sydney-doctor-claims-poo-transplants-curing-diseases/5329836: An Australian news article of Professor Tom Borody