The ecologist will see you now

We're not individuals, we're ecosystems full of bacteria. Understanding how these microbes interact with our bodies is set to transform medicine.

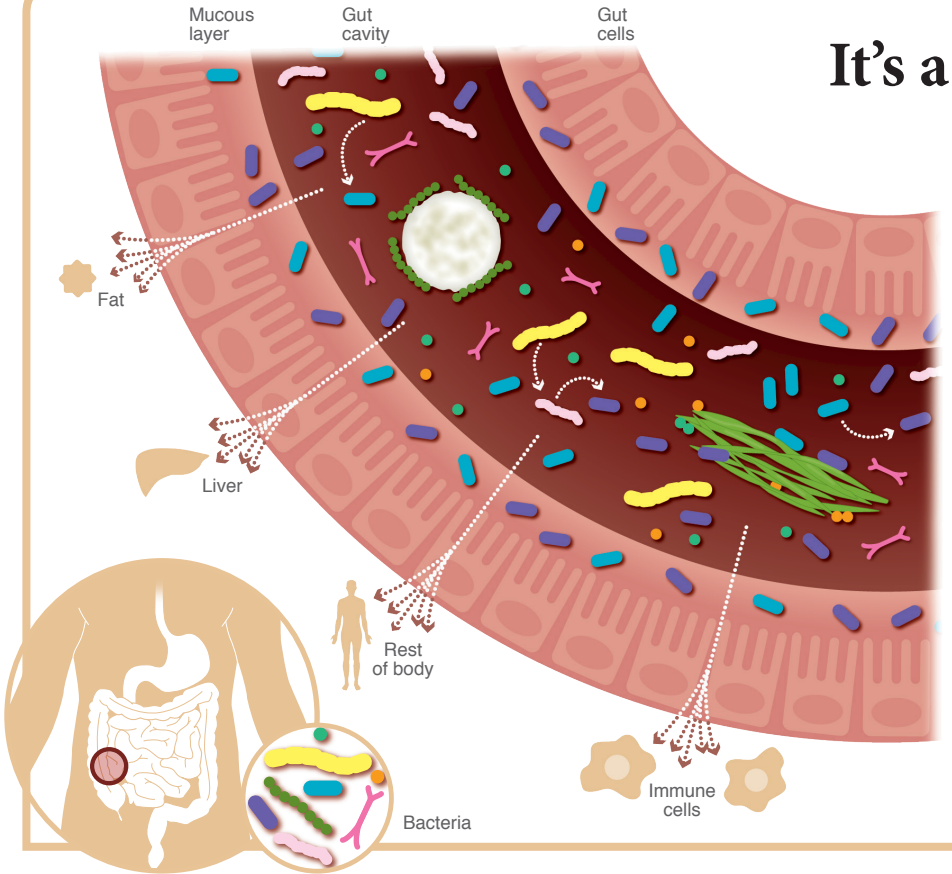
If you think cough medicine tastes bad, spare a thought for Ge Hong's patients.[1] In the 4th century AD, Hong, a traditional Chinese medical doctor, would prescribe a drink made of human faeces to treat food poisoning or severe diarrhoea. The only thing more remarkable than the fact that he persuaded anyone to swallow his concoction is that it seems to have worked. According to his book, "Handy Therapies for Emergencies", the treatment could restore health even in people close to death.

Seventeen centuries on, scientists have realised that Ge Hong was on to something. Not the idea that drinking poo is a good plan (it definitely is not), but that the microbes contained in faeces could hold the clue to transforming human health. Many diseases could be the result, scientists say, of ecological disasters taking place in the microbial communities that live in our guts.

"So from that point of view, you are only 10 per cent human"

This new view has arisen from a sea-change in scientists' understanding of the microbes that live in and on us and how our relationship with them affects us in sickness and in health. Rather than simply being either good guys that help us or bad guys that cause disease, it now seems as though the bacteria that live in our guts form a dynamic and complex ecosystem, rather like a rainforest. In the same way that insects and worms in a forest break down old leaves and logs into nutrients for the soil, so our gut bacteria digest foods and supply nutrients we would otherwise be unable to exploit.

But the effects of this ecosystem reach far beyond the gut. Just as Earth's rainforests pump oxygen and water into the planet's atmosphere and affect the global



It's a jungle in there

The human gut is home to a teeming ecosystem of bacteria that help digest our food and produce substances that affect our immune system, metabolism, development and possibly even our mental health.

Our guts provide lots of "niches", opportunities for different bacterial species to carve out a specialised living for themselves. Some live in the flow of food, digesting starches (shown as a white sphere), while others degrade plant fibres (shown as green fibres), and also feed on the substances produced by other bacteria (white arrows). Others live in the mucous layer next to the lining of the gut.

As well as digesting food, the bacteria produce substances that fuel our gut cells, influence our immune system, and escape the gut (brown arrows) to affect other parts of the body, including our fat cells and liver.

Illustration: Nigel Hawtin

climate, so the microbial ecosystem in our gut produces molecules that affect many aspects of our physiology, from our immune systems to our mental health. **Alterations in this ecosystem are associated not only with gut diseases such as inflammatory bowel disease or diarrhoea, but also conditions such as obesity, diabetes and cancer.** Researchers hope that by studying the myriad interactions these microbes have with each other and with us, they will be able to find ways of tweaking the ecosystem to prevent or treat disease.

Most of the microbes living in our guts are bacteria (see **Meet the microbes**). Bacteria are different from the cells that make up our bodies: they are smaller, simpler and do not form multicellular bodies. But small and primitive doesn't mean unsophisticated. Bacteria are hugely diverse and multi-talented; they can exploit a vast range of habitats from scalding hot springs thousands of metres under the sea to the frozen wastes of the Arctic permafrost to the inside of your bowels.

Inside your gut, these bacteria form a thriving, complex community called the gut microbiota. Neither friendly nor hostile, these microbes exploit us as a warm food-rich environment, and we exploit them as ways to outsource jobs our bodies can't handle. Each species carves out a living for itself, with some breaking down food remains and converting these into other substances that are, in turn, used by other bacteria. These microbes can communicate, collaborate and compete with each other, and indulge in a form of chemical warfare to keep out harmful intruders.

Until very recently, this hive of activity was largely hidden from human eyes. For many years, scientists studied gut bacteria by extracting them from faecal samples and growing them in lab dishes. But many gut bacteria don't grow or survive in those sorts of conditions, meaning that researchers had only a limited picture of what was living inside us.

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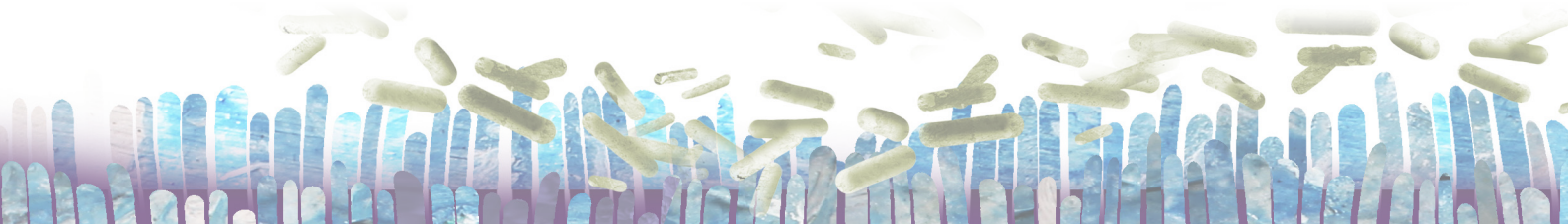
This picture changed in the mid-2000s, when scientists developed the technology to quickly identify nearly all the microbes in the large intestine without having to grow them in a lab dish first. This involves reading the DNA sequences - the molecular instructions inside each bacterium that tell the bacterium how to build and run itself – in each kind of microbe. Some of these DNA sequences are unique to each species of bacterium, meaning that scientists could do a census of our gut microbes by testing faecal samples from people around the world.

Their findings, which began to emerge in 2005, have transformed the way we see ourselves. **Your large intestine is home to 100 trillion bacteria of more than 1000 different kinds. If you count the bacteria living in or on our bodies, they outnumber our own cells by 9 to 1. So from that point of view, you are only 10 per cent human.**

By combining the DNA information with what they already know about the biology of gut bacteria, researchers are building up a picture of what the bacteria are doing (see **Meet the microbes**). The most obvious thing is digestion. Alone, your body is unable to break down the dietary fibre and many of the starchy molecules found in the plants we eat, for example. Gut bacteria ferment fibre and starches to produce molecules called fatty acids, which your gut cells can use as fuel. These fatty acids also reach other organs such as the liver, where they are converted into fats or sugars for storage. Gut microbes produce vitamins, such as B vitamins (needed for cell metabolism) and vitamin K (needed for blood clotting). The molecules produced by gut bacteria can also affect how well a person responds to medicines such as paracetamol[2] and cholesterol-lowering drugs called statins[3]. In fact, in terms of their metabolic abilities, your gut bacteria rival your liver, which has led some scientists to suggest we should view them collectively as an additional body organ.

But bacteria are far more than our metabolic sous chefs. It is now emerging that they help shape the body's form and function in many ways. Without bacteria, for example, the lining of the gut fails to develop properly and does not renew itself as often. Bacteria play a vital role in the development and control of the immune system, encouraging immune tissue to grow in a baby's gut, influencing the behaviour of the white blood cells that police the body's defences and producing substances, including fatty acids, that can affect inflammation. They also help to keep infections at bay, by crowding out disease-causing bacteria and by making substances that kill them. What's more, research in rats and mice suggests that the bacteria in the gut can affect how the brain develops and influence moods such as anxiety and depression. This raises the intriguing possibility that our gut microbes may have a say in our mental health, although this has yet to be proved in humans.

Our bodies, in turn, shape our microbiota. The immune system polices which bacteria get to join our microbial club, as do our genes and what we eat. The upshot of all of this is that bacteria and the genes that they contain are almost as much a part



of us as the cells of our own bodies. The boundary between us and what we used to think of as "germs" has become very fuzzy indeed.

Given its important influence on our health, scientists have been striving to work out what a healthy gut ecosystem looks like. When they started deciphering the microbiota, scientists expected to find a "core" set of species that everyone had in common. What they found was quite the opposite: the combinations and abundances of species are hugely variable from person to person, and may even be unique to each individual.

One way scientists have cut through the complexity is to ask what "jobs" the ecosystem as a whole is performing, rather than focusing on individual species. So, for example, is the ecosystem digesting dietary fibre into fatty acids, and if so, which fatty acids is it making? This has revealed that although people might not share the same collection of bacterial species, there is a "core" set of functions found in all healthy people, in the same way that a body organ such as the liver has a set of functions it performs.

It's perhaps not surprising, then, that having a large variety of species, or "biodiversity", in the gut is important. Losing biodiversity can spell trouble. The most obvious example of this is a crippling and potentially fatal diarrhoeal illness caused by a microbe called *Clostridium difficile*. This bacterium normally lives harmlessly in the gut, where its growth is kept in check by other microbes. The disease often strikes hospital patients who have had strong doses of antibiotics that wipe out vast numbers of gut bacteria. This decimates the biodiversity of the microbiota and gives *Clostridium difficile* the chance to grow and spread like a virulent weed after a forest wildfire.

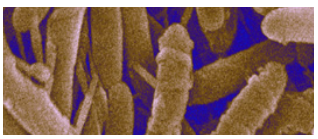
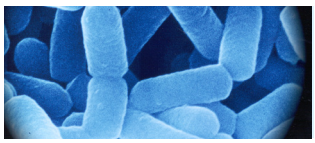
Evidence is now growing that a loss of biodiversity may also be involved in a range of other diseases. Inflammatory bowel conditions, such as ulcerative colitis and Crohn's disease, result when the body's immune system attacks the lining of the gut. People with these conditions have fewer different kinds of species in their bowels, and the proportions of different kinds of bacteria (see **Meet the microbes**) in their microbiotas differ from those seen in healthy people. Similar findings are emerging for diseases that extend beyond the gut, such as obesity, diabetes and liver disease.

This research is in its early stages, so it's not yet clear what all the findings mean. Scientists aren't yet absolutely sure, for example, whether changes to the microbiota are the main cause of these diseases, or whether the diseases cause the changes to the microbiota. But hints are emerging that for some conditions, these changes can affect the "core" set of functions carried out by the gut ecosystem. So, like conservationists trying to reintroduce plants and animals into a damaged rainforest, researchers are

Meet the microbes

Although there are hundreds of different bacterial species living in your gut, they can be grouped together into a few main types based on the features they have in common. This is like way that the squirrels, birds and frogs living in a forest can be grouped together a being animals that have a backbone, or spiders, flies and centipedes being animals with a hard, jointed outer casing.

Two main bacterial groups, the Firmicutes and the Bacteroidetes form the majority of the microbiota in most people, with other groups, such as Actinobacteria and Proteobacteria playing a much smaller role. This balance is disrupted in conditions such as inflammatory bowel disease. Many of the different species in these groups carry out useful functions for us. A few examples are listed below:

Species pic	Function
 *Clostridium, Eubacterium,* and *Roseburia (shown left)*	Digest dietary fibre into fuel molecules called fatty acids. These fuel colon cells, are stored in body fat and influence the immune system.
 *Lactobacillus (shown left), Bifidobacterium, Enterobacter, Clostridium*	Synthesis of vitamins such as folic acid, vitamin B12, vitamin K

looking for ways to restore the normal balance of species in patients' guts.

The most recent attempts to do this involve transplanting faeces (and the microbes they contain) from healthy people into the guts of patients suffering from *Clostridium difficile* diarrhoea. The treatment has been astonishingly successful, curing the majority of patients after a single treatment and restoring the normal bacterial biodiversity in their guts.[4] Preliminary studies suggest that some patients with other gut conditions, such as ulcerative colitis, might also benefit. Clinical trials are currently underway to confirm whether or not this is true.

In the meantime, scientists are also exploring easier, less invasive ways of tweaking gut ecology. These include probiotics, foods containing live bacteria that benefit the health of the person consuming them. Probiotics are non-invasive, easy to administer and lack the "yuck" factor of faecal transplants. What's more, they have been around for a long time, having first been developed from fermented dairy products such as yoghurt in the early 1900s. Probiotics containing a range of different bacterial species are now available.

Unlike transplants, however, existing probiotics don't dramatically alter the balance of species in the gut. This is because the gut ecosystem is stable and resists change, even if it is dysfunctional. Instead, the probiotic bacteria are more like migrating birds making a transient stop in a forest on their way south: they interact with the ecosystem and so alter how it behaves. The upshot of all this is that probiotics can alter the functions of the gut microbiota and the behaviour of the body's immune system for as long as the patient takes the probiotic.

But tweaking something as complex as the gut ecosystem won't be easy. Researchers have published more than 9000 studies looking at the effects of probiotics on a range of diseases, from inflammatory bowel disease to cancer. The results are mixed: some studies show benefits in some conditions, while others do not. It seems as though the particular breed or "strain" of bacterial species in the probiotic is important, as is the microbial makeup of the patients being tested, meaning that more research is needed before doctors can routinely prescribe them.

"perhaps it won't be long before we all become amateur ecologists"

Intriguingly, these studies also suggest that healthy people can also benefit, with some probiotics reducing a person's chance of catching coughs and colds or tummy bugs, meaning that actively managing the gut microbiota could help prevent as well as treat disease. Many questions remain to be answered, however, before this becomes routine. What, for example, are the core microbiota functions each person needs to stay healthy? What bacterial species can deliver these functions and how do they work together to do so? And how are missing species or functions involved in causing disease?

To help answer these questions, scientists are now trying to define the "minimal microbiome", the simplest set of species needed for a healthy gut ecosystem. They hope this will help them design more sophisticated treatments, such as bespoke mixtures of bacteria to replace fecal transplants and probiotics tailored to tackle specific diseases.

Their efforts are timely. The incidence of inflammatory bowel disease and allergic conditions such as asthma is rising sharply in western nations. Scientists suggest that the over-use of antibiotics and our increasingly hygienic lifestyles may be causing a biodiversity crisis in our gut microbiotas. **Perhaps it won't be long before we all become amateur ecologists, each carefully managing the species in our own unique ecosystem.**

Claire Ainsworth

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[1]Zhang F et al (2012) *The American Journal of Gastroenterology* **107**:1755. [2]Clayton TA et al (2009) *Proceedings of the National Academy of Sciences USA* **106(34)** 14728–14733.
[3]Kaddurah-Daouk R et al (2011) *PLoS ONE* **6(10)**:e25482. [4]van Nood E et al (2013), *New England Journal of Medicine* **368(5)**:407-15.