

had an equivalent negative impact. Indeed, participants in a 2007 workshop sponsored by the National Academy of Sciences, entitled 'Genetically Engineered Organisms, Wildlife, and Habitat', agreed on the importance of proper comparisons. Referring to the findings of meeting participant LaReesa Wolfenbarger from University of Nebraska, a summary of the workshop said, "The conclusion Wolfenbarger drew from these studies was that GE crops do affect wildlife food, but that variations in agricultural practices, including cultivation itself, and the use of insecticides, can have larger effects."

The other significant concern among environmentalists and scientists alike is the potential for gene flow between GM crops and wild flora to erode biodiversity. The worry is that if GM crops are grown in close proximity to wild species that are closely related, hybridization between the two could lead to genetic contamination. This is especially likely if the gene introduced into the wild population confers a fitness advantage, allowing it to spread via natural selection. The issue has been of particular concern in places like Mexico where numerous landraces of maize and its wild progenitors are grown next to each other. In fact, the Mexican government has banned the planting of GM maize since 1998. Despite the ban, several recent studies have found evidence of GM genetic material in cultivated maize grown in Mexico, though it's unclear from where this material originated.

At this stage, there are many unknowns when it comes to the potential impact on biodiversity. In those cases where the potential for hybridization is low, such as maize grown in the US, the risk is likely minimal. But what about crops like sunflowers, pecans, blueberries, and some squashes, which are native to the US? Should GM versions of these crops emerge, is there cause for concern? As advocated in the 2007 workshop, when the potential for hybridization does exist, it will be necessary to both quantify the extent of gene flow between populations and, importantly, assess the potential fitness advantages conferred by the genes in question. However, as in the question of food safety, it's not clear that the environmental issues raised by GM crops should be any different from traditionally created varieties. Both have the potential to affect wild gene pools.

Weighing the risks

As with any technology, at some point there has to be a cost/benefit analysis done. While all of the food safety scares surrounding GM food continue to be debunked as fast as they materialize, there are no doubt potential risks that are not yet fully understood, as can be seen in the ecology aspect of the debate. And there is nothing to say that new varieties of GM food could, in principle, potentially be harmful. On the other side of the ledger, however, we have the enormous challenge of feeding the world's population, which is rapidly growing on a planet with finite resources. Of course, malnourishment has many causes, including local politics and war, but agricultural technology will certainly factor importantly. And GM food has lived up to its promise of providing increased yields with less pesticide use and at a lower cost to the consumer. Not only this, but genetic engineering has the potential to provide much needed micronutrients (i.e., vitamins) to the malnourished of the world. A case in point is the recent development of an engineered form of rice that produces a precursor of vitamin A, dubbed 'golden rice'. This remarkable and easily implementable technology has the potential to mitigate hundreds of thousands of cases of blindness in the developing world, and yet it remains shelved due to unsubstantiated health concerns.

Many western consumers can afford to stock their refrigerators with organic produce, but can the rest of the world? Do the potential risks really trump malnourishment and starvation? While the interested parties continue to debate, science marches on. On the horizon are GM crops that can grow in inhospitable corners of the earth, such as the dry and salty environs. And we are now seeing the application of GM technology to animals, such as salmon engineered to reach market weight more quickly through the expression of genes encoding growth hormones. Whether these technologies are taken up or left to gather dust on the shelf will likely depend on the ability of scientists and the government to make a convincing case to the public. If they fail, we potentially handcuff ourselves and will be forced to rely on 20th century technology to solve 21st century problems.

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Does the gut microbiome hold clues to obesity and diabetes?

As high-throughput genome sequencing technology now enables researchers to study the microbiota in our digestive system both in breadth and in detail, the hope is that mysteries of common problems, including obesity and diabetes, will finally be solved. **Michael Gross** reports.

In antiquity, soothsayers used to inspect the entrails of animals, specifically the liver and intestines, to derive information about people's fates. One famous example of the practice resulted in the warning to Julius Caesar to "beware the Ides of March".

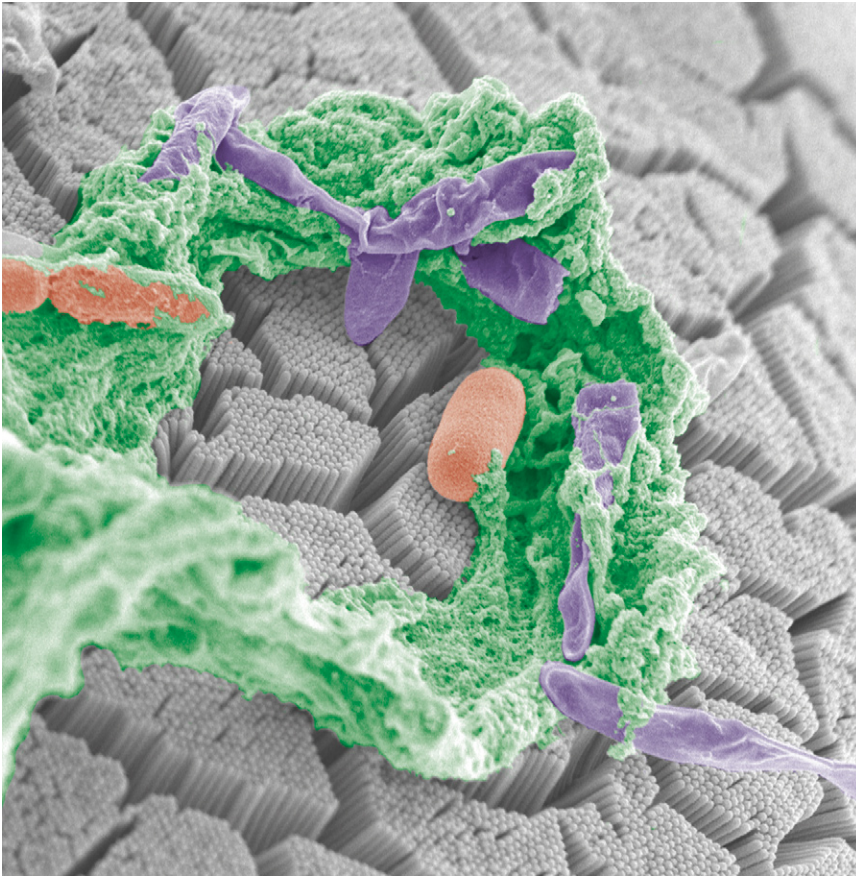
Modern times have been quick to dismiss this procedure, known as extispicy, which was widespread from the Hittites through to the Etruscans and Romans, as pure superstition. Now that we have learned to decipher DNA sequences, the fate of each living thing and each person (apart from unpredictable external influences) is surely to be read from their genomes.

Accordingly, researchers have studied genomes in great detail and learned a lot about evolution, development, and biological function, but they still haven't discovered the ultimate causes for common problems like obesity, heart disease, diabetes, and autism.

Maybe the clues to a person's fate are in the intestines after all? Since the publication of the first catalogue of microbial genes from human guts, the 'gut microbiome' (i.e. the collective genome of the resident species) in 2010, genomic analysis of our commensal bacteria has become a widely used approach that could even be called fashionable. But first signs are indicating that some of the long-lost answers to important medical questions may actually show up in the intestines.

Life inside us

In March 2010, researchers from the BGI in Shenzhen, China, and the international MetaHIT (Metagenomics of the Human Intestinal Tract) consortium reported a catalogue of 3.3 million different gene sequences from human intestines, representing around 150 times as many genes as are found



Gutsy guests: Bacterial cells in our bowels outnumber our own body cells ten to one, and they carry more than 100 times more different genes than our own genome. Recent research suggests that the composition of the gut microbiota can have dramatic effects on human health. (Image: Courtesy of Mattias Bergentall and Fredrik Bäckhed, University of Gothenburg.)

in the human genome (*Nature* (2010) 464, 59–65). The study led by Jun Wang and Dusko Ehrlich created more than 500 gigabases worth of sequence length using faecal samples from 124 people.

The researchers concluded that each individual typically harbours at least 160 different bacterial species and that the number of species covered by the sequences obtained is just over 1,000. They described a minimal gene complement for human gut bacteria as well as a minimal gut metagenome, defined as the set of genes represented in all individuals studied.

Since then, further studies have added to our understanding of the diversity of life within our bowels. Recently, the groups of Peer Bork at the EMBL in Heidelberg, Germany and George Weinstock at Washington University, St. Louis, USA, expanded the range of analysis by combining MetaHIT's gut metagenomes from 207 European individuals with the results of the US Human Microbiome Project

based on 51 individuals (*Nature* (2013) 493, 45–50).

With these data, the researchers carried out a detailed analysis of the variability of the gut metagenome. They identified more than 10 million single nucleotide polymorphisms (SNPs), along with more than 100,000 insertions/deletions. In their detailed analysis of the SNPs, the researchers found that the rate of synonymous to non-synonymous variations is constant across individuals. From this, they concluded that the parameters specific to each human host are relatively unimportant for the evolution of the bowel bacteria compared to the constraints that are common to all humans.

Comparing different samples taken from the same individual at time points up to one year apart, the researchers also found that the specific metagenome variation profile of each host individual remains constant over that time. However, as this part of the study was limited to 43 individuals and one year, the authors acknowledge

that a longer and wider analysis is required to confirm that conclusion. Larger datasets will also be needed to establish which role geographical and ethnic divisions between human populations are reflected in the diversity of their gut microbiomes.

Can bacteria make us fat?

Scientists are now scrutinising our 'second genome' — much larger than the one in our cells — for clues to common diseases, an area where the search for SNPs in the human genome has been largely disappointing. One key area where the intestinal microbes may very well decide our fates is that of obesity and related diseases, such as diabetes and heart disease.

Several researchers have found connections between the gut microbiota and body weight. In an early contribution published in 2004, Jeffrey Gordon's group at the Washington University School of Medicine in St. Louis used germ-free mice to show that gut microbiota could make mice accumulate more fat by regulating some key genes in lipid metabolism. (*Proc. Natl. Acad. Sci. USA* (2004) 101, 15718–15723).

Inspired by Gordon's findings, Liping Zhao, who had put on an unhealthy amount of weight during a postdoctoral stay in the US, monitored his gut microbial communities when he returned to his native China and embarked on a slimming programme. Losing 20 kg in two years with the help of prebiotics and traditional Chinese medicinal food, he also drastically changed the composition of his commensal microbiota. For instance, the bacterium *Faecalibacterium prausnitzii*, which is thought to have a beneficial, anti-inflammatory effect in the intestines, rose from being undetectable to making up 15% of his intestinal flora.

Following this successful self-medication, Zhao embarked on several studies into the connections between gut microbiomes and body weight, including both animal models and clinical trials. Most recently, he studied the changes of the gut flora of a morbidly obese volunteer who lost more than 50 kg starting from a peak of 175 kg.

Zhao and his colleague Na Fei, both now at the Shanghai Jiao Tong University in Shanghai, China, observed that an endotoxin-producing species of *Enterobacter* was the most drastically

reduced microbial species during that transition. The species had made up 35% of the microbiota before the slimming course, and became undetectable after 23 weeks. After transplanting an isolated strain of this bacterium into the guts of germfree mice, which are normally resistant to gaining weight from a high-fat diet, they found that all mice fed a high-fat diet became obese (except one which died from an infection in the first week). The researchers concluded that this *Enterobacter* species is likely to be causally linked to obesity in humans (ISME J. (2013) 7, 880–884).

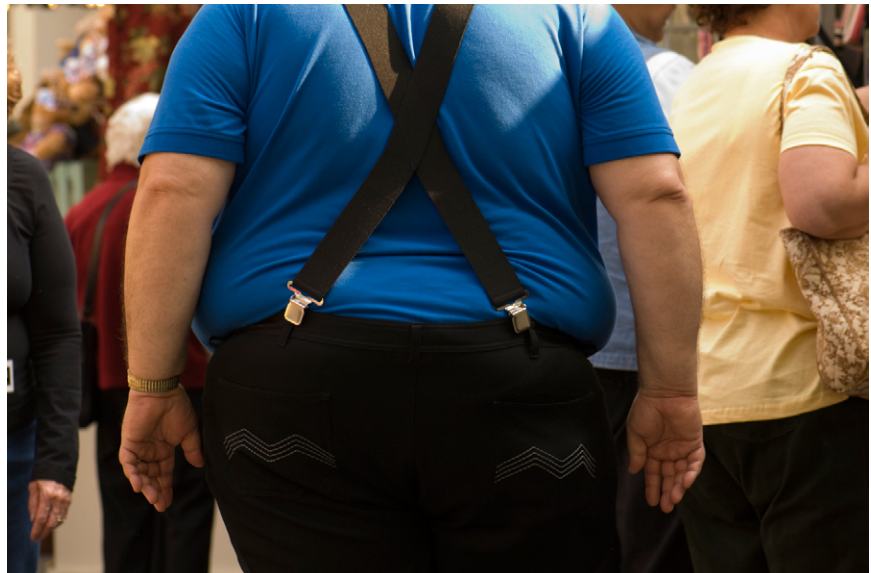
“As we followed the essence of Koch’s postulates for identifying the pathogen for a disease, we regard this strain of *Enterobacter* as a ‘pathogen’ for obesity disease,” Zhao explains. “We expect to find more such ‘obesity pathogens’ following the protocol established in this study.”

... or thin?

Intestinal bacteria may even be behind weight-loss effects hitherto considered as purely a question of plumbing. The groups of Peter Turnbaugh at Massachusetts General Hospital and Lee Kaplan at Harvard University showed that gastric bypass operations (technically referred to as Roux-en-Y gastric bypass or RYGB) induce shifts in the gut microbiota, and that a transplant of bacterial communities has exactly the same slimming effect as the operation (Sci. Transl. Med. (2013) 5, 178ra41). Thus, instead of invasive surgery, patients with dangerous obesity might in the future be treated with faecal transplants from slimmer people.

At the moment, the ‘yuck factor’ and the poorly defined nature of the cure, which might also contain pathogens, means that only a few doctors are transplanting faeces, and only in situations where no other treatment exists, such as severe *Clostridium difficile* infections. This opportunistic bacterium can invade the guts when the native bacterial community is decimated by broad-spectrum antibiotics, and is therefore very difficult to treat with antibiotics.

In the last chapter of her new book, *Gulp: Adventures on the Alimentary Canal*, famously fearless science writer Mary Roach investigates the current use of faecal transplants. She reports that Alexander Khoruts from the University of Minnesota has so far carried out more than 40 such transplants to



Holding up: Although there is no shortage of reminders that obesity leads to a whole host of health problems, the richer countries are in the grip of an obesity epidemic that resists all educational approaches. Gut microflora is likely to be part of the problem and may also help to find new solutions. (Image: iStockphoto.)

treat *C. difficile* problems, with a success rate of over 90%. She traces the practice back to the 1950s, when doctors tried out bacterial transfers as a way to combat severe diarrhoea after early antibiotics treatments.

The group of Max Nieuwdorp at the Academic Medical Centre in Amsterdam, Netherlands, carried out a clinical trial to assess the effects of faecal transplants on patients with metabolic syndrome, a type of obesity linked to insulin resistance and identified as a risk factor for diabetes. The placebo-controlled trial found that the insulin response nearly doubled in morbidly obese patients six weeks after infusion with gut microbiota from lean donors (Gastroenterology (2012) 143, 913–916).

In a follow-up study, researchers from the same institution are now investigating whether multiple transfers have a stronger long-term beneficial effect than a single transfer (trial registration number: NTR 2705).

Hormones have their say

Just how the gut microbiota interact with their hosts and can make them thin or obese remains to be fully understood. One additional complexity comes from the involvement of hormones, which may also explain gender bias in certain disorders related to metabolism.

The group of Jayne Danska at the Hospital for Sick Children in Toronto, Canada, studied the three-way

interactions between microbiota, hormones, and host metabolism in a mouse model of type 1 diabetes known as non-obese diabetic (NOD) mice. The research found that commensal microbes can elevate testosterone levels of the host, which in turn protects the host from type 1 diabetes. This protection depends on the function of androgen receptors (Science (2013) 339, 1084–1088).

In the mouse model — unlike in the human population, where the disease onset is typically before puberty — females are more at risk of type 1 diabetes. However, transplanting gut microbiota from adult male mice to immature females, the researchers were able to reduce the females’ risk to a level comparable to that of the males. By contrast, NOD mice lacking a bowel flora (germ-free conditions) had a very similar diabetes risk for both sexes.

Screening for metabolites, the researchers identified a group of glycerophospholipid and sphingolipid metabolites that are markedly different in mice harbouring the typically male or typically female microbiota. Like other sex differences, these microbiome differences appear to emerge with sexual maturation.

Another recent study has found similar sex differences between fatty acids in humans (PLoS Genet. (2011) 7, e1002215). From this, Danska and colleagues conclude that the underlying principles are conserved

between mice and human and that a similar triangular regulation network between gut microbiota, sex hormones, and lipid metabolism also exists in humans and may hold clues to understanding and treating type 1 diabetes and other autoimmune diseases such as rheumatoid arthritis and multiple sclerosis (which both have a strong female-to-male bias in middle age).

Outlook

Following the first gene catalogue for the human gut microbiome, a rapidly growing volume of research has suggested that bowel flora could be very helpful in curing diseases that still pose challenges. Beyond the obvious metabolism-linked diseases like diabetes, some researchers have also suspected the bowel to be involved in neurological conditions such as autism.

It is perhaps an unhelpful side effect of the modern knowledge about bacterial pathogens and hygiene that there are still large psychological barriers to be overcome. Systemic problems also reside in the ill-defined nature of microbiota transfusions and the lack of a route to commercialisation. The pharmaceutical industry will naturally only develop an interest in such faecal matters if there is reasonable hope of developing a preparation that can be patented, packaged, and sold at a profit.

Researchers generally don't have much patience for the yogurt industry's claims of providing 'friendly bacteria' for our bowels, as many crucial species are anaerobic and wouldn't survive administration via yogurt. Still, it does not appear completely impossible that a generic package with helpful bacteria for our bowels can be developed.

Still, the ancient cultures weren't entirely wrong about consulting intestines to find out about people's fate. It has been argued that prehistoric herders may in fact have come up with the practice in an attempt to find out about health problems in their herds by autopsy.

In any case, it now seems plausible that people's chances for a long and healthy life depend not only on their genes and general good luck, but also on the specific composition of the microbial communities in their guts.

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Frugal fishing at hand

The European Union is on the cusp of major reforms to its fishing industry. First up on the agenda is a ban on fish discarding that is expected to be approved in June. But as **Cyrus Martin** reports, the solutions are complex, involving a combination of improved technology, better enforcement, and creative thinking.

In late February, the European Council of Ministers emerged from an overnight session with the news that they had finally reached an agreement on legislation to ban fish discards, the wasteful practice of throwing perfectly edible fish overboard. In recent years, it is estimated that 25% of the fish caught in EU waters, on average, are discarded, though this figure fluctuates widely depending on the species and fishery in question. Many of the fish heaved over the side are already dead or dying and benefit no one save the seagulls circling overhead. While clearly a priority, the proposed ban on fish discards is just one pillar of a much broader effort to reform the Common Fisheries Policy, which outlines the rules and regulations governing EU fisheries. Highlighting the need for reform, a recent report from the European Commission suggested that perhaps 75% of species in EU waters are overfished, and the Commission has put forward a range of proposals to both rescue fisheries that are in danger of collapse and promote sustainable fishing practices more generally.

EU policy makers have modeled their reforms on what are seen as successful management schemes elsewhere. The US approach in particular has served as a template with its comprehensive Magnuson-Stevens Fishery Conservation and Management Act, which in 2007 was overhauled in response to data suggesting overfishing in US waters. Part of the problem in the US was older, ineffective management schemes, such as approaches that dealt with the problem of overfishing by limiting the length of the fishing season, a window that could be adjusted based on the perceived health of fish stocks. This created a competitive situation among

fishermen that led to greater fishing effort in the form of bigger boats and more sophisticated technology, a battle played out in popular television shows such as *The Deadliest Catch*. The end result of this marine arms race was and is overfishing, which in turn leads to even shorter fishing seasons, starting the cycle anew. Not only does fishing become unsustainable under this scheme but the consumer suffers as well, as the short but intense fishing season leads to unpredictable gluts of product on the market and unstable prices.

To address the issue of overfishing, one of the key provisions of the updated Magnuson-Stevens Act is to set fishing quotas on each species and mandate that such quotas are set with the goal of achieving the maximum sustainable yield from the fishery. In the past, the total allowable catch in the US was influenced heavily by interested parties, such as the fishermen and processors, leading to inflated quotas and overfishing. Critically, the total allowable catch under the current US system is determined based on scientific advice, a practice European reformers hope to reinforce with the new reforms. And to specifically address the issue of competition between fishermen, the Magnuson-Stevens Act encourages the use of catch-share systems, in which each fisherman is allotted an individual quota, allowing him/her to fish at their leisure.

Though quotas are seen as the way forward, when combined with other factors they ironically can lead to increased fish discarding. At the heart of the problem is the crude nature of industrial fishing itself, in which huge trawling nets are dragged across the ocean bottom, collecting both target and non-target species alike. Under traditional quota systems, a boat might only be able to legally land certain species of fish and, though economically valuable, other species would have to be thrown overboard. In the past, vessels would illegally bring these fish to the black market by conspiring with producers on shore. This problem recently plagued the Scottish mackerel fishery, and the fishery is rather unique in Europe in having been answerable to the law. As fisheries scientist Paul Fernandes explains, "This was probably commonplace up until