Slimming for slackers

Imagine being able to eat exactly what you liked and stay magically svelte. A new set of bugs living in your digestive system might do the trick, says **Bijal Trivedi**

IN A nondescript building on the medical campus of Washington University in St Louis, Missouri, among the parking lots blazing in the summer sun, lives a group of remarkable mice. Housed in miniature plastic bubbles, the mice lead a sterile existence separated from dirt and microbes by a double airlock that ensures that their food and water arrives untainted by bacteria. These mice are germ free. The trillions of microbes that would normally live inside their guts are entirely absent. But this is no experiment in ultra-cleanliness. These mice may hold the key to tackling the global obesity epidemic.

Worldwide, more than a billion people are overweight; of these, 300 million are obese. In the US, 65 per cent of adults are either overweight or obese. And the numbers, like our waistlines, just keep on growing. It seems that most of us are either unwilling or unable to make the lifestyle changes necessary to stay slim. Despite billions of research dollars spent on weight loss schemes, we're no nearer to finding that magic bullet. And that's what makes the St Louis mice so intriguing.

Encapsulated in their sterile bubbles, the germ-free mice gorge on rodent chow. They eat and eat and eat, and yet they do not get fat. If a normal mouse ate that much it would quickly balloon up. But the mice in the bubble stay magically svelte. According to Jeffrey Gordon, director of the Center for Genome Sciences at Washington University, who is orchestrating the experiments, that's because of what is going on – or rather, not going on – in their guts.

Late last year Gordon and Fredrik Bäckhed, a postdoctoral fellow in his lab, published a study comparing the germ-free mice with a group that were genetically identical but had a normal complement of gut bacteria. They found that the germ-free mice were indeed unusually slim – they had 42 per cent less body fat than their normal counterparts. The finding was particularly intriguing because the germ-free mice ate 29 per cent more food than the conventional mice (*Proceedings of the National Academy of Sciences*, vol 101, p 15718).

But when Gordon and Bäckhed exposed the germ-free mice to microbes, filling their guts with the normal complement of bacteria, they packed on the pounds, so to speak, and hit the same weight as the other mice in just two weeks, despite eating less. Somehow, being germ-free was keeping the mice thin.

And Gordon thinks he knows why. Gut microbes, he says, play an important, if unquantified, role in digestion. For one thing they wrest calories from otherwise indigestible material such as plant fibres. The sugar-loving *Bacteroides thetaiotaomicron*, for example, which accounts for about 6 per cent of all microbes in the colon, produces the largest arsenal of carbohydrate-busting enzymes of any microbe sequenced so far – more than 240 compared with 98 in humans. These enzymes enable it to break down fibres packed with xylose and arabinose sugars and feed those otherwise inaccessible nutrients to its host.

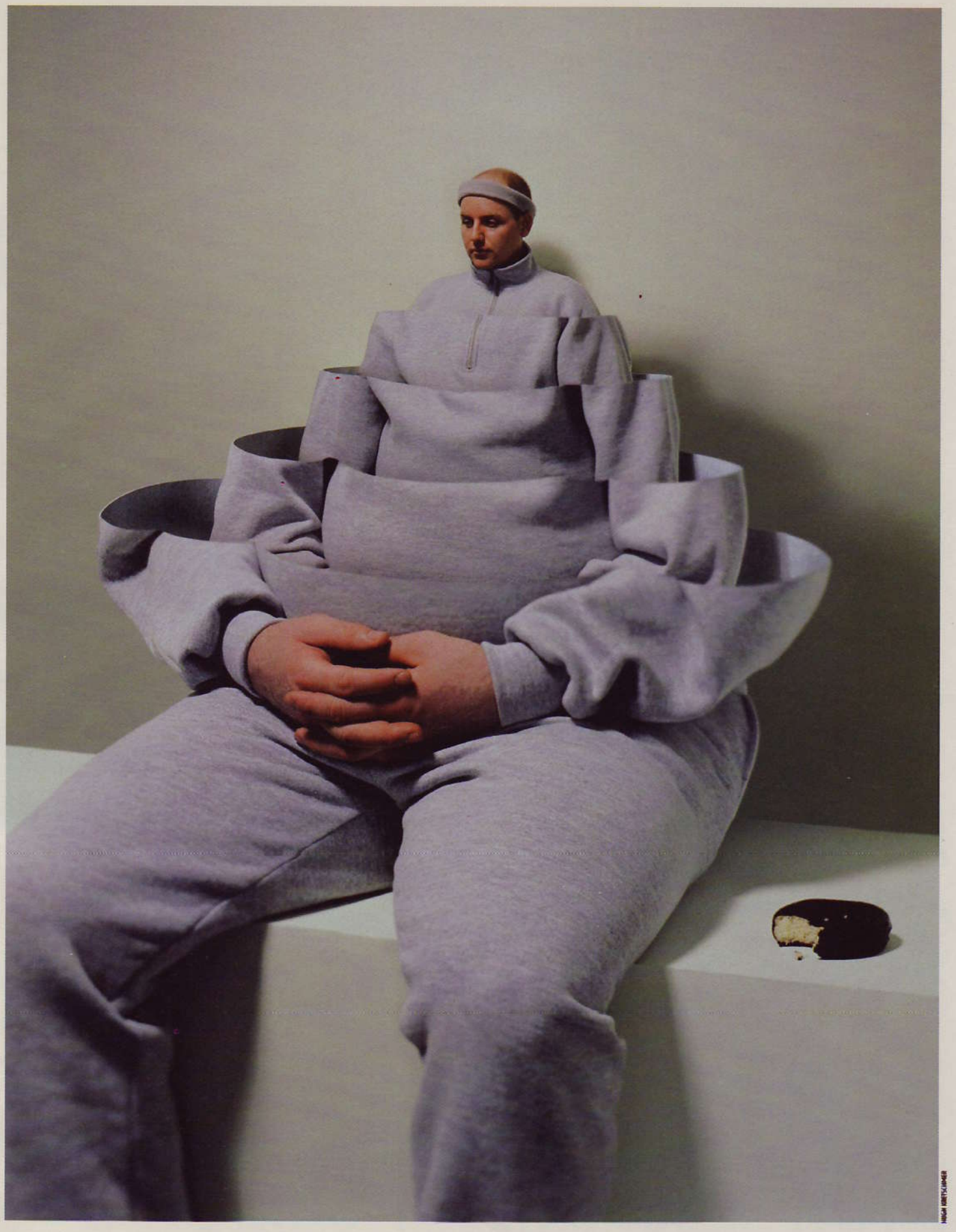
Little manipulators

But bacteria don't just supply us with extra calories. "The microbes have evolved elegant strategies for manipulating our genes," says Gordon. In mice, Gordon and Bäckhed found that the gut bacteria collectively and selectively suppress a protein called Fiaf (fasting-induced adipocyte factor). Fiaf inhibits fat storage, so suppressing it encourages the laying down of fat. Germ-free mice have nothing suppressing Fiaf , which helps them stay trim.

Of course, it's unlikely that anyone would opt for life in a sterile bubble to avoid piling on the pounds. But even so, Gordon thinks the mouse studies are directly relevant to people.

"We are not alone," says Gordon gleefully. He takes a mischievous pleasure in the fact that the human gut houses a staggering 10 to 100 trillion microbes from 500 to 1000 species – more than 10 times the number of cells that make up the human body. Genetically speaking, says Gordon, we are more microbe than human.

The identity of almost all of these microbes, and what they are doing, remains largely unknown. In the 1960s, scientists led by ▶



"For one person a serving of Cheerios could have fewer calories, depending on their gut bacteria"

Edward and Lilian Moore of the Virginia Polytechnic Institute in Blacksburg started cultivating, characterising and naming human gut bacteria, collectively known as the gut flora. They catalogued several hundred species but the work was gruelling and slow, and eventually the funding dried up. But in the past few years the study of gut bugs has enjoyed a renaissance, says microbiologist Abigail Salyers of the University of Illinois at Urbana-Champaign. With advances in gene sequencing and molecular phylogenetics and the advent of PCR for amplifying DNA, a high-speed head count of the gut flora is now feasible.

As a result of such studies, it's becoming clear that our gut microbes play a significant role in digestion. Our microbes have co-evolved with us, forging mutually beneficial relationships. They receive room and board in exchange for labour and chemical currency. Just as in mice, our microbes break down otherwise indigestible plant fibres into basic nutrients such as simple sugars and short chain fatty acids, which are absorbed into the bloodstream. Each species of bacterium brings with it a unique set of genes, and Gordon estimates that all the genomes combined probably contain 100 times as many genes as those in the human genome. "The microbes endow us with traits that we didn't need to evolve on our own."

But not everybody has the same complement of gut microbes. An individual's microbial brew is unique and reflects the history of the first two years of their life. In humans, as in other mammals, the fetus is bacteria-free. A newborn gets its first major bacterial inoculation as it slides down the birth canal. A baby's bacterial community continues to expand during suckling and weaning. After the first few months of life, some bacteria from food and other environmental sources take up residence. By age 2, the gut's dramatis personae is complete.

We don't yet know how many different species of bacteria exist in the human gut, but there are some clues. In June, David Relman, a microbiologist at Stanford University in California, published a molecular census of the gut flora in three healthy adults (*Science*, vol 308, p 1635). Relman and his colleagues discovered 395 phylotypes (the bacterial equivalent of species), 62 per cent of which appear to be n ew. Relman calculated that if he continued to sample DNA from these three individuals, the total number of phylotypes would reach about 550, in line with the current best guess of 500 to 1000 phylotypes in total. But the study also revealed that each of the three adults carried varying microbial assemblies, leading Relman to believe that even 1000 phylotypes is probably a huge underestimate. "The number of species of gut microbes might be many thousands – five, six, seven thousand. It's impossible to say."

Gordon's hypothesis is that this variation between individuals might mean that some people are significantly better than others at extracting energy from food and routing it for storage in the fat bank. In other words, your individual gut flora could predispose you to obesity. "For one shopper a 170-kilocalorie serving of Cheerios could actually have significantly fewer calories," says Gordon, "whereas another shopper could be getting the full caloric load depending on the type of bacteria in their gut." And it doesn't take a lot of excess calories to make you gain weight. Just 20 more a day than you need – about the amount in four pistachio nuts – will add about a kilogram of fat over a year.

Your gut bugs extract calories from fibrous material such as vegetables and feed them to you

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Relman agrees this is an intriguing idea. "You can't exclude the possibility that differences in flora might be linked to differences in fat storage," he says.

But Gordon isn't just interested in whether your gut bacteria can make you fat. He thinks that by deliberately manipulating them he could make you thin again.

The first step was to find out whether gut flora differs in a quantifiable way between the lean and the obese. In August Gordon and another postdoc, Ruth Ley, published a study of three types of mice, genetically identical except for mutations in the *obese* gene, which codes for a hormone called leptin that controls energy balance. Mice in the first group had both copies of the gene disabled and were grossly fat, eventually gaining so much they couldn't walk. The other two groups, with one or two functional leptin genes, were both lean.

The comparison revealed a huge difference

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in gut flora (*Proceedings of the National Academy of Sciences*, vol 102, p 11070). In the lean mice, microbes belonging to the *Bacteroidetes* division dominate, but in obese mice the proportion of *Bacteroidetes* plummeted by 50 per cent and another division, *Firmicutes*, rose by 50 per cent to claim the top spot.

So far so good. But that doesn't tell you whether the change is cause or effect. Do the microbes contribute to obesity, or does obesity simply reshape the gut flora? Answering that question will be enormously difficult, especially as the mouse gut flora has yet to be fully catalogued, but perhaps not impossible. For example, you can "seed" germ-free mice with specific microbes – a process known as creating "intentional communities" – to see what effect it has on their weight.

It's also not yet clear how relevant the mouse findings are to humans. To probe that question, Gordon has embarked on a new project with gastroenterologist Samuel Klein, an expert on obesity and weight loss at Washington University. Together the pair will study what happens to gut bacteria as 20 obese people lose weight by going, either a low-calorie, low-fat or low-carbohydrate diet. Gordon will sample the gut bacteria before, during and after the trial to see if and how the gut flora changes. The experiment should provide some initial information about the relationship between gut bacteria and obesity in humans, though it is not aimed at finding whether gut flora is the cause.

Less is more

"I would expect a change in gut bacterial flora with these dramatic changes in diet," says Klein. And though he acknowledges that the experiment won't separate cause and effect, he says the link between gut flora and fat storage is a tantalising lead. "[Helping] people eat fewer calories without focusing on their calorie intake – that really is the zillion dollar question," he says.

One person who has no doubt that the gut flora can play a role in obesity is Jeremy Nicholson, who heads the biological chemistry division at Imperial College London. "There are 1 to 1.5 kilograms of gut microbes in the average human body – 10 times as many microbial cells as there are cells in your body – so it's not surprising that they have a big contribution to make toward metabolism," he says.

Nicholson spends his days analysing biochemicals in urine and other body fluids to create "metabolic profiles", and he has seen for himself what a difference the gut flora makes.

> "We are in a new world where microbes are much more in control of us than we can imagine"

Abnormal gut microbes, for example, profoundly change the biochemistry of urine. "Gut bugs seem to influence everything," he says. "Drug metabolism, toxicity, efficacy, and, of course, food digestion."

Nicholson's own experiments with germ-free mice show that introducing gut microbes leads to "astronomical" metabolic changes. More intriguingly, he has found that changing the fat content of mouse or rat diets also has a huge effect. "One of the most profound effects we see as soon as we put them on a high-fat diet is the gut microbial metabolic signature changes," says Nicholson. "We are not sure whether this is because the microbe species change or whether gene activity changes in response to dietary input – probably both."

"We are in a new world now where the microbes might be in much more control of us than we can possibly imagine," Nicholson says, adding that gut bacteria could be the source of at least 30 per cent of our dietary calories. "The gut microbes could be the most important part of the jigsaw puzzle. They connect diet to our metabolism. They could be the linchpin in the whole problem."

This offers a ray of hope, because we are learning to manipulate our gut microbes. Glenn Gibson is a microbiologist at the University of Reading in the UK who studies how our gut biology affects our health. He says there are two known nutritional routes to altering your gut flora. The first is probiotics, which contain live bacteria and other microbes. The other is prebiotics, non-living dietary supplements that encourage the growth of bacteria already in the gut. Together these are a thriving industry with a market worth upwards of $6 billion a year.

One prebiotic Gibson has tested extensively is fructo-oligosaccharide, which is present in many fruits and vegetables, including chicory, artichokes, bananas and onions, and enhances the proliferation of certain bacteria that are depleted in some gut diseases. "But you would need to eat a few sackfuls of onions to get the 5 grams a day needed to change your gut flora, so we take the active ingredient and put it in supplements or food," says Gibson. Fructo-oligosaccharide isn't implicated in obesity, but lab experiments and double-blind human studies using it suggest that it is indeed possible to deliberately alter the inhabitants of your gut.

Whether it will ever be possible to tweak gut flora to cure obesity remains to be seen. But even if it isn't, Gordon believes his research will lead to important insights. He wants to use the gut microbes as guides to learn which genes to target with new therapies. Manipulating *Fiaf*, for example, could potentially be a way to prevent weight gain. Gordon also believes that his work can benefit people in the less well-fed portion of the planet. He suggests that by manipulating people's diet to match their gut flora, you could ensure maximum extraction of calories. In the end, says Gordon, there's a lot to be gained from extending our view of ourselves as a life form. ●

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