Gut reaction

Drugs and the microbiome can change each other in complex and little-understood ways. **By Neil Savage**

If cholesterol-lowering drugs are being impeded by the bacteria in some people's guts, Sony Tuteja is hoping to work out how.

Statins sometimes do a great job at reducing the amount of low-density lipoprotein (LDL), the 'bad' cholesterol that raises the risk of heart attacks and stroke, in the blood. But a lot of people see less of a benefit, and some none at all. In a 2016 study, 46% of those treated with the drug rosuvastatin saw their LDL drop by 50% or more[1]. But 43% saw a less than 50% decrease, and 11% had no reduction, or even had an increase in LDL.

The reason for the variation isn't clear, but Tuteja, a pharmacogeneticist at the University of Pennsylvania in Philadelphia, thinks the hundreds of species of bacteria in the intestinal tract might be involved. It could be that the drug throws the microbes out of balance in a way that alters cholesterol metabolism, or that certain strains of bacteria render the drugs less effective. Or, Tuteja suggests, "it could be bidirectional – the microbiome is affecting the drug and the drug is affecting the microbiome".

Her hypothesis, which she is testing in a clinical trial, is that statins reduce circulating LDL by promoting the growth of gut bacteria that produce bile salt hydrolases – enzymes that break down the bile acids used to digest fatty foods. The liver makes bile salts out of cholesterol, so as bile acids are broken down, the organ pulls more cholesterol out of the blood to replace them – lowering the levels of LDL in the blood. If some strains of bacteria don't produce as many hydrolases, that could explain why statins are less effective in some people. Or perhaps, as statins lower LDL levels, the gut is made more congenial for some bacteria and less so for others. In Tuteja's trial, about 50 volunteers will take rosuvastatin for 8 weeks; she will then compare the count of difference species of bacteria in their guts with that in people taking a placebo, to see whether the drug changes the make-up of the microbiome. Tuteja and her team will also compare the distribution of bacteria with levels of bile acid in blood and faeces and the amount of LDL in the blood, to see whether the species present in the microbiome at the beginning of treatment can predict statin effectiveness.

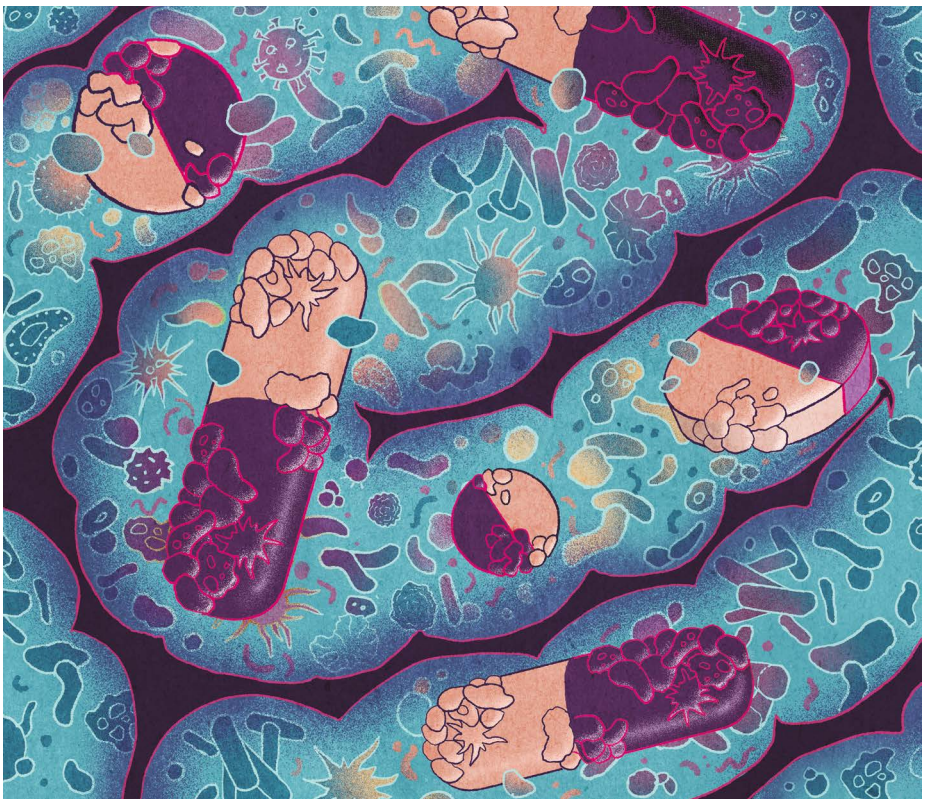

ILLUSTRATION BY ANTOINE DORÉ

Tuteja is one of a growing number of researchers looking into the gut microbiome's role in drug metabolism, and whether it accounts for variations in how people respond to pharmaceuticals. A whole variety of drugs could be altering the balance of bacterial species, disrupting the digestive system or causing other problems. And gut bacteria produce a range of enzymes and metabolites that might chemically alter drugs as varied as psychotropics and cancer treatments, rendering them less useful or leading to more side effects.

Understanding the interplay between microbes and medicine could lead to new therapies, or to changes in how existing drugs are prescribed. For example, physicians might be able to predict how a person will respond to a particular drug on the basis of their gut bacteria, and change a person's prescription accordingly. Dietary changes or antibiotics might also be recommended to make a person's gut microbiome more receptive to a drug.

The gut microbiome should be seen as a virtual organ in its own right, argues Ted Dinan, a psychiatrist at APC Microbiome Ireland, a research centre at University College Cork. Such is its importance to drug metabolism, he says, "in a few years neither the US Food and Drug Administration nor the European Medicines Agency will license any drug unless its impact on that virtual organ has been studied". (Another researcher at Microbiome Ireland, Niall Hyland, has received a €100,000 (US$110,000) Global Grant for Gut Health, which is supported by Nature Research – part of *Nature*'s publisher, Springer Nature – and probiotic company Yakult, based in Tokyo.)

Back and forth

Pharmaceuticals and bacteria have an undeniable effect on each other. In 2018, researchers screened more than 1,000 drugs, marketed for various conditions, against 40 strains of human gut bacteria. They found that nearly one-quarter of those drugs had antibiotic

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effects, even though none of them were being sold as antibiotics[2]. And in 2019, another team found that of 271 drugs incubated with gut microbes, 176 were metabolized to such an extent that the level of the drug dropped by more than 20%[3].

Dinan and his colleagues are examining what part the microbiome plays in mental health, including whether it interacts with psychotropic drugs. Evidence suggests that low diversity of gut microbes is associated with mental-health conditions such as schizophrenia. Researchers at Microbiome Ireland showed that it was possible to essentially transplant a mood disorder into rats by wiping out their native microbes with antibiotics and then giving the rats a dose of gut bacteria from people whom Dinan was treating for depression[4]. "When they got a transplant from depressed patients, their behaviour was significantly altered," Dinan says. That's a strong sign that the microbiome can affect mental health, he says.

This finding might have implications for the practice of faecal microbiota transplantation, an emerging treatment for gastrointestinal illnesses such as irritable bowel syndrome. Currently, donated faecal matter is tested for infections that could be passed on, such as hepatitis C. "Because of our study," Dinan says, "I'm convinced they should be looking at the psychiatric profile of the donor as well."

Researchers have also found that some bacteria can synthesize neurotransmitters, such as dopamine or acetylcholine, as well as precursor chemicals such as tryptophan, which is used to make the mood-regulating chemical serotonin. "We now know that certain good bacteria — bifidobacteria — are capable of synthesizing tryptophan," Dinan says. But the molecule is also found in foods such as turkey, and it is not known how much of the tryptophan that makes it to the brain comes from diet and how much is produced by bacteria.

Hearts and minds

As they learn more, physicians might want to take into account a person's particular mix of microbes when prescribing psychotropic drugs. Two species of gut bacteria, *Enterococcus faecalis* and *Eggerthela lenta*, metabolize the drug L-DOPA, which is used to treat Parkinson's disease[5]. Scientists have long known about an enzyme in the body that breaks down the drug and decreases the amount that makes it to the brain. Usually, physicians prescribe a second drug alongside L-DOPA to partially counteract the breakdown, but breakdown of the drug by bacteria is not currently factored in. Researchers have, however, identified a molecule that inhibits *E. faecalis*'s activity. "There is some potential for translating this data if a company or someone was interested," says Peter Turnbaugh, a microbiologist at the University of California, San Francisco, who collaborated on the discovery.

The idea that bacterial metabolism affects how well drugs work is not new, Turnbaugh says. Back in 2013, he and his colleagues found a pair of genes in *E. lenta* that give it the ability to digest the heart-disease drug digoxin[6]. When they fed mice the amino acid arginine, however, digoxin levels stayed high. The researchers are not sure why that's so, but it means that giving arginine along with digoxin could protect the drug. And there are signs that the bacterium might be responsible for the variation in how people respond to the rheumatoid-arthritis drug methotrexate. "We've known for almost a century now that the microbiome matters for drugs, but people have sort of ignored it," Turnbaugh says. "Most development of drugs, as well as their use in the clinic, is microbiome-naive."

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A detailed understanding of which microbiota interact with which drugs, and the mechanisms behind those interactions, could suggest ways to either inhibit or enhance the interaction between drugs and the microbiome. Some mechanisms are known. For instance, the colon-cancer drug camptothecin-11 is metabolized by the liver into an inactive molecule; enzymes produced by gut bacteria, however, can reactivate it into a toxic form, causing severe diarrhoea. Researchers at the University of North Carolina at Chapel Hill have come up with a compound that could target the enzymes without disrupting the microbiome — a potential treatment for the diarrhoea. And their spin-off company, Symberix, is developing treatments to reduce side effects caused by gut bacteria.

Complicated undertaking

But untangling the complex interaction between drugs and the microbiome won't be an easy task. For one thing, the various species of bacteria in the human gut have 150 times more genes than the human genome. And the selection of microbes present in the gut can vary a great deal from person to person. "My microbiome is really different from yours," says Anukriti Sharma, a microbiologist at the University of California, San Diego. "That means we might also have very different genes that are involved in metabolism." In fact, one of the limitations of microbiome studies is that they have mainly taken place in the United States, Europe and China, but microbiomes are known to vary widely from region to region. That can have consequences for medicine, says Turnbaugh. "If you test a drug in America, it could behave completely differently in Africa or in South America," he says.

Another issue is that there doesn't seem to be one common mechanism for how bacteria and drugs affect each other. "Each drug seems to have its own unique way of interacting with the microbiome," says Filipe Cabreiro, a biochemist at Imperial College London. That, he says, makes it difficult to draw any general conclusions.

Still, Cabreiro says, there are broad similarities in how certain classes of drugs work with the microbiome. Antipsychotics often change the balance of gut bacteria. Some cancer drugs are degraded or modified by chemistry in the gut that either enhances or reduces their effects (see page S16). Metformin, a common diabetes drug that Cabreiro is studying for its anti-ageing potential, seems to trigger certain signalling pathways in bacteria that changes the production of metabolites, which then have their own effects on the body. "We have to take it a drug at a time, a microbe at a time, and a disease at a time," Sharma says.

If that complexity can be worked out, the next step will be to look at altering the microbiome to enhance drugs' effectiveness or decrease their side effects. As with the heart medication digoxin, that could mean supplementing a drug with another compound that influences its mechanism of interaction. It could also mean trying to change the make-up of the bacterial community, whether through strategic use of antibiotics, dietary changes to promote or discourage particular microbes, or even faecal transplants to replace 'bad' gut bacteria with 'good' ones.

And it could make precision medicine more precise, with physicians sequencing not only the genes of patients but also of their microbes to predict response to a treatment. "For the future of personalized medicine," Cabreiro says, "you have to take into account not just the host, but the microbiome too."

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