Faced with the grim prospect of a world without antibiotics, we're discovering microbes could be more important to our health than even our genes. **Bruce Munro** talks to those who say radically rethinking our relationship with our body's 39 trillion microbes could literally be a matter of life and death.

GERMS ARE US

Kurt Krause has had a rotten few hours.

The University of Otago biochemistry professor has already had a full day, including giving a lecture and tutorial at the medical school.

Then things started to go wrong in one of the laboratories he oversees. A chromatography machine broke down mid-job. An attempted repair did not work. Frantic calls were made to technicians, to no avail. The samples were spoiled beyond retrieval.

It is now after 6pm, and Prof Krause is still at work. It has been a "cluster of horror", but he has still taken this telephone call because he believes the topic is important. People need to know.

He talks about one of many patients he saw during his years as an infectious diseases clinician.

"The patient had a left ventricular assist device. It's an enormously sophisticated mechanical device that is almost like an artificial heart," Prof Krause says.

"He was dying of heart failure. So, he had the device implanted to try to extend his life while he was waiting on a heart transplant.

"He developed an infection of this device. It was an incredibly resistant bacteria, resistant to all the antibiotics we had.

"His wife said, 'He's on a heart transplant list. What can we give him to kill this bug?' And I had to say,'I'm sorry. We don't have any antibiotic to give him'."

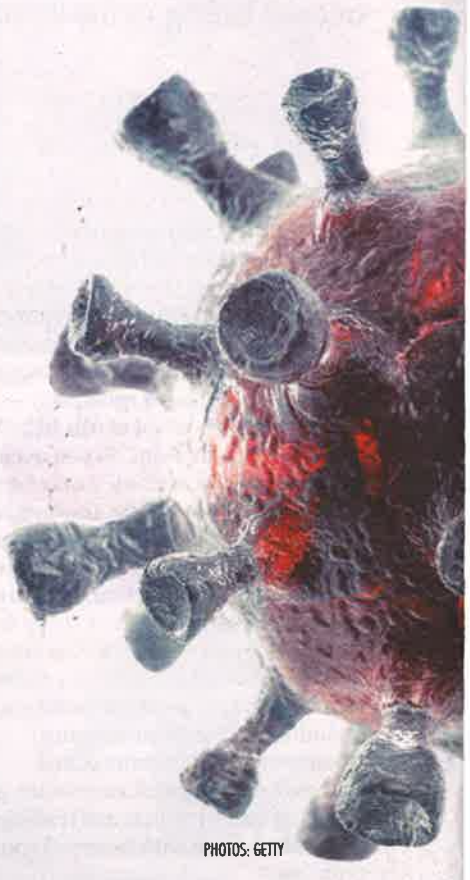
It is a story that is becoming alarmingly common says Prof Krause, who is now part of University of Otago efforts to help tackle the looming global threat of antimicrobial resistance.

> You cannot eliminate all microbes; all you do is create a space for tougher microbes

The World Health Organisation has called the rapidly growing number of bacteria, viruses and parasites that can no longer be killed by existing antibiotics, antivirals and the like, a "serious threat to global public health".

Already, almost half a million people a year worldwide develop multi-drug-resistant tuberculosis (Tb).

Drug-resistant strains of malaria are on the increase and are threatening to spread beyond northern South-east Asia.



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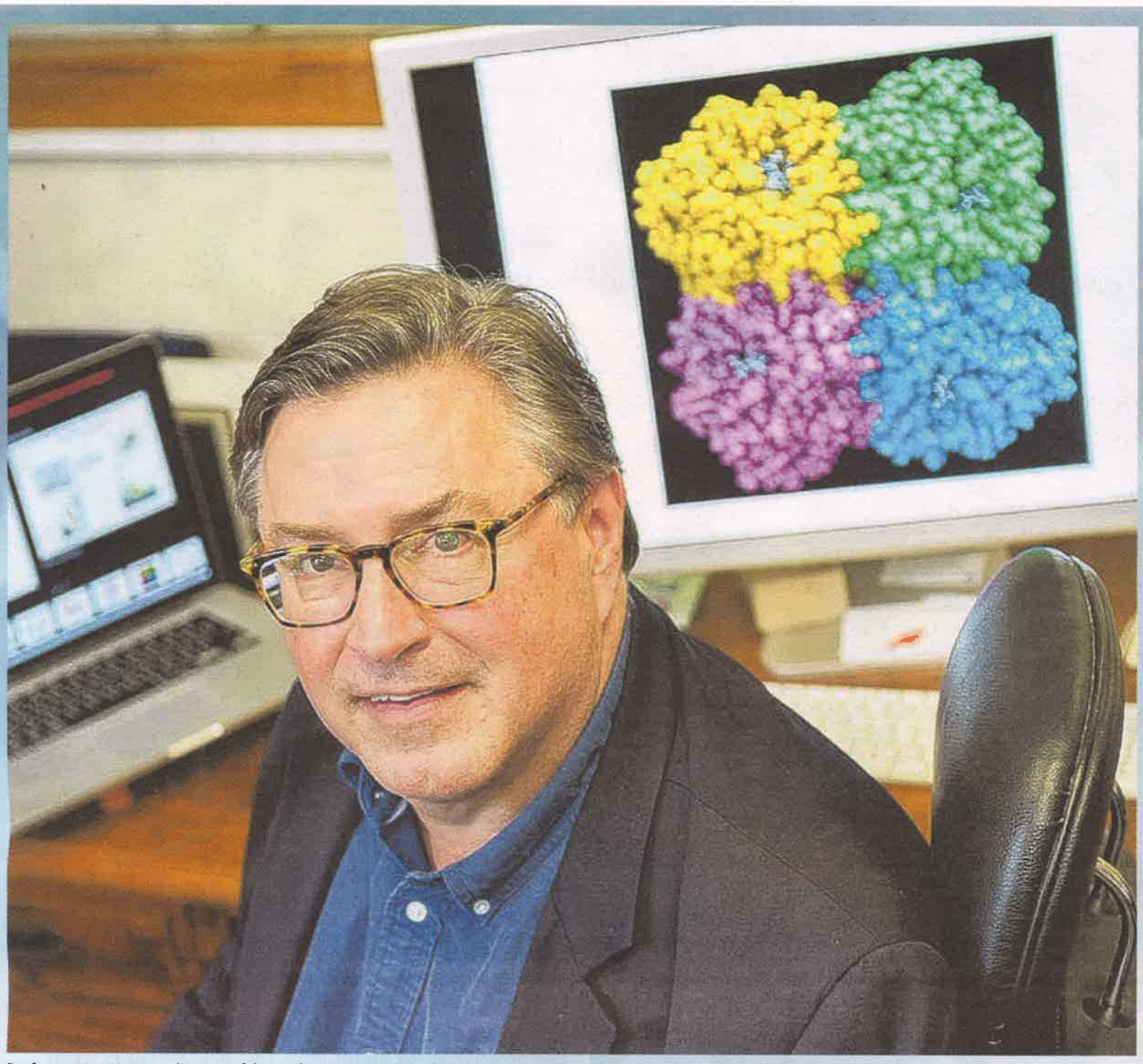

Professor Kurt Krause, director of the Webster Centre for Infectious Diseases, at the University of Otago, says microbial resistance demands an urgent rethink of our relationship with our microbes.

PHOTO: ALAN DOVE PHOTOGRAPHY

During the past seven years, the number of people with drug-resistant HIV has doubled in some countries, where it now accounts for up to 40% of people who are restarting antiretroviral therapy.

Without effective antimicrobials, medical procedures that need seriously sterile environments, such as major surgery and chemotherapy, would be much more risky, resulting in more deaths through infections.

And when it comes to influenza, virtually all influenza A viruses in humans are now resistant to at least two antimicrobial drugs.

Late last month, in the face of growing antimicrobial resistance in New Zealand, the Government announced it was taking new steps to understand and tackle the threat.

For decades, humans have been waging war on microbes, Prof Krause says.

But trying to wipe out disease-causing microbes has had exactly the opposite effect.

Doctors dishing out antibiotics too freely, patients not completing prescribed courses, a plethora of antimicrobial cleaning agents and heavy use of antibiotics in agriculture, it has all resulted in more and more microbes that cannot be killed by the limited number of antimicrobials in our armoury.

"You cannot eliminate all microbes; all you do is create a space for tougher microbes," Prof Krause says.

"If you use something that kills 99% of all bacteria, then the 1% it doesn't kill will grow there. And if you kill those bacteria, then the 0.1% that are really tough will grow there, right?"

It is a warning we have not yet grasped.

The number of antimicrobial drugs that are still effective in New Zealand is higher than in many other countries. But instead of using them sparingly, the rate of antibiotic prescribing in this country during the eight years to 2014 increased by almost 50%.

In the year to mid-2016, about 180,000 surgical operations were carried out in New Zealand hospitals, including almost 10,000 in the Southern District Health Board area.

Each year about 100,000 New Zealanders are hospitalised with infection as the primary cause.

Imagine, say doctors and scientists, the scale of the tragedy if there were no longer any effective antimicrobials to give those people.

In response, the World Health Organisation (WHO) has drawn up a global action plan and the United Nations has held a high-level meeting to try to speed up internationally-co-ordinated efforts to combat antimicrobial resistance.

Locally, University of Otago staff are involved in a variety of ways.

The WHO action plan was developed using software co-invented by Associate Prof Paul Hansen, of Otago's economics department. The software helped WHO prioritise the bacteria of greatest threat to humans.

Microbiology department senior lecturer Dr James Ussher has called on the government to

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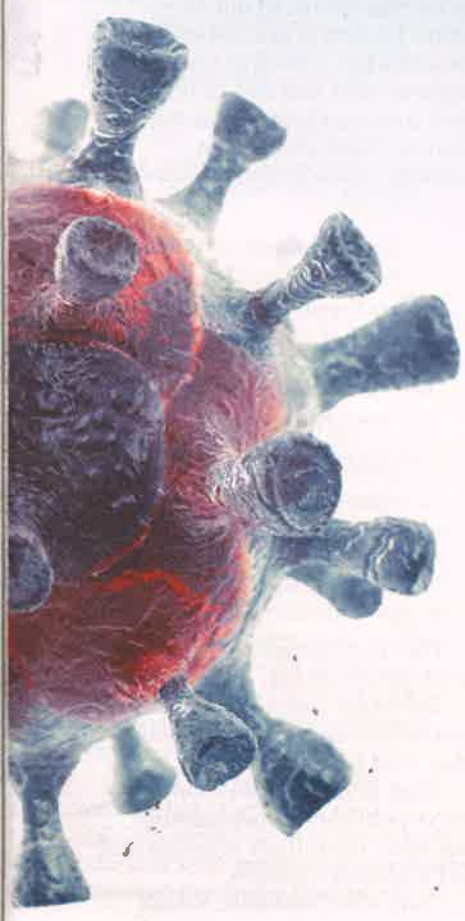

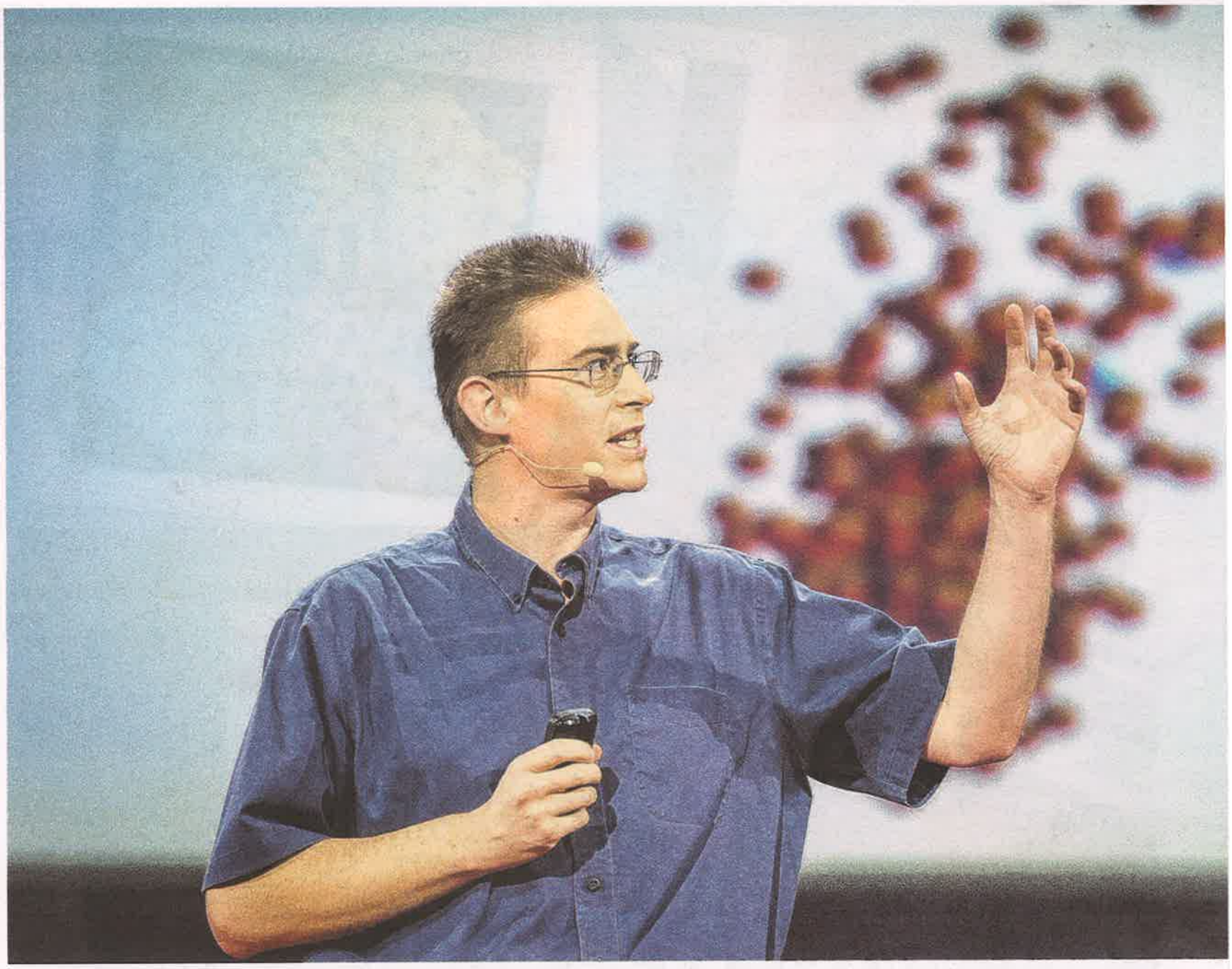

Dunedin-raised Prof Rob Knight, pictured in his San Diego laboratory, is at the cutting edge of a revolution in health driven by new understandings of the microbes in our gut. PHOTO: UNIVERSITY OF CALIFORNIA SAN DIEGO HEALTH

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invest more and district health boards to make sure antibiotics are used wisely.

Researchers in the biochemistry department are working to identify new compounds that could be part of the next generation of antibiotics.

But a "more of the same" approach will not be enough, Prof Krause, who is one of those researchers, says.

"We are trying to make new antibiotics — and we still need new antibiotics, no question about that — but I'm telling you, I think we have to go beyond that," he says.

He believes we need to completely rethink our relationship with microbes.

"For too long, the view has been that everything in our environment has to be sterile; we have to get rid of all that bacteria.

"There are thousands and thousands of species of bacteria. But only a very small number of them are pathogenic. The great majority of them are neutral — they don't care about us — or they are even helpful.

"So, rather than thinking about eliminating all bacteria from our surroundings, maybe we need to think about getting rid of bad bacteria and leaving the good bacteria."

And, he asks, could there be a way to "calm" threatening bacteria?

"When something revs them up and they start to act like they're going to cause disease . . . one approach is to say 'We have to eradicate it'.

"Maybe another way to go is to calm the bacteria down."

His comments reflect a worldwide seismic shift in thinking about microbes that is currently under way in academic and research circles.

Pioneering work on this was carried out by Otago's Prof Gerald Tannock.

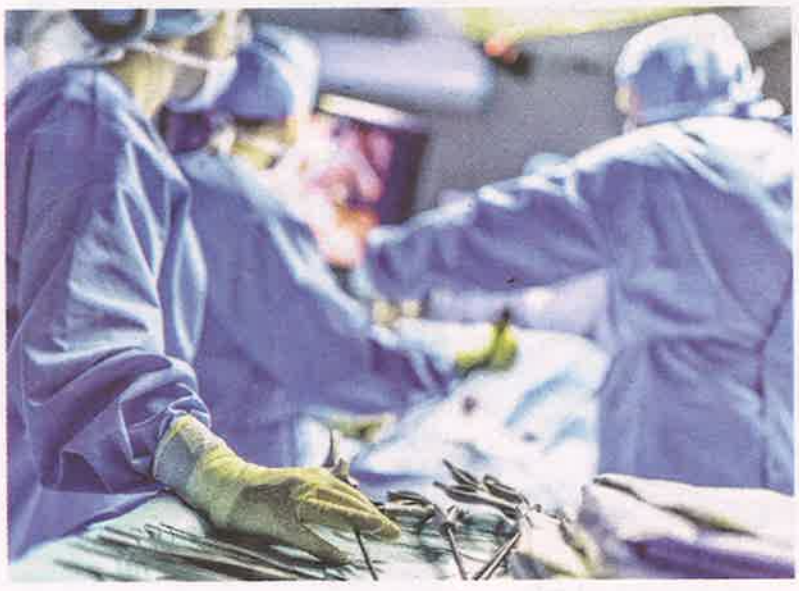
By the time the dust settles, the shake-up will probably fundamentally reshape our view of microbes and our practice of health.

At the forefront of the revolution is someone else with an Otago connection.

Rob Knight was raised in Dunedin. In 1996, he graduated from the University of Otago with a BSc in biochemistry. He did his PhD at Princeton, studied and taught elsewhere in the United States and then, in 2015, became director of the Microbiome Initiative at the University of California, San Diego (UCSD).

Prof Knight is a busy man.

He is professor of paediatrics and computer science and engineering at UCSD. His research focuses on improving the understanding of the human microbiome, the 39 trillion-odd microbes that each of us has living in and on our body. He is integrally involved in the US Government-funded Human Microbiome Project. He is co-founder of the American Gut Project and the Earth Microbiome Project. His research interests include understanding how the human microbiome relates to diseases ranging from obesity to mental illness. He is also developing new ways to give visual representations of the "big data" being generated by the current explosion in knowledge about microbes.



Each year about 100,000 New Zealanders are hospitalised with infection as the primary cause. Scientists say it would be a tragedy if there were no longer any effective antimicrobials to give those people. PHOTO: GETTY IMAGES

In 2012, a colleague said of Prof Knight, "Unless he burns out in the next 20 years, I think we'll look back at him as a pioneer".

Right now, Prof Knight is running errands before a flight to yet another conference, but still agrees to a phone interview.

A lot of what we know about human microbes we have only learned in the past five to 10 years, he says.

"A revolution in DNA sequencing made it literally a million times cheaper to sequence microbes from your gut," he says.

What we now know about those microscopic organisms that we have been waging war against, is that they are extremely important to human health.

"In addition to digesting our food, which we have known about for a long time, they are also really important to preventing a wide range of chronic diseases . . . They are doing a lot that we had no idea about until recently.

"The three pounds [1.5kg] of microbes that you carry around with you might be more important than every single gene you carry around in your genome," he says.

It is an astonishing and still somewhat controversial claim.

But the evidence is beginning to stack up.

Prof Knight has shown human microbes can be separated into distinct types, depending on where on and in the body they are found; oral, skin, vaginal and faecal.

It turns out that a newborn's microbes reflect the mother's microbiome, vaginal or skin, depending on whether or not the baby is delivered by Caesarean section. During the next two years, the child's microbiome slowly changes, developing the typical, distinct, human microbial communities.

But how the child is delivered seems to have some lasting impacts. Children delivered by C-section have higher rates of conditions such as asthma, allergy and obesity.

Prof Knight wondered whether microbes could be playing a role.

The evidence, from his laboratory and others, is that their role is far greater than could possibly have been imagined just a few years ago.

Mice given transplants of human microbes have grown either fatter or leaner, depending on whether they were given microbes from an obese or lean person.

In separate research, mice given transplants of microbes from children in Malawi with kwashiorkor, a form of severe malnutrition, lost 30% of their body mass in three weeks, but bounced back when given microbes from healthy children.

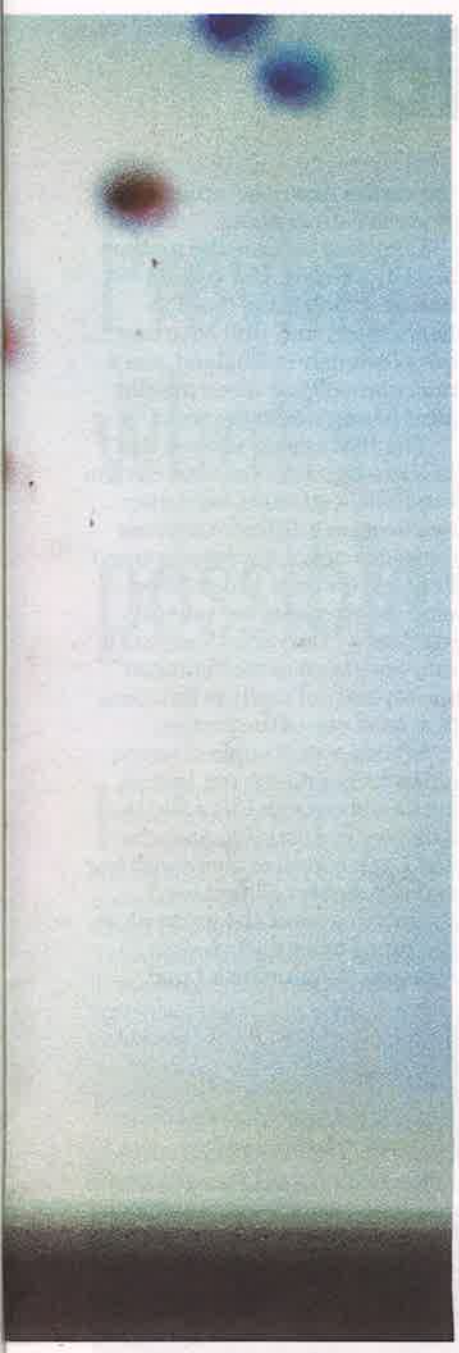
> The three pounds of microbes that you carry around with you might be more important than every single gene you carry around in your genome

The transformative promise it holds is tantalising.

The same applies to depression and autism and who knows what else, Prof Knight says.

"Just in the last few months we've published papers linking microbes to multiple sclerosis and to Parkinson's disease.

"And other labs have shown



Dr Monica Gerth, of the University of Otago's Maurice Wilkins Centre for Molecular Biodiscovery, is researching an antibiotic alternative, an enzyme that could "calm" bacteria before they cause disease. PHOTO: SUPPLIED

Keep calm and carry on

Dr Monica Gerth wants to become bacteria's equivalent of a horse whisperer.

In a world fast running out of effective antibiotics, she and other researchers at the University of Otago's biochemistry department want to swap the shoot-on-sight attitude to disease-causing microbes for a more soothing approach.

Dr Gerth is developing an innovative way of "calming" bacteria before they can cause infection. If effective, it could provide a new, less harmful means of preventing up to two-thirds of all human infections.

Many of our most deadly bacteria hang out on our skin or in our noses or respiratory tracts, but do not cause disease. Meningococcus, listeria, *Streptococcus pneumoniae*, *Staphylococcus aureus*; they all cause nasty and potentially fatal diseases. But each of them can be found in a quarter of human noses, doing not much.

It is only when they somehow get excited that they go from co-existing to overgrowth to disease-causing.

When overgrowth begins, many bacteria produce a biofilm, an inorganic matrix that allows them to evade antibiotics and grow undisturbed.

That is the point in the process that Dr Gerth's research is focused on.

"My research group is targeting a process that many bacterial pathogens use to communicate with one another, called quorum sensing," she says.

"We are engineering enzymes that work by degrading the chemical signals used by bacteria for quorum sensing.

"Blocking this communication stops biofilm formation before it can start, thus preventing a serious infection from occurring."

This process would have a massive advantage compared with traditional antibiotics. It does not try to kill the bacteria so it does not give the bacteria any reason to fight back and develop resistance.

Dr Gerth plans to file a provisional patent on the bacteria-calming enzyme later this year, but an effective product is probably still several years away.

they are linked to depression and autism. And what is amazing about that is it's not just a linkage but proving causality, at least in mouse models. So, in mice you can give a probiotic that acts as an antidepressant.

"In mice you can also transplant poo from someone who is depressed versus someone who is not depressed. And depending on whose they got, that changes the behaviour of the mice. And once again you can link that with particular molecules the microbiome is producing that interact with the immune system."

The autism research is "remarkable", Prof Knight says.

Prof Sarkis Mazmanian, a friend of Prof Knight's at the California Institute of Technology, showed that mice pups that had features of human autism such as compulsive behaviours and communication and social defects, which had been triggered by simulating a viral attack on the pregnant mouse before the pups were born, could be fixed with a probiotic.

"And most remarkably," Prof Knight says, "earlier this year, an alliance of different institutions in Arizona did a faecal transplant where they took a human with autism and transplanted faeces from a healthy donor.

"They showed you could relieve both the GI [gastrointestinal] symptoms and the cognitive symptoms of autism through the faecal transplant."

Faecal microbiota transplants have also provided extraordinary results for people with *C. difficile*, a bacteria that can cause colitis, a serious inflammation of the colon. Most people with the infection are hospital patients who have been given antibiotics that destroy their gut microbes, allowing the bacteria to take hold.

People who have had the painful and debilitating condition have reported dramatic and lasting improvements as quickly as one day after a faecal transplant from a healthy donor.

At Wellington Hospital, some colitis sufferers have been successfully treated with faecal transplants.

At Dunedin Hospital, there have been about eight faecal transplants for a variety of conditions, Dr Jason Hill, who is clinical leader of gastroenterology, says.

"Apart from *C. diff*, the rest have been pretty average results," Dr Hill says.

"I think the future will be producing fake poo . . . which contains 35 to 50 different organisms . . . in a laboratory setting, which can then be given as a probiotic.

"That's probably the answer in the next 10 years. But we are just learning at the moment."

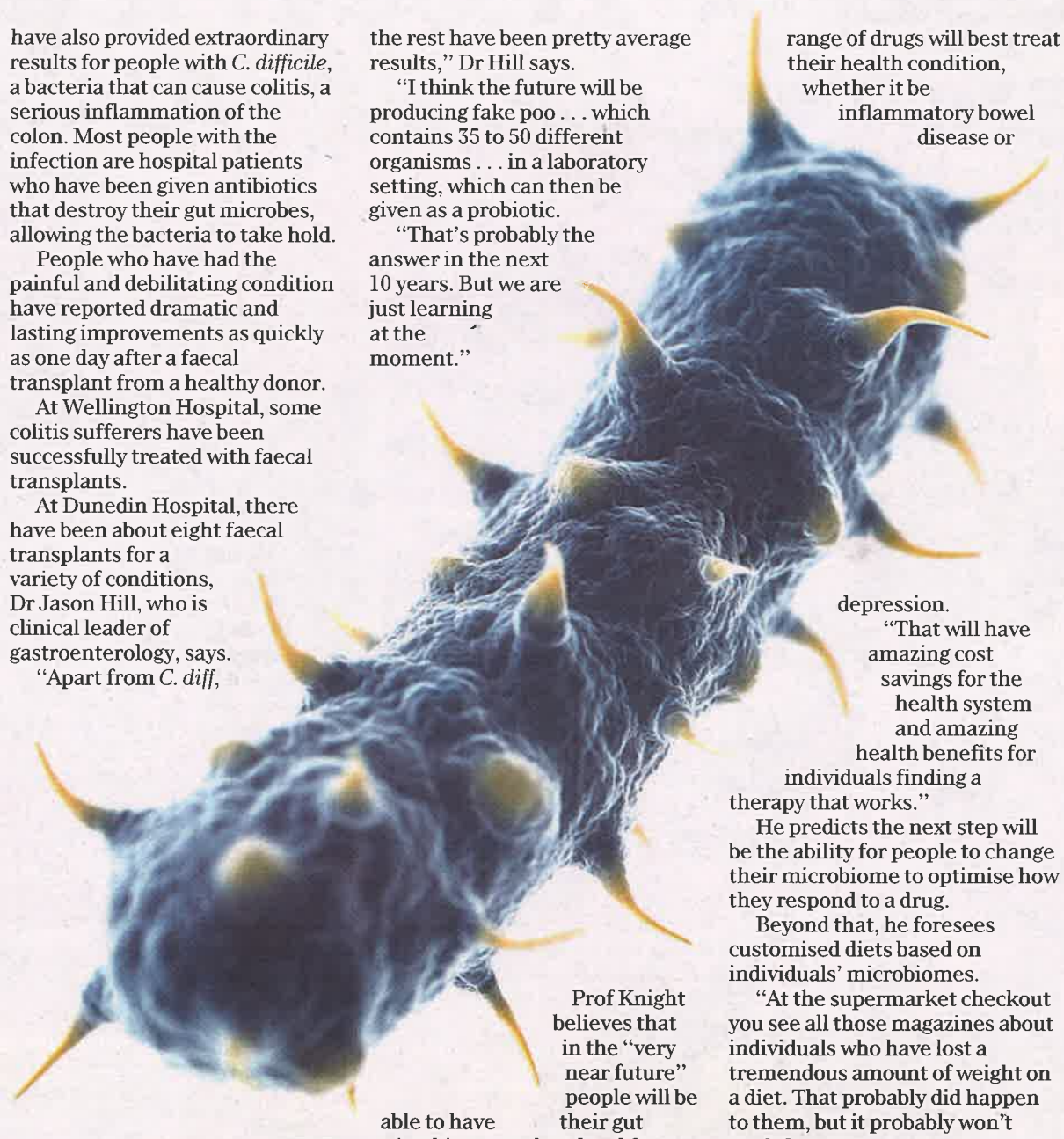


PHOTO: GETTY

Prof Knight believes that in the "very near future" people will be able to have their gut microbiome analysed and from that quickly identify which of a range of drugs will best treat their health condition, whether it be inflammatory bowel disease or depression.

"That will have amazing cost savings for the health system and amazing health benefits for individuals finding a therapy that works."

He predicts the next step will be the ability for people to change their microbiome to optimise how they respond to a drug.

Beyond that, he foresees customised diets based on individuals' microbiomes.

"At the supermarket checkout you see all those magazines about individuals who have lost a tremendous amount of weight on a diet. That probably did happen to them, but it probably won't work for you.

"But there probably is some diet out of the hundreds out there [which, through its interaction with your microbiome,] would have that kind of dramatic effect.

"That could be incredible, not just for preventing obesity but for preventing all kinds of other chronic diseases from becoming long-term."

Right now, however, there is still a lot to discover about how our bodies' microbes have helped us for many millennia. And much to learn about how we could once again make best use of them.

But unfortunately, in our war on microbes, we may have already done that relationship some serious harm.

"We absolutely need a change of attitude," Prof Knight concludes.

"Instead of just dumping a bunch of pesticide on them, we need to figure out how to shape the whole ecosystem so that it remains healthy and resilient.

"It is very much like we are creating a 'silent spring' situation in the gut.

"If you look at hunter-gatherer populations in Tanzania and South America for example, what you see is entire biota of microbes that we don't have in Western populations, things that don't even have names yet. You could look at 100,000 people in New Zealand and never find someone who had those microbes.

"We don't know what those microbes are doing in their bodies. But we co-evolved with those microbes for millions of years and now we've lost them.

"So, all bets are off as to what the consequences of that are."