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Cheatobiotics: Send in the subversive superbugs

28 September 2011 by **Clare Wilson**
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Breeding strains of bacteria too lazy to attack us could help the fight against deadly bugs like MRSA

IT IS a superbug with quite a few tricks up its sleeve. Found pretty much everywhere, from soil and water to your skin and lungs, it thrives with oxygen and without. It can
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Now we may have discovered why. It turns out that the armies of *Pseudomonas* are often greatly weakened by indiscipline in the ranks. They come to be dominated by cheaters and layabouts, who feast on the spoils of victory but ignore all orders to attack. These selfish bacteria multiply faster than the obedient ones, resulting in a less aggressive infection.

This discovery opens up the possibility of a radical new way to tackle superbug infections: deliberately encouraging the growth of cheater strains, perhaps by injecting them into people. Some think it is a crazy and dangerous idea. For others it is a bold approach that is sorely needed as antibiotic resistance grows.

Long seen as simple, solitary creatures, in the past few decades we have come to understand that bacteria are actually highly social. Large groups of bacteria can cooperate closely - and it is this ability to work together that makes some species so dangerous to us.

Many disease-causing bacteria have dual personalities. In small numbers they live independently and peaceably within us, staying beneath the immune system's radar. On reaching a critical mass, however, they turn nasty or virulent, and start to behave like an army. Sometimes these armies build fortifications, cementing their bodies together to form tough biofilms. Or they may march together in vast swarms and launch an all-out attack. Now they get noticed, but their sheer force of numbers can overwhelm the immune system.

Don't cooperate

These discoveries made researchers realise that it might not be necessary to kill bacteria to prevent them harming us. Instead, we could just stop them ganging up on us.

The most obvious way to do this is to stop them talking to each other. Bacteria gauge their population size through a system called quorum sensing. They continuously pump out a chemical signal; if only a few individuals are around, its level remains low, but in a crowd the chemical gets more concentrated. When the bacteria detect that numbers are on their side, they turn virulent.

Several groups have been trying to develop drugs that block these signals.

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Unfortunately, progress on such "quorum quenchers" has been slow, with compounds that work well in the Petri dish failing in tests on animals. Having other ways of subverting bacterial cooperation wouldn't hurt.

That's where the cheater bacteria come in. Their significance was discovered not by microbiologists but by sociobiologists, who study the evolution of societies and of traits such as altruism and spite. In the animal kingdom, whenever some individuals cooperate for the greater good, others evolve to take advantage. In other words, some animals benefit from the community's hard work without doing anything themselves, which can sometimes lead to the community's downfall.

Sociobiologists suspected the same must be true of bacteria - and they were right. The first cheaters were spotted in populations of a soil-dwelling microbe called *Myxococcus xanthus*. When food runs low, thousands of individuals behave as if they are a multicellular organism, clustering together to form tiny towers, called fruiting bodies, that release spores.

Only a few bacteria actually get to form spores, though - around nine out of 10 sacrifice themselves in the process of producing the fruiting body. In 2000, it was shown that some mutant strains cheat by always trying to form spores rather than sacrificing themselves (*Nature*, vol 404, p 598). When these cheaters take over a population, they can destroy its ability to form fruiting bodies, sometimes even leading to extinction.

Does the pattern hold for disease-causing bacteria? When they attack en masse, bacteria start pumping out toxins and other chemicals. These "virulence factors" take a lot of energy to manufacture so cheaters would reap the benefits of these compounds without paying the price of making them.

The first evidence of this in *Pseudomonas* related to iron scavenging. Bacterial growth is often limited by a lack of iron, so when *Pseudomonas* turn virulent, they usually release a virulence factor called pyoverdin, which scavenges iron from human proteins. Some mutants had been discovered, however, that don't produce pyoverdin. Looking at it from an evolutionary perspective, sociobiologists realised that these mutants thrived because they were cheaters: why go to the trouble of making a costly molecule like pyoverdin if you can hang around and steal iron freed by the pyoverdin made by others?

Other strains are even bigger cheaters - they have mutations in a master switch that controls production of many virulence factors, and so can coast along doing very little work. In 2007, two groups published work around the same time showing that if these strains are introduced into a colony of normal *Pseudomonas* bacteria growing in a test tube, the mutants take over.

"These mutants had been found naturally and nobody really knew why," says Steve Diggle, a microbiologist at the University of Nottingham in the UK, who led one of the groups. His team's work proved that not spending precious energy making virulence factors gives the cheaters a big competitive advantage (*Nature*, vol 450, p 411). "That raises the question of, can you use this?"

Yes, says Christian van Delden, an infectious disease specialist at Geneva University Hospitals in Switzerland. Van Delden has long battled *Pseudomonas* in his intensive care units. The bacteria colonise the breathing tube of anyone who has one in place for long enough, and some people develop pneumonia as a result.

The infection is hard to fight as resistance develops to whatever antibiotics are used, and the patients are too sick to cope with the drugs' side effects. "The first time you can treat with not too many problems, the second episode will be more difficult and the third will be a nightmare," says van Delden.

What has long baffled doctors is why *Pseudomonas* infection causes pneumonia in only 10 to 15 per cent of people on ventilators. "There are no risk factors that clinicians could identify on the patient's side," says van Delden. "This suggests the bacteria are different."

As more and more papers were published on bacterial cheating, van Delden began to suspect that this could be the explanation. Perhaps people who didn't develop pneumonia had *Pseudomonas* infections weakened by cheaters.

The chance to test this idea arose when van Delden was involved in a trial of an existing antibiotic called azithromycin. Though poor at killing *Pseudomonas* in the Petri dish, van Delden's team had found the drug somehow blocks its quorum-sensing systems. A Swiss biotech firm called Ambix applied for a new patent on the antibiotic based on its quorum-quenching activity, and asked van Delden to test it on people on ventilators. To show the drug was working

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through quorum quenching, repeated sputum samples were taken and the bacteria analysed to see if they had responded to quorum-sensing signals and turned virulent.

The trial ended abruptly when Ambix's US patent application was rejected, but van Delden realised he could still make use of the data. He teamed up with Angus Buckling, an evolutionary biologist at the University of Oxford who had done some of the early work on *Pseudomonas* cheating. "It was a fantastic opportunity," says Buckling.

Sure enough, their team found that more than half of people infected with non-cheater bacteria got pneumonia, compared with less than a tenth of those infected with cheater strains (*Thorax*, vol 65, p 703).

If other studies confirm these results, it could change the treatment of people in intensive care. Because *Pseudomonas* evolves resistance so easily, at the moment doctors wait until people show signs of pneumonia before giving them antibiotics. But if they could identify the 15 per cent of people likely to get pneumonia, they could treat them earlier, potentially saving lives.

A more radical approach would be to inoculate the vulnerable 15 per cent with a dose of cheater bacteria. In theory they would outcompete the virulent bacteria and stop the infection progressing. But it would be risky. "Who is going to sanction introducing a pathogen?" says Buckling. "All it's going to take is one case going wrong."

Instead van Delden's group is exploring ways to encourage the spontaneous evolution of cheating. One way to do this is to stop cheaters being punished.

When *Pseudomonas* turn virulent, among the toxins they produce may be pyocins that kill other bacteria. At the same time, they start producing pyocin-blocking compounds to avoid shooting themselves in the foot. Cheaters that ignore the signal to turn virulent, however, do not ready their defences, and thus are killed along with unrelated bacteria. So if we could find drugs that block pyocins, they should help cheating mutants to survive and take over populations, rendering the infection harmless.

Diggle's group in Nottingham, meanwhile, is exploring the radical approach. In 2009 his team deliberately infected the wounds of mice with various strains of *Pseudomonas*. They found that those infected with cheater strains were twice as likely to survive as those infected with normal bacteria. Mice dosed with a 50-50 mix of cheaters and normal bacteria were also twice as likely to survive, which suggests giving cheaters to people already infected with normal strains might help save lives (*Current Biology*, vol 19, p 341).

Diggle hopes to try out this daring strategy in people with burns with severe *Pseudomonas* infections. He is in talks with regulators to work out how the first cautious tests could be done. "I don't think it's as crazy as it seems," he says. "It's early days and there are huge regulatory hurdles to overcome, but there's potential for it to work."

Subversive superbugs

If it fulfils its promise, the approach could help treat many kinds of infections. In 2008, Richard Novick, a microbiologist at New York University, showed that cheats that ignore quorum-sensing signals exist among *Staphylococcus aureus*, another common cause of wound infections and pneumonia, especially in hospital patients (*Microbiology*, vol 154, p 2265). That's big news because the spread of *S. aureus* resistant to the antibiotic methicillin, better known as MRSA, is a huge problem. In a study that has not yet been published, Novick's colleague Bo Shopsin found that in people with pneumonia caused by *S. aureus*, the presence of cheaters made them more likely to survive.

Whether any of the strategies to exploit bacterial cheating will bear fruit remains to be seen. But these discoveries are changing the way researchers think. At first, mainstream microbiologists were doubtful about applying theories about social evolution to bacteria. "They are interested in the 'how' questions, we are interested in the 'why'," says Diggle. "It was received with a bit of scepticism."

Combining these approaches is leading to a wealth of new insights. For instance, Sarah Reece, a parasitologist at the University of Edinburgh, UK, has found that the organism that causes malaria alters its reproductive strategy depending on how many of its fellows are present in the same human and how closely related they are (*Nature*, vol 453, p 609). "This could be a new opportunity to control these creatures," says Reece.

It is even relevant to industry. Cheating among *Lactococcus lactis* has been found to explain why some batches of cheese fail to ferment properly.

It's one thing to inject bacteria into a Stilton, quite another to stick them into a person. Yet it is no exaggeration to say that the rise of antibiotic resistance is one of the biggest threats to our health. If a time comes when people are dying because conventional antibiotics are no longer any use, injecting them with "cheatobiotics" instead might look a lot less crazy.

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