Svartediket reservoir (right) was the source of a 2004 giardiasis outbreak in Bergen, Norway.

KNUT-ARNE WENSAAS

INFECTIOUS DISEASE

Something in the water

Infections have long been thought to cause irritable bowel syndrome, but it has not been clear how. It seems that pathogens might be changing the behaviour of our gut microbiota.

BY SUJATA GUPTA

In October 2004, Guri Rørtveit, a primary-care physician in Bergen, Norway, was concerned about a noticeable rise in the number of patients complaining of persistent diarrhoea, flatulence and nausea. She began discussing the problem with colleagues over lunch breaks, but it wasn't until she got a call from the doctor across the road who had patients with the same symptoms that she really began to worry.

That doctor, Knut-Arne Wensaas, told Rørtveit that one of his patients had tested positive for the protozoan parasite *Giardia lamblia*. People become sick with giardiasis, as the resulting disease is called, when they consume contaminated food or water. A common cause of travellers' diarrhoea, *Giardia* is rare in developed countries such as Norway, where it is almost always related to travel overseas.

But Wensaas' patient had not left the country or done anything else to put herself at risk. Concerned, Wensaas and Rørtveit asked the other nine doctors in their practices to request microscopic analyses of stool samples from all of their patients with diarrhoea. Realizing that something was amiss, the lab workers who processed the requests at the Haukeland University Hospital began testing other stool samples to see if these also contained the parasite.

On 29 October, the hospital notified city officials of a giardiasis outbreak. Within days the source was traced to one of the city's main reservoirs, located some 3 kilometres from Rørtveit's office. Local residents were advised to boil their tap water, and the outbreak was finally contained.

About 1,300 people were diagnosed with giardiasis, and there were another 1,200 unconfirmed cases. In about half of these 2,500 people, the symptoms persisted for months, sometimes after repeated treatment, even though tests showed that the parasite was gone. "We knew then that there was something else going on," says Rørtveit, who is also a family medicine researcher at the University of Bergen.

The Bergen case added to a body of work showing that infections can trigger a form of irritable bowel syndrome known as post-infective (PI) IBS, which represents 6–17% of all IBS cases. There are several hypotheses about how this happens, but it seems that infections can lead to long-term changes in the gut. Understanding how IBS develops could provide clues to how some cases might be treated, or even prevented.

LINGERING ILLNESS

Even before IBS had a name, it was suspected that infection could trigger prolonged gastrointestinal problems (page S102). In his 1918 second edition of *Medical Diseases of the War*, British physician Arthur Hurst wrote: "Patients who have recovered from an acute attack of dysentery frequently remain unfit for a considerable period, which may even extend to years."

Over the next few decades, evidence slowly accrued for a link between infection and

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chronic bowel problems. Then, in 1962, Sidney Truelove and Nazir Chaudhary of the University of Oxford, UK, studied 130 patients with irritable colon syndrome, as IBS was then called. They found that one-quarter of patients had developed chronic bowel problems after a bout of gastroenteritis (which many acquired while they were serving overseas during the Second World War).

This finding was largely ignored until the 1990s, when several researchers started investigating the phenomenon in earnest. Nick Read and Kok Ann Gwee, both then at the University of Sheffield, UK, were intrigued by the observation that those who developed PI-IBS were more likely to have psychological problems than those who recovered from their gastroenteritis.

Meanwhile, Robin Spiller, a gastroenterologist at the University of Nottingham, UK, was interested in how pathogens triggered PI-IBS, and whether this was distinct from other forms of the condition. Spiller's team studied 544 people who had confirmed diarrhoeal infection and found that one-quarter said that their bowels had not returned to normal after 6 months. In patients who developed IBS, the most common pathogens were bacteria from the genus *Campylobacter* (R. C. Spiller *et al. Gut* **47,** 804–811; 2000). Furthermore, rectal biopsies revealed an increase in T lymphocytes that lasted at least three months after the infection had passed — a sign of a prolonged inflammatory response. The inflammation seemed to increase the number of serotonin-containing cells in the gastrointestinal tract, which is a potential trigger for diarrhoea.

> *"IBS was supposed to be a condition where there weren't any changes in the gut."*

When Spiller's team published this work, the prevailing wisdom was that the brain drove the bowel symptoms found in IBS. But here was evidence that, at least for PI-IBS, the problem lay in the gut itself. "IBS was supposed to be a condition where there weren't any changes in the gut — and here I was finding them," Spiller says. "It certainly went against the accepted dogma of the time."

TOXIN TROUBLE

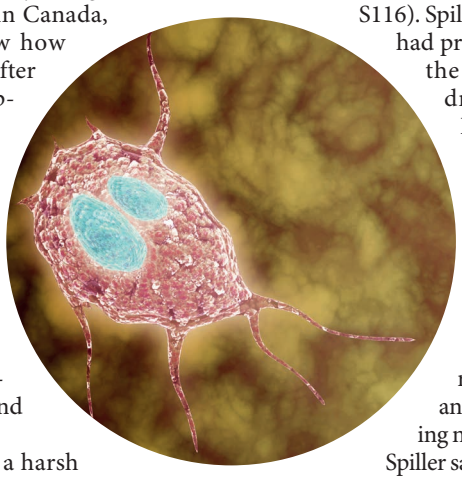
Other researchers linked PI-IBS not only with *Campylobacter* but also with *Escherichia coli*, *Salmonella* and *Shigella* bacteria, all of which produce a toxin called CdtB. Mark Pimentel, a gastroenterologist at Cedars-Sinai, a medical centre in Los Angeles, California, showed that CdtB cues the development of antibodies that in turn cause an autoimmune response. This alters gut motility and initiates the symptoms common in people with IBS. Pimentel's work suggests that in up to half of these patients, CdtB also leads to an overgrowth of bacteria in the small intestine.

But *Giardia* does not produce CdtB, making the situation in Bergen all the more mysterious. Nevertheless, the parasite somehow triggers the same symptoms as CdtB seems to, as Rørtveit and her team have shown (K.-A. Wensaas *et al. Gut* **61,** 214–219; 2011). For each confirmed giardiasis case, they identified two uninfected local people matched by age and sex but otherwise randomly selected, and found that 46% of patients still had chronic bowel problems 3 years after infection, compared with just 14% in the control group.

"It's not clear how *Giardia* might trigger IBS," Pimentel says. "It throws me off a little."

ZOMBIE BACTERIA

Andre Buret, a pathophysiologist at the University of Calgary in Canada, thinks he might know how *Giardia* triggers IBS. After hearing about what happened in Norway, he decided to see whether pathogens such as *Giardia* alter the body's microbiota. He used a technique that he and his team had developed several years earlier that allows researchers to grow a human gut microbiota outside the body and watch what happens.



***Giardia lamblia*, the parasite responsible for giardiasis.**

Gut bacteria inhabit a harsh environment that is subject to constant flushing and exposure to foreign substances. To survive, the bacteria create communities known as biofilms that are coated with protective polysaccharides. Buret wondered whether some pathogens might modify these bacterial films, inducing abnormalities that persist after the pathogen is gone. To test this idea, he put some microbial samples in a dish and infected them with *Campylobacter* and *Giardia*.

Buret's team found that *Giardia* and *Campylobacter* disintegrate the protective biofilms, so the once-beneficial bacteria can move to other parts of the gut where they become disruptive. Buret has also shown that these pathogens can alter the gene expression of freed gut bacteria, making them toxic. This interaction, he says, "transforms them into pathobionts" — the bacterial equivalent of zombies.

Like their human equivalents, zombie bacteria wreak havoc. In an unpublished study on germ-free mice, Buret found that these pathobionts target and kill the cells of the small intestine. Long after the instigating pathogen has gone, the actions of the pathobionts continue to cause gut inflammation. And with no way to get rid of the zombie menace, the inflammation can persist indefinitely.

MILITARY MIGHT

Cases of PI-IBS are particularly common in members of the armed forces who have served overseas. "Within the military, this is an underappreciated burden of disease," says Mark Riddle, a vaccine researcher at the Naval Medical Research Center in Silver Spring, Maryland.

Military service exposes people to not one but two major risk factors. First, many of those who serve overseas develop travellers' diarrhoea, which is one of the main causes of illness and lost duty days. And second, as the Sheffield researchers confirmed back in the 1990s, people are at greater risk of developing IBS if they have psychological problems — and many soldiers have post-traumatic stress disorder.

This knowledge is already affecting the hunt for treatments for PI-IBS (see page S116). Spiller and his team have had promising results with the anti-inflammatory drug mesalazine (C. Lam *et al. Efficacy Mech. Eval.* http://dx.doi.org/10.3310/eme02020; 2015). They gave the drug to 136 people with IBS. It had no effect overall, but the 13 people with PI-IBS reported less diarrhoea and cramping. The finding needs to be confirmed, Spiller says, but it supports the idea that the symptoms of IBS may arise from persistent activation of the immune system.

In 2015, Pimentel's work led to the approval by the US Food and Drug Administration of rifaximin — an antibiotic that was already used to treat travellers' diarrhoea — as a treatment for PI-IBS. Pimentel has also developed a blood test that looks for the presence of CdtB, and says that this could be an important step towards finding a cure.

Riddle has been trying to take things one step further with a preventive vaccine, and has conducted several small-scale trials of promising candidates. Volunteers receive either a placebo or a trial vaccine, and then consume a drink that contains a pathogen. He intends to test promising candidates on travellers within the next five years. Riddle also notes that those who do develop diarrhoea are immediately treated with antibiotics — and no one has gone on to develop IBS.

Despite the apparent success of antibiotic treatments, many researchers are cautious about using them to treat PI-IBS. When the microbiota have already been ravaged by infection, is it helpful to use drugs that further target the fragile intestinal ecosystem? "Knowing how precious one's microbiome is," says Spiller, "I would be very reluctant to disturb it." ■

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