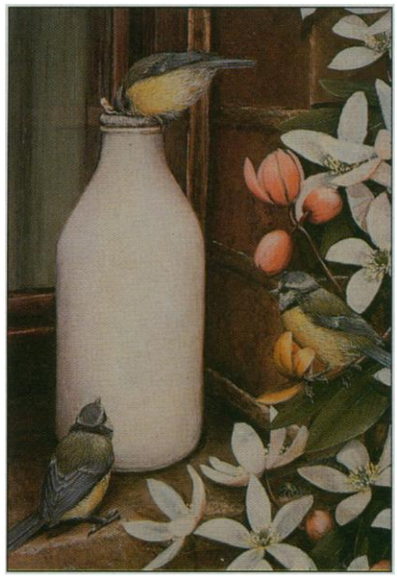
MICROBIAL GENOMICS

First Food-Borne Pathogen Sequenced

Nature lovers used to marvel over avian ingenuity when they saw a bird peck its way through a foil bottle cap for a sip of milk. The clever bird sometimes left an unwelcome present in return: *Campylobacter jejuni*, a bacterium that causes severe gastrointestinal upsets in humans. Milk rarely comes in bottles these days, but *Campylobacter* has become a major health problem over the past 20 years, often passing from its natural avian hosts to humans through undercooked poultry or contaminated water. Now, *C. jejuni* has a new—and more auspicious—claim to fame: It's the first food-borne pathogen whose genome has been sequenced.

At the Microbial Genomes III meeting held earlier this month in Chantilly, Virginia, microbiologist Brendan Wren of St. Bartholomew's Hospital in London reported that a team lead by Bart Barrell and Julian Parkhill at the Sanger Centre in Cambridge, U.K., has determined the exact order of the 1.64 million bases that make up the pathogen's genetic code. The sequence has already revealed how *C. jejuni* might evade immune system detection, information that might help researchers develop vaccines to protect against the bacterium, which last year caused nearly 300,000 cases of food poisoning in the United States alone.

It is also shedding light on an occasional aftermath of *C. jejuni* infections: a temporarily paralyzing neuromuscular disorder called Guillain-Barré syndrome, thought to be an autoimmune reaction touched off by the bacterium. What's more, because *C. jejuni* is a close relative of *Helicobacter pylori*, which causes ulcers, comparing the two genomes should help researchers better understand that pathogen as well. "The *Campylobacter* sequence is going to help the field no end," predicts Richard Alm, a microbiologist at Astra Research Center in Boston, Massachusetts.



Direct deposit. Birds stealing milk sometimes leave behind pathogenic bacteria.

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Microbiologists have found *C. jejuni* difficult to study because it grows poorly in the lab. But sequencing it proved much less of a problem, taking less than 16 weeks from start to finish. "It sequenced like a dream," Wren said, opening up an entirely new view of the organism.

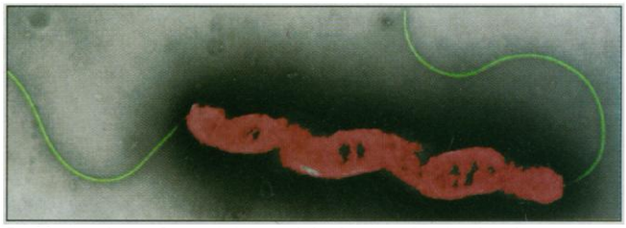
Not all of *C. jejuni*'s potential genes have been identified yet, but those that have may solve some puzzles about the organism. For example, the Sanger group discovered repeated sequences of either guanine or cytosine bases—anywhere from 7 to 13 copies of each—in 25 of the microbe's genes. Such repeats are not unusual, but in this case they helped Wren and his colleagues see how the bacteria might evolve to evade the host immune system.

These repeated sequences are particularly prone to mutation when the bacteria replicate their DNA before dividing, because in those regions the strand being synthesized may slip relative to the one being copied, with the result that bases are lost or gained depending on the direction of the slippage. And Wren and his colleagues found that the same gene could contain, say, nine guanines in a row in one sample and 13 in another, changes that could affect the structure and activity of the gene's protein product.

These mutations primarily affect genes that help produce lipopolysacharides, the sugars that coat the surface of *C. jejuni*. By frequently altering these genes, *C. jejuni* may change how its surface looks to the immune system and may thus avoid recognition by antibodies made during previous infections, suggests Julian Ketley, a microbiologist at Leicester University, U.K. The sequence also revealed what may be another countermeasure in *C. jejuni*: three not-quite-identical copies of a gene called *NeuB*. These genes, which make proteins that help cause acidic sugars to be added to various other molecules in a process called sialation, might help disguise bacterial components so that they look more like those of the host and are thus harder for the immune system to detect.

Besides shielding the bacterium from an immune response, these similarities could cause trouble when the immune system does succeed in recognizing the camouflaged molecules. Wren reported preliminary experiments suggesting that one *NeuB* gene may cause a surface molecule on *C. jejuni* to look like a ganglioside, a type of lipid found in high concentrations in the nervous system. That close resemblance could trick the immune system into attacking nervous tissue as well as the invading bacteria, perhaps causing Guillain-Barré syndrome.

So far, however, the genome hasn't provided many other clues about how the microbe does its dirty work. For example, researchers thought a toxin similar to that made by the cholera pathogen might be the cause of the diarrhea and other symptoms caused by *C. jejuni*. "But there doesn't seem to be any evidence of that," says Ketley, who has teamed up with several other U.K. researchers to identify all of *C. jejuni*'s proteins and their functions as a way of pinning down the source of its virulence.



Bad bacterium. *Campylobacter jejuni* causes food poisoning.

In the meantime, Wren and others have begun comparing the *C. jejuni* sequence with that of the closely related *H. pylori*. Until now, "no one had sequenced different, side-by-side species," Alm notes. The differences are surprisingly large, he adds: "The genomes are indistinguishable by size and yet 17% of the genes are specific to *Helicobacter*."

Some of the differences appear to be related to the different lifestyles of the two organisms. For example, *H. pylori* settles only in the stomach and has several genes that appear to help it cope with the stomach's acid environment by coding for enzymes that break down urea. This "may create an alkaline cloud around the *Helicobacter*," Wren explains. *C. jejuni*, for its part, has about twice as many genes as *H. pylori* that are involved in sensing and initiating coordinated responses involving multiple genes. These presumably enable the microbe to adjust to a new environment, be it the gut of a bird, milk in a bottle, or a human intestine.

Over the next few years, Wren and his colleagues will study the role of the newly identified genes by using DNA microarrays, glass slides spotted with DNAs representing all of *C. jejuni*'s genes, to see which genes are active over the course of an infection. In the near future, Wren predicts, "[*C. jejuni*] will go from being one of the least well-studied pathogens to one of the most well-studied ones." —ELIZABETH PENNISI