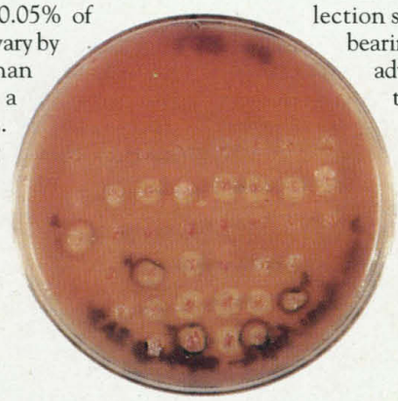
EVOLUTION

Bacteria Diversify Through Warfare

ARNHEM, THE NETHERLANDS—It's a civil war in there for many gut-loving bacteria, and the battles between the strains may help explain a microbial mystery: why *Escherichia coli* and other microbes are so genetically diverse. Peg Riley, an evolutionary biologist at Yale University, notes that while two humans might differ in 0.05% of their DNA, *E. coli* strains vary by 5%—"more diversity than you expect to find [in a single species]," she says. At the recent meeting here of the European Society for Evolutionary Biology, Riley described evidence that a chemical arms race could be helping to drive this genetic diversification by dividing group from group and descendants from ancestors.

P. RILEY



Mortal combat. Bacterial colonies shrivel when exposed to bacteriocins, chemical weapons made by competing strains.

The weapons in question are colicins, one of a group of chemical compounds collectively known as bacteriocins, which bacteria use to defend themselves and kill other, closely related strains. These weapons are often deployed in the gut, which houses several dominant strains of *E. coli* in the average mammal. When a new strain begins competing with a resident strain and resources grow scarce, both may release colicins.

"Colicins may be their number one line of defense and offense," says Riley. Designed to recognize specific receptors on other *E. coli* cells, the colicins are transported inside the enemy bacterium and kill it by disrupting cellular functions, for instance by chewing up the DNA.

Each strain escapes harm from its own weapon by producing an immunity protein that turns off its own colicin's killer mechanism. "If it's not their strain of colicin, then they die," explains Riley. "Normally, the bacteria don't have immunity to anything but their own colicin," she adds. But just as a strain of *E. coli* can develop resistance to antibiotics (see below), it can also evolve resistance to its competitors' colicins.

That ability led Riley to suspect that like superpowers in an escalating arms race, the *E. coli* are under constant pressure to develop new defenses and weapons—and that they do so by a seldom-seen form of evolution called positive selection. Most mutations are harmful, and nearly all mutations—whether "good" or "bad"—are simply lost through genetic drift, explains Riley. "We don't have many examples of 'good' mutations that overcome the power of genetic drift. We suspected that this might be one."

Riley and her colleague Ying Tan tested their idea with several strains of *E. coli* carrying extra immunity genes that give them protection from the colicins of other strains as well as their own. In nature, natural selection should give an individual bearing the extra gene a huge advantage. "Because it's protected, it won't be swept out of the population by drift. That buys it time" to increase in numbers, says Riley. Indeed, the researchers found that just a single "superimmune" cell put in a flask with 100 million or more ancestral bacteria always ended up invading its competitors.

Riley thinks such a strain's initial advantage might open the way to an additional—if Oedipal—blessing: a second genetic change that alters the *E. coli*'s colicin and turns the strain into a "superkiller" that can eliminate its ancestor as well as other strains. "As the strain increases in frequency [because of the extra immunity gene], the greater the chance that it will evolve this second mutation: a colicin that its ancestor doesn't recognize" and thus can't disarm, explains Riley. Evidence that such genetic changes can happen comes from Japan, where researchers have actually created a superkiller strain via a single point mutation.

Inevitably, says Riley, the advent of a superkiller strain will elicit a response from other *E. coli*, as new strains develop that carry new immunity proteins and new colicins that can overcome the variant strain's defenses. "This kind of experiment shows that such positive selection can act to produce more and more variety," says Riley.

Riley and Tan's findings go far to explain a molecular puzzle that Riley uncovered 5 years ago. In studying the evolutionary history of colicins to determine which were ancestral to which, she found an odd pattern in their DNA sequences: There was always a block, centered on the immunity gene and the end of the colicin gene, with astonishingly high levels of diversity. "I remember thinking, Wow! What could possibly explain that?" she recalls. She now thinks she has the answer: "This is the region that selection is actually acting on" as the *E. coli* evolve.

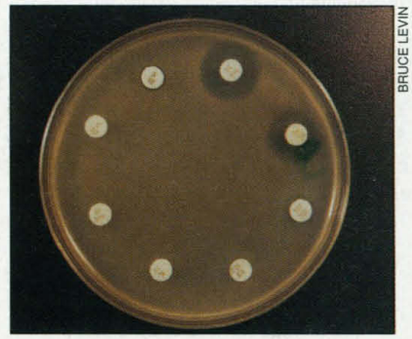
"It's super work," says Bruce Levin, an evolutionary biologist at Emory University in Atlanta, Georgia, "and goes a long way toward explaining how that enormous variation in *E. coli* arises and is maintained."

–Virginia Morell

EVOLUTION

Antibiotic Resistance: Road of No Return

ARNHEM, THE NETHERLANDS—They are one of medicine's biggest headaches: bacteria that have evolved resistance to those former wonder drugs, antibiotics. Now it appears that—contrary to everyone's hopes and microbiologists' expectations—these troublesome microbes will remain resistant long after doctors stop prescribing the drugs. That was the grim prognosis offered by Bruce Levin, a population geneticist at Emory University in Atlanta, at the recent meeting here of the European Society for Evolutionary Biology. Drawing on studies of bacteria from a day-care center and in the lab, he said, "I'm afraid I can't be optimistic. We can't go back again" to antibiotic-sensitive bacteria. "The best we can do is slow the pace at which resistance evolves and increases in frequency."



BRUCE LEVIN

A match for medicine. *E. coli* is unaffected by six of eight antibiotics.

Researchers had hoped that bacteria that have become resistant to overused antibiotics would "evolve backward," losing their resistance, because the resistant strains wouldn't be able to compete with the sensitive ones once the drugs were removed. "Theoretically, the genes responsible for resistance are supposed to adversely affect the bacteria's fitness," Levin explains. "You're altering a gene's normal function and therefore expect it to have a disadvantage."

But a random survey last year of *Escherichia coli* bacteria collected from a day-care center in Atlanta by Levin and an Emory undergraduate, Bassam Tomah, suggested that the theory may not hold up. In a quarter of the bacteria sampled from the dia-