Life of the Mind

ANTIBIOTIC RESISTANCE

Invasion of the Superbugs

The stubborn problem of drug-resistant bacterial diseases is escalating

When the first antibiotics were discovered 70 years ago, they were a medical miracle: Bacterial infections that once killed people in huge numbers now could easily be cured. But over the last several decades, the number of drug-resistant strains of diseases has been growing. Each year more than 2 million people in the United States are infected with "superbugs" that have developed resistance to most antibiotics, according to the Centers for Disease Control and Prevention (CDC), and 23,000 of them die.

Pharmaceutical companies have had little incentive to develop new antibiotics, because the cost of research is high and the profits relatively small. The Food and Drug Administration approved 30 new antibiotics in the 1980s, but only nine in the last 15 years. In 2012, Congress passed legislation that could spur companies to develop new drugs by giving priority to new antibiotic applications and extending the period when antibiotics are on the market without a generic version. Two new antibiotics are under FDA review under the new law.

"The loss of useful antibiotics threatens our ability to practice modern medicine as we know it," says Ramanan Laxminarayan, an economist at the Princeton Environmental Institute who studies antibiotic resistance and works with governments on policies to combat the problem. Not only do antibiotics treat existing infections, they make surgeries and other medical procedures safer by reducing the risk of infections.

There are now drug-resistant versions of all bacteria that cause human

Professor Mark Brynildsen is studying how *Staphylococcus aureus* bacteria go into a hibernation state that allows them to become tolerant of antibiotics.

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diseases. For some particularly resistant strains, the only available treatments are extremely toxic antibiotics that can damage the liver and other organs. One of the diseases of most concern is gonorrhea: Each year in the United States there are some 246,000 cases that are resistant to all but the most powerful antibiotics, and some strains are not treatable at all — which can lead to pelvic inflammatory disease and put patients at a higher risk for HIV. Resistant strains of MRSA, or methicillin-resistant *Staphylococcus aureus* — bacteria typically found in hospitals — have been increasing outside of health-care settings, causing a total of more than 11,000 deaths every year in the United States.

The main culprit for antibiotic resistance is improper use: The CDC estimates that 50 percent of antibiotic prescriptions are unnecessary or not prescribed in the correct dosage. Many patients expect to leave a doctor's visit with an antibiotic prescription, and CDC guidelines that aim to minimize improper use often are disregarded, Laxminarayan says. He is collecting data on antibiotic use around the world to study patterns of resistance, including whether antibiotic-resistant strains found in farm animals in certain areas correlate with similar strains in people.

Agriculture is an important factor in creating drug resistance, according to the Centers for Disease Control. In the United States, about 70 percent of antibiotics are used on farm animals to prevent disease and make animals bigger, creating opportunities for pathogens to develop resistance. Last December, the FDA announced a plan for the voluntary withdrawal of some antibiotics from livestock feed, but Laxminarayan is skeptical that farm practices will change voluntarily.

Laxminarayan hopes that social norms about antibiotic use begin to change as the public becomes more aware of the problem. "People start paying attention when people start dying," he says, "and many more people are now dying from bacterial infections around the world."

*By Anna Azvolinsky *09*

Tackling antibiotic resistance one bug at a time

Zemer Gitai, associate professor of molecular biology

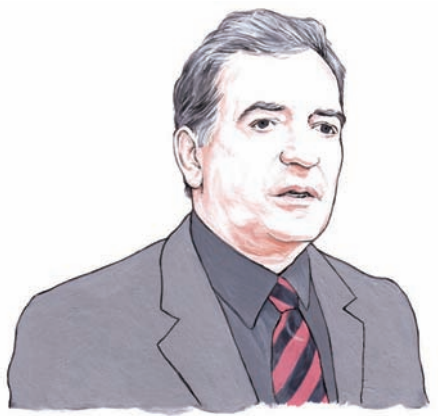
***Pseudomonas aeruginosa* is the bane of many hospitals. The rod-shaped bacterium has several skinny tails that help it to slink through catheters, water pipes, and our respiratory and urinary tracts, against the flow of moving liquids.**

"It can act like a bacterial salmon, moving upstream of flow," Zemer Gitai says. This mobility allows it to colonize environments that are inaccessible to other surface-attaching bacteria, including the tissues and organs of those who have compromised immune systems, causing inflammation and sepsis.

In collaboration with Howard Stone, a Princeton professor of mechanical and aerospace engineering, Gitai's lab has shown that these tails — called pili — act like hooks to pull the bacteria forward, resulting in a twitching, zigzag movement against liquid flow. The lab is trying to identify chemicals that can inhibit this unique motion. Rather than killing bacterial cells by targeting their ability to multiply, these drugs could block *Pseudomonas* from colonizing people's bodies and hospital pipes, preventing infection. "If the bacteria does not have the capability to move through the hospital equipment or our tissues, we may be able to prevent people from getting sick," Gitai says.

Robert Austin, professor of physics

How do bacteria develop resistance in the real world? In the laboratory, bacteria are grown in test tubes and Petri dishes. But these environments do not necessarily mimic bacteria's real-world habitats, which are complex and constantly changing. Robert Austin has developed a device that exposes bacteria to antibiotics in gradually increasing amounts rather than in a constant concentration, which more closely imitates true conditions. In an experiment with Princeton



Pseudomonas aeruginosa **bacteria swim upstream to get into hospital pipes and patient catheters. Professor Zemer Gitai studies how these bacteria are able to move into hard-to-reach environments.**

Illustrations: Peter James Field; photo: CNRI/Science Photo Library

microbiologist Julia Bos, Austin found that *E. coli* that are gradually exposed to the antibiotic Cipro evolve resistance to the drug within 10 hours, or about 20 bacteria generations — much faster than under normal lab conditions.

Bos and Austin are working to understand exactly how resistance develops and spreads within the bacterial population. Low concentrations of antibiotics appear to speed up the emergence of antibiotic resistance, the scientists say. "There are a lot of tricks the bacteria have. They are more sophisticated than we thought," Austin says.

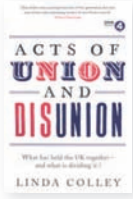
Mark Brynildsen, professor of chemical and biological engineering

Mark Brynildsen is working to develop antibiotics that target bacteria more precisely. Existing antibiotics attack bacteria indiscriminately, which results in more rapid development of resistance. Brynildsen is working on an approach that would cripple only the bacteria in the host that are causing illness.

His lab also focuses on combating bacterial persistence, a type of hibernation state that allows bacteria to become tolerant or immune to antibiotics. "In the presence of antibiotics, persisters lie dormant for long periods of time, and when the antibiotic is removed, they wake up and re-populate the environment," Brynildsen says. He is working to devise methods to identify these cells and find drugs to prevent their formation. ***By Anna Azvolinsky *09***

FACULTY BOOKS

"Islam today has a higher political profile than any of its competitors," writes **Michael Cook,** a professor of Near Eastern studies, in *Ancient Religions, Modern Politics: The Islamic Case in Comparative Perspective* (Princeton University Press). He explores why that is the case, and compares the roles of Islam, Hinduism, and Christianity in modern politics.



Acts of Union and Disunion: What Has Held the U.K. Together — and What Is Dividing It? (Profile Books), by history professor **Linda Colley,** examines forces that have united and divided England, Wales, Scotland, and Ireland, and some of the "wider, international unions and would-be unions" in which they have been involved. The book is based on a BBC radio series.

"I'm the kind of guy who's always wanted to be elsewhere," **Edmund White,** a creative writing professor, writes in his memoir *Inside a Pearl: My Years in Paris* (Bloomsbury). In the summer of 1983, White moved to Paris and stayed for 15 years. He recounts the people he met, his friendships and romances, and his work as a writer.