

LESS THAN A CENTURY AGO, the age-old evolutionary relationship between humans and microbes was transformed not by a gene, but by an idea. The antibiotic revolution inaugurated the era of modern medicine, trivializing once-deadly infections and paving the way for medical breakthroughs: organ transplants and chemotherapy would be impossible without the ability to eliminate harmful bacteria seemingly at will.

But perhaps every revolution contains the seeds for its own undoing, and antibiotics are no exception: *antibiotic resistance*—the rise of bacteria impervious to the new “cure”—has followed hard on the heels of each miracle drug. Recently, signs have arisen that the ancient relationship between humans and bacteria is ripe for another change. New drugs are scarce, but resistant bacteria are plentiful. Every year, in the United States alone, they cause two million serious illnesses and 23,000 deaths, reflected in an estimated \$20 billion in additional medical costs. “For a long time, there have been newspaper stories and covers of magazines that talked about ‘The end of antibiotics, *question mark*,’” said one official from the Centers for Disease Control and Prevention (CDC) on PBS’s *Frontline* last year. “Well, now I would say you can change the title to ‘The end of antibiotics, *period*.’”

After 10 years in obscurity, the compound caught the attention of Oxford researchers Howard Florey and Ernst Chain. In 1941, the scientists conducted the drug’s first clinical trial. The patient, a policeman suffering from a severe staphylococcal infection, died a month later—supplies of penicillin had run out after just five days—but his initial improvement had been remarkable. The drug shot to prominence against the backdrop of World War II. In the Allied countries, penicillin production increased exponentially, and the compound helped save thousands of soldiers’ lives. “Thanks to penicillin...he will come home!” promised an advertisement in *Life* magazine in 1944, when the drug became available to the general public.

For all of prior human history, minor injuries carried the threat of severe illness and even death: the first recipient of penicillin, for instance, developed his deadly infection after being scratched by a rose bush. *Staphylococcus aureus*, named for its colonies’ golden color, was a frequent culprit. Though it resides harmlessly in the noses and on the skin of some 30 percent of the population, *S. aureus* has long exploited scrapes and cuts to cause ailments ranging from boils and abscesses to life-threatening sepsis. But with the beginning of the antibiotic age, humanity gained a powerful,

SUPERBUG

An epidemic begins.

If the end is here, it has been a relatively long time coming. Its complex roots are evident in the lengthy relationship between humans and *Staphylococcus aureus*, a resilient species that has met each antibiotic challenge with new, more resistant incarnations. If the gains of the antibiotic revolution are to be preserved, the lessons to be learned lie in this relationship as well. *S. aureus*, after all, was present at the antibiotic era’s very beginnings.

Newton meets Darwin

IN AUGUST 1928, Scottish scientist Alexander Fleming had just returned to his London laboratory from vacation when, amid the usual clutter, he found a petri dish that gave him pause. At the edge of the dish was a colony of mold, and around it, a halo within which the *Staphylococcus* bacteria that dotted the rest of the dish were conspicuously absent.

“That’s funny,” Fleming is said to have remarked to his assistant. Fleming was no stranger to compounds that could kill bacteria; seven years earlier, he had discovered the enzyme lysozyme, which inhibits bacterial growth, by culturing his own nasal mucus. Suspecting another antibacterial compound, he set about investigating the mold, *Penicillium notatum*, and the substance he later named penicillin.

almost miraculous, new weapon—a “magic bullet” that fulfilled Nobel laureate Paul Ehrlich’s vision of a chemical that would specifically eliminate pathogens, without harming patients.

Yet wrapped up in penicillin’s serendipitous beginnings were hints of challenges to come. “It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them,” Fleming warned in 1945 when he received the Nobel Prize in medicine or physiology, together with Florey and Chain, “and the same thing has occasionally happened in the body.”

His remarks proved ominously prescient: penicillin-resistant strains of *S. aureus* began appearing in hospitals just years after the drug was introduced. “It’s Newton meets Darwin,” says Michael Gilmore, Osler professor of ophthalmology at Harvard Medical School and Massachusetts Eye and Ear Infirmary, and director of the Harvard-wide Program on Antibiotic Resistance (HWPAR). “For every biological action, there’s an equal and opposite reaction.”

What Fleming understood was that antibiotics confer an unfortunate advantage on those bacteria that happen to be naturally resistant through some mutational twist of luck. Penicillin, for instance, kills bacteria by binding to and incapacitating an enzyme that maintains the cell wall, a critical bar-

by Katherine Xue



rier between the cell and its surroundings. By chance, one bacterium might have a mutant enzyme that the drug cannot recognize, allowing the organism to escape the compound's effects. As Fleming warned: given a sufficiently large number of bacteria, at least one is bound to survive.

But even Fleming did not anticipate the magnitude of the resistance problem to come. In the 1950s, amid postwar outbreaks of dysentery, Japanese researchers led by Tsutomu Watanabe began to encounter bacteria simultaneously resistant to *multiple* drugs—impossibly unlikely for pathogens acquiring random mutations. By 1955, researchers were reporting several strains of *Shigella dysenteriae* resistant to the same four antibiotics at once. Even worse, the resistance itself was contagious. Related species, when mixed with multidrug-resistant *S. dysenteriae*, also became resistant to multiple antibiotics.

“Resistance works differently in the bacterium,” explains Stuart Levy, director of the Center for Adaptation Genetics and Drug Resistance at Tufts University School of Medicine. Drug resistance itself is common in all microorganisms: bacteria, viruses, and parasites alike can gain mutations or otherwise adapt to escape the toxic effect of drugs. But bacteria have an added feature, says Levy, who studied with Watanabe. “*Their* resistance can be *transferred*.”

What was happening, Watanabe and others later deduced, was that bacteria were exchanging small, circular pieces of DNA called plasmids, which happened to carry genes for resistance. Most genetic material is transmitted only from parent to offspring, but

plasmids can be transferred *horizontally*—from neighbor to neighbor. This unique ability makes bacteria an even greater threat. Many resistance genes can gather on a single plasmid and spread to different species as the host bacterium moves through the environment; in clinical settings, horizontal gene transfer is by far the most common mechanism through which bacteria become drug-resistant. “It’s a little frightening,” says Levy, “to realize that you’re running after something that can transfer its football to somebody else right away.”

In the case of penicillin, plasmids helped spread naturally occurring resistance genes. In 1940, before the compound had even undergone its first clinical test, Chain and his colleagues were studying *Escherichia coli*, one of many bacterial species unaffected by penicillin, when they found an enzyme, penicillinase, capable of destroying the drug altogether. Indeed, as scientists began to uncover more natural molecules with antibiotic effects, they likewise encountered more enzymes seemingly dedicated to those molecules’ destruction.

In retrospect, the discovery is unsurprising. As Fleming’s serendipitous discovery suggests, most antibiotics derive from naturally occurring compounds that likely evolved to aid in inter-microbial warfare, as different species compete to colonize limited spaces. In response, some bacteria evolved to harbor natural resis-

Michael Gilmore directs the Harvard-wide Program on Antibiotic Resistance. He has used genomic techniques to trace the evolution of antibiotic-resistant bacteria.

tance mechanisms—enzymes that pump hostile compounds out of the cell, for instance, or chemically alter drugs to render them ineffective. Recent studies have found soil bacteria that are naturally resistant to most known antibiotics; some of these species can even use antibiotic molecules as food.

As penicillin's popularity grew, therefore, *S. aureus* did not have far to look for a means of defense. Unbeknown to scientists at the time, plasmids carrying penicillinases entered the staph population, and resistant strains spread rapidly. In one English hospital, the proportion of resistant staph infections quadrupled from 14 percent in 1946 to 59 percent just two years later. By mid century, the world was in the midst of its first pandemic of antibiotic-resistant infections. As a commercially available drug, penicillin was not yet 10 years old.

The hunt for new drugs

HELP CAME in the form of new antibiotics. In the wake of penicillin's immense impact, drug companies rushed to search for new compounds. The 1940s and 1950s marked the golden age of antibiotic discovery: streptomycin, chloramphenicol, tetracycline, and erythromycin were isolated within a 10-year span. The molecules expanded the antibiotic arsenal with new classes of chemical compounds that employed distinct strategies to achieve their deadly effect.

In the meantime, another drug-discovery strategy helped scientists make better use of existing compounds. Early penicillin production involved growing enormous vats of the fungus that made the precious molecule; in the hope of improving production, chemists embarked on a decade-long quest to synthesize the compound from scratch. It was no easy task—molecules produced in nature, and antibiotics in particular, are often far more complex than what can readily be produced in labs. As MIT chemist John Sheehan remarked to *The New York Times* after achieving the first successful total synthesis, “Nature designed the penicillin molecule to teach organic chemists a little humility.”

Nevertheless, Sheehan's method ushered in a new wave of drug development. Scientists synthesizing the molecule could now make chemical modifications to improve drug activity—and, in doing so, develop molecules able to combat resistance. “Widespread germ succumbs to a new synthetic penicillin,” declared the *Times* in 1961 after new treatments saved the life of actress Elizabeth Taylor, who had developed penicillin-resistant staphylococcal pneumonia on the set of *Cleopatra*. To avoid being destroyed by penicillinases, the new drug had an extra chemical group: a methyl tail, which earned it the name methicillin.

Methicillin was introduced in 1960, and strains of methicillin-resistant *S. aureus*, better known as MRSA, appeared two years later. Since methicillin was mostly immune to the enzymes that could destroy penicillins, MRSA acquired a different resistance mechanism: a mutant target protein, borrowed from another *Staphylococcus* species, that was unaffected by the drug. Within a few years, strains of MRSA began spreading in hospital wards around the world, mirroring the rise of penicillin-resistant *S. aureus* less than two decades earlier.

But even as the danger of MRSA intensified in the 1970s and 1980s, drug development began to slow down. New antibiotics were developed, but they, like methicillin, were closely related

to drugs that had come before. Chemical modifications could breathe new life into older drugs, but rarely more than a few years' worth: the bacteria adapted. “It's a Red Queen race,” says Cabot professor of biology Richard Losick. “We're running as fast as we can just to stay in the same place.”

Meanwhile, the risks from MRSA have grown steadily worse. Early on, infection occurred almost entirely in hospitals, among patients already weakened by other illnesses, and by 2002, nearly 60 percent of *S. aureus* cases in American hospitals were methicillin-resistant. Adding to the toll, a new, more virulent MRSA strain began circulating in communities in the early 1990s, sickening otherwise healthy people. In 2005, an estimated 100,000 Americans suffered severe MRSA infections, and nearly 20,000 of them died—more than from HIV and tuberculosis combined.

Drug discovery has yet to catch up. “All the low-hanging fruit has been picked,” says Levy. Following the introduction of synthetic quinolones in 1962, no new chemical classes of antibiotics were developed until 2000. Most large pharmaceutical companies have abandoned antibiotic research and discovery altogether because of its unfavorable economics: drug development is risky and expensive, and antibiotics do not generate revenue the way drugs for chronic infections do (see “Encouraging Antibiotic Innovation,” page 48). “We have, at this point, a perilously thin pipeline,” warns John Rex, head of infection development at AstraZeneca, one of the few pharmaceutical companies still pursuing antibiotic discovery. “There are very few new drugs coming.”

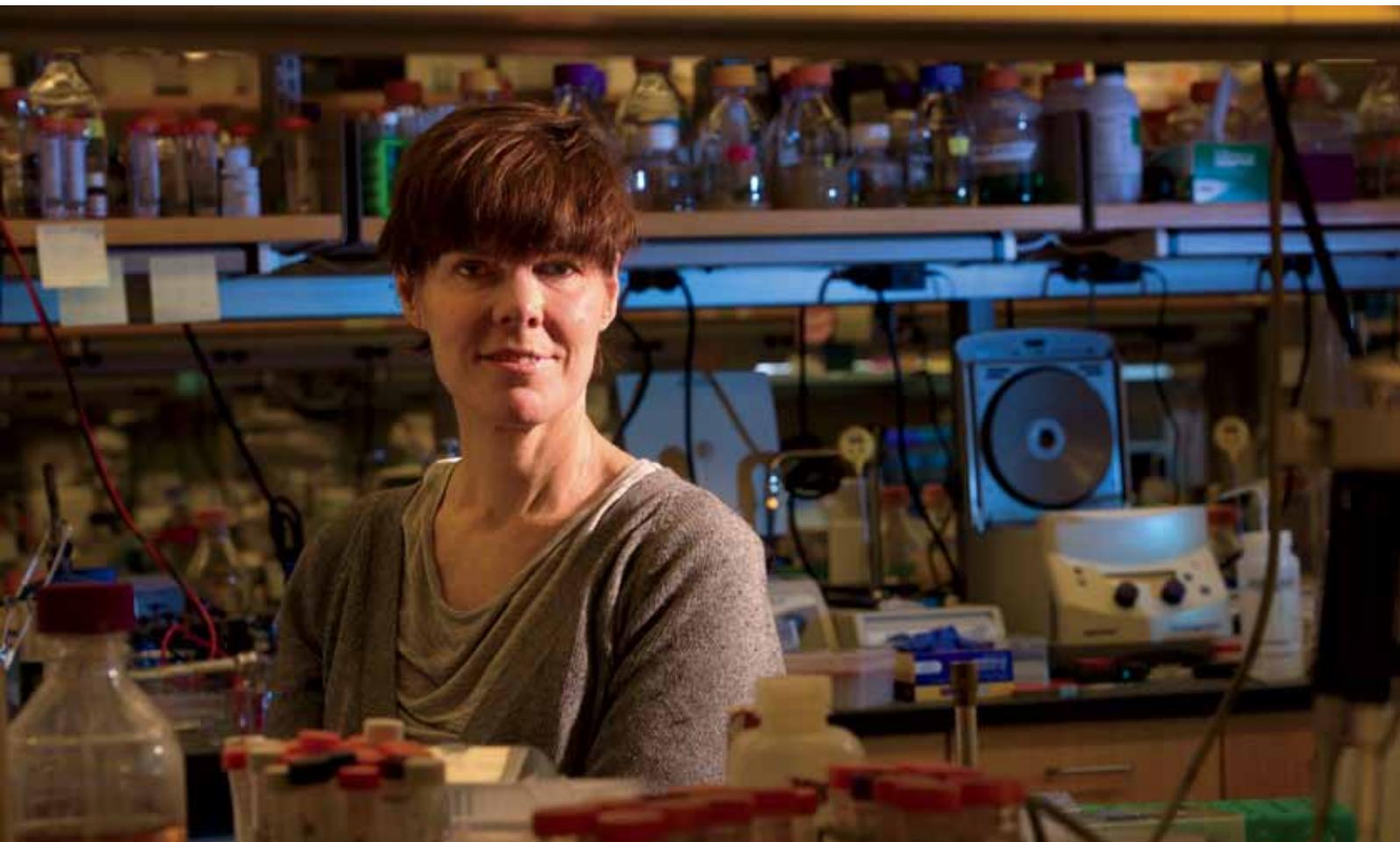
Part of the problem is that, more than 80 years after Fleming's serendipitous discovery, there are still no hard and fast rules for what makes a good drug. Antibiotic discovery remains largely a matter of chance: in high-throughput screens, pharmaceutical

“It's a Red Queen race. We're running as fast as we can just to stay in the same place.”

companies test hundreds of thousands of molecules on live bacteria or key enzymes and look for evidence of inhibitory effects. But finding a hit is just the beginning. An antibiotic is the exceedingly rare mole-

cule that survives a gauntlet of contradictory requirements—killing a broad spectrum of bacteria while being absorbed harmlessly by the human body—and there is no way to predict where a compound might fail. Sifting through early leads is expensive, risky, and time-consuming: it takes approximately 10 years and a billion dollars to bring a new drug to market.

Consequently, the responsibility for research is falling increasingly to academic researchers. Michael Gilmore organized Harvard's Program on Antibiotic Resistance in 2009: a multimillion-dollar project grant from the National Institutes of Health (NIH) currently funds the collaborative effort of HWPAR's seven independent laboratories to study antibiotic-resistant *S. aureus*. The goal of the academic program is less to develop new drugs—a task better suited to companies, given their superior financial resources and specialized pharmacological knowledge—than to develop innovative approaches to finding them. “We explore new drug targets that are higher risk than those a company would work on,” explains professor of microbiology and immunobiology Suzanne Walker, one of Gilmore's collaborators. “It's hard to beat a company at developing a compound, and there's no reason to



do that. But I think it's up to academics to lay the groundwork."

In 2009, Walker's lab discovered the compound targocil, which prevents bacterial growth by interfering with a cellular pathway that creates a critical component of the *S. aureus* cell wall. Targocil is potentially useful for treating drug-resistant strains like MRSA: the compound restores the lethal effect of antibiotics like penicillin and methicillin by disabling bacterial modes of resistance. Other such molecules have been clinically useful; to combat the naturally penicillin-resistant species *E. coli*, for instance, some treatments like augmentin combine a penicillin-like antibiotic with a second compound that inhibits the enzyme that confers resistance, and targocil combination treatments have likewise succeeded in overcoming MRSA in mice. Moreover, targocil has proven to be a useful tool for understanding *S. aureus* biology. "The more we understand about the physiology of MRSA, the more likely we are to find new ways to intervene," says Walker.

Some researchers are looking beyond Ehrlich's magic bullet. That paradigm of treatment has dominated medical research since penicillin's discovery, in part because it perfectly suits the setting of a lab. A good drug molecule kills bacteria in a petri dish—an effect that, as Fleming's discovery evidenced, is easy to observe. But the realities of an infection are far more complex. In its interactions with a host or with other bacteria, a microbe takes on distinct properties that can diminish an antibiotic's success—or provide new avenues for drug discovery.

Many bacteria, *S. aureus* included, form dense communities

called biofilms that are difficult to eradicate, particularly on devices, like catheters, that are inserted into the body. Sticking together helps bacteria shield each other from an antibiotic's effects, however susceptible they may be when isolated in a lab. "There is no *genetic* change, but the physiology has changed," explains professor of microbiology and immunobiology Roberto Kolter, who, with Richard Losick, studies the genetic basis of biofilm formation as part of HWPAR. "A few bacteria might survive antibiotic treatment because they were in the right *physiological* state."

Other scientists are delving deep into the intricacies of infection, targeting biological properties that may not be apparent in lab settings. "If we learn more about the host-pathogen interaction, we can be more surgical about our intervention," says Deborah Hung, associate professor of microbiology and immunobiology. Her lab searches for molecules that interfere with a pathogen's ability to cause disease. For infections like diphtheria and botulism, for instance, antitoxins are often prescribed alongside antibiotics to neutralize the pathogen's toxic proteins.

Natural immune processes may provide additional opportunities for targeted intervention. "I think it's important to understand pathogenesis—not just from the pathogen's point of view, but also from the host's point of view," says professor of genetics Fred Ausubel, another of Gilmore's collaborators. Using the nem-

Suzanne Walker discovered targocil, a molecule that blocks certain mechanisms of drug resistance.

atode *Caenorhabditis elegans* as a model, he has identified more than a hundred compounds that he describes as anti-infectives: they cure a range of infections in the worm without killing the bacterial pathogens, some by modulating natural immune processes. “If you really understand how a pathogen causes disease and how a host resists,” he says, “then you can intervene a lot more easily with a targeted therapeutic, or a vaccine.” Such novel approaches may soon become a standard part of antibiotic therapy. Small companies are beginning to make use of recent academic discoveries, and last year, HPWAR and AstraZeneca brought together experts from academia and industry to discuss collaborative approaches to combatting antibiotic resistance.

After its long stasis, drug discovery shows signs of picking up. The approvals of linezolid in 2000, daptomycin in 2003, and tigecycline in 2005 have introduced three new chemical classes of drugs,

more than in the previous three decades combined. The Infectious Diseases Society of America (IDSA) has launched an initiative to develop 10 new antibiotics by 2020, and new public-private partnerships are helping draw large pharmaceutical companies back into antibiotic discovery. Even so, treatments for some pathogens remain worryingly sparse, and the continually evolving nature of bacteria means that constant cycles of drug discovery will be necessary for the foreseeable future if medical care is to remain ahead of antibiotic resistance. Yet the *entire* 2013 budget for the NIH, at just under \$30 billion, falls short of the CDC estimate of the yearly cost of antibiotic-resistant infections—as high as \$35 billion, when accounting for lost productivity.

“I’m not pessimistic about the science,” says Losick. “But it needs the proper investment.”

Societal drugs

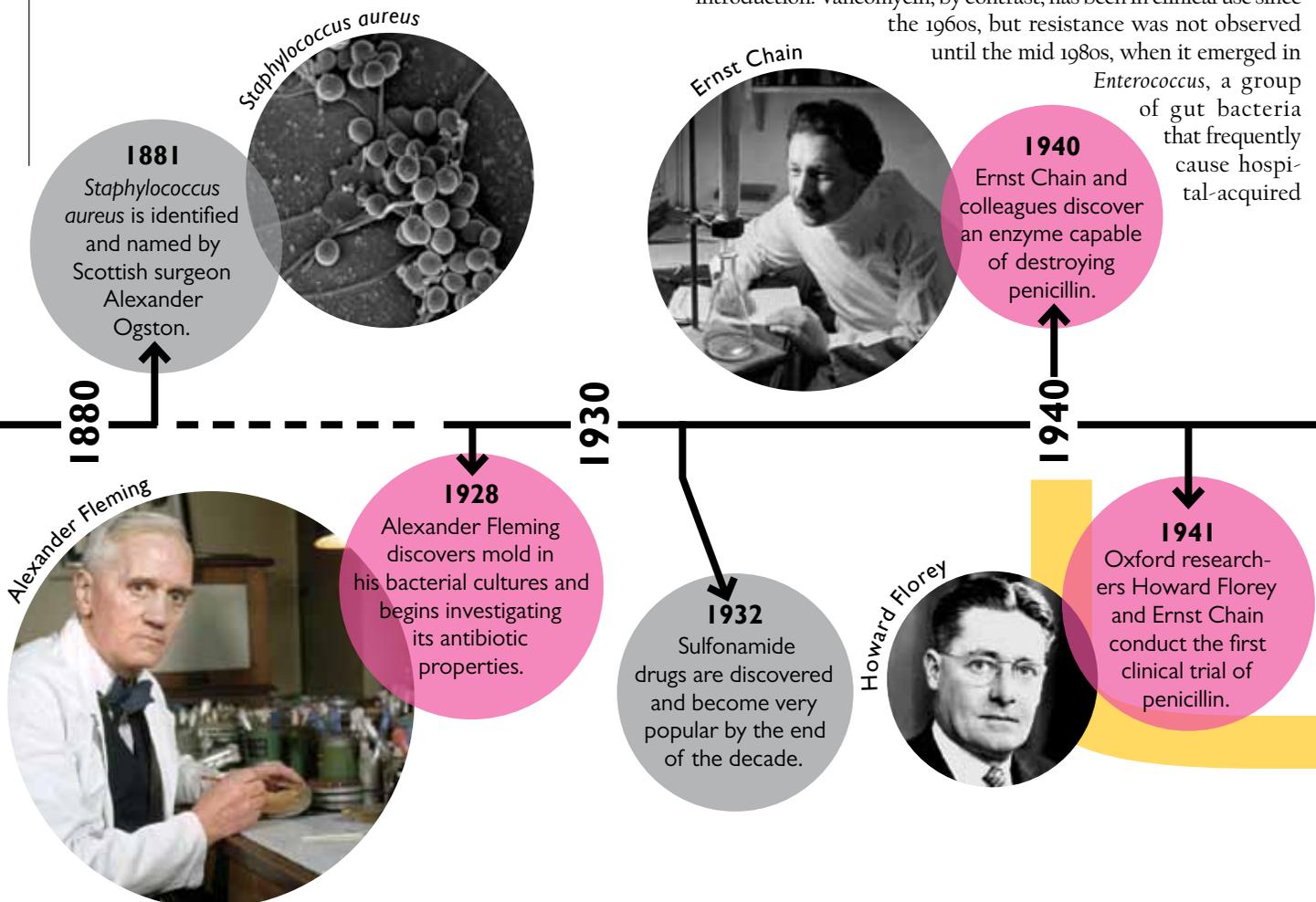
SINCE THE 1970s, vancomycin has been the last-line drug against MRSA. Isolated in 1953 from a soil sample collected in the forests of Borneo, vancomycin never gained the widespread popularity of penicillin and its derivatives. Impurities in its early production (its discoverers at pharmaceutical company Eli Lilly nicknamed initial preparations “Mississippi mud”) had toxic effects, and even after the drug was refined, it was mainly given intravenously rather than orally.

Perhaps because of its more limited early use, vancomycin has enjoyed a relatively lengthy life. Resistance to most antibiotics has historically become widespread within one to three years of their introduction. Vancomycin, by contrast, has been in clinical use since the 1960s, but resistance was not observed until the mid 1980s, when it emerged in *Enterococcus*, a group of gut bacteria that frequently cause hospital-acquired

Timeline of Antibiotic Use

- Penicillin-related
- Methicillin-related
- Vancomycin-related
- Historical landmarks
- New classes of antibiotics introduced or discovered

Given the complexity of scientific investigations, all dates (though carefully checked) are necessarily approximate.



CLOCKWISE FROM FAR TOP LEFT: GARY D. GAUGLER; SCIENCE SOURCE; UNITED KINGDOM GOVERNMENT; NOBEL FOUNDATION; UNITED KINGDOM GOVERNMENT

infections, typically of the urinary tract and blood. Vancomycin-resistant *S. aureus*, or VRSA, did not appear until 2002, and as of 2013, there had been only 14 reported cases in the United States.

Concealed behind vancomycin's apparent longevity, however, are concerns about antibiotic use and abuse. As a last-line drug administered only in hospitals, vancomycin's use was strictly limited, in turn limiting the selective pressure for bacteria to become resistant. In the late 1970s, though, two changes took place. Avoparcin, a closely related drug, was approved for use on farms in Europe. And in the United States, vancomycin usage grew exponentially with the escalating MRSA epidemic, increasing 100-fold in the next 20 years.

The farm use of avoparcin and other antibiotics has drawn fierce criticism. For decades, scientists have called agricultural antibiotic use unnecessary and harmful, because the main function of antibiotics on farms is to promote animal growth, not treat disease. For reasons still poorly understood, small amounts of antibiotics regularly mixed into feed make young animals gain weight up to 8 percent more quickly, which can help farmers cross the line from loss to profit. The practice benefits both the agricultural and pharmaceutical industries: the Food and Drug Administration (FDA) estimates that 80 percent of American antibiotic use today takes place on farms.

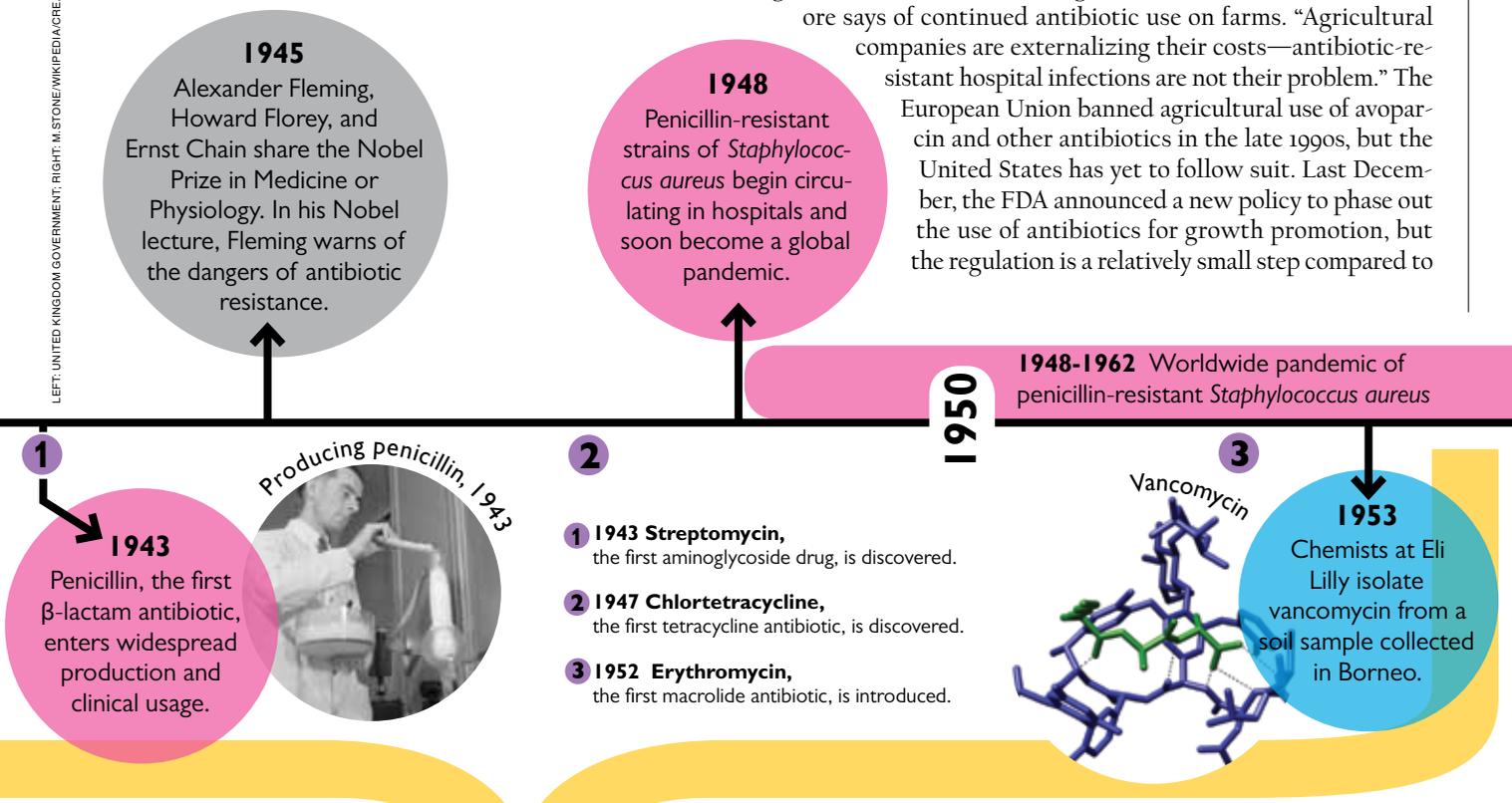
In 1976, Stuart Levy of Tufts led perhaps the only prospective study to investigate whether small amounts of antibiotic use in livestock could lead to the spread of resistant bacteria to humans. His team began feeding tetracycline to some chickens on a small farm in Sherborn, Massachusetts, that had never before used

antibiotics in animals. Within a week, tetracycline resistance appeared in the chickens' gut bacteria, and then in untreated chickens in neighboring pens—and, a few months later, in the intestinal flora of the farmers. Even more alarming was the fact that with time, the tetracycline-resistant bacteria also developed resistance to other, unrelated antibiotics to which they had never been exposed. The finding was attributed to the aggregation of resistance genes on mobile plasmids, as described in Japan, that then spread to other bacterial species. The farm acted as an incubator for multidrug resistance.

In 1981, Levy founded the Alliance for the Prudent Use of Antibiotics, a global nonprofit group that disseminates information about and sponsors advocacy for the proper management of antibiotics. His call for a ban on antibiotic use in agriculture has been echoed by many other groups, including the IDSA, the Union of Concerned Scientists, and, recently, the Pew Charitable Trusts. "We have a lot of good antibiotics, we just haven't known how to use them," says Roberto Kolter of HWPARG, who is also past president of the American Society for Microbiology. "We have abused them."

Indeed, evidence now suggests that agricultural use of avoparcin shortened the lifespan of vancomycin, the last-line drug. Gilmore's lab established that the strains of vancomycin-resistant *Enterococcus* (VRE) that cause an estimated 20,000 hospital infections in the United States each year are descended not from relatively innocuous strains in the human gut, but rather from strains that live in the guts of livestock. From VRE, they found, the DNA trail leads to the dozen known American cases of VRSA, each of which occurred when MRSA acquired resistance genes from its *Enterococcus* neighbors. "This is a real issue," Gilmore says of continued antibiotic use on farms. "Agricultural companies are externalizing their costs—antibiotic-resistant hospital infections are not their problem." The European Union banned agricultural use of avoparcin and other antibiotics in the late 1990s, but the United States has yet to follow suit. Last December, the FDA announced a new policy to phase out the use of antibiotics for growth promotion, but the regulation is a relatively small step compared to

LEFT: UNITED KINGDOM GOVERNMENT; RIGHT: M. STONE/WIKIPEDIA/CREATIVE COMMONS



1940s to 1950s

During the Golden Age of antibiotic discovery, pharmaceutical companies isolate many new classes of antibiotics, frequently from exotic soils.

what many scientists have been demanding for decades.

The controversy over farm use of antibiotics illustrates their complex role as what Levy described in his book *The Antibiotic Paradox* as “societal drugs.” Antibiotic resistance begins with a random mutation or chance transfer of genes, but without the selective pressure of antibiotic exposure, a mutant never comes to dominate the bacterial population. It is *human* society, through antibiotic misuse and overuse, that gives a rare event its pandemic potential. “Each individual use,” Levy wrote in 1997, whether human or animal, “contributes to the sum total of society’s antibiotic exposure. In a broader sense, the resistance problem is ecological.”

No other medications carry the same societal consequences for abuse. Yet in the United States, an astonishing half of antibiotic use in humans is estimated to be unnecessary. Drugs are often prescribed needlessly for ailments like the common cold and the flu, which are not even caused by bacteria, but by viruses—which are not susceptible to the same drugs.

“It’s bewildering,” admits Jeffrey A. Linder, associate professor of medicine and associate physician at Brigham and Women’s Hospital. Opponents of *agricultural* antibiotic use can point to specific culprits, but antibiotic *over-prescription* has complex roots. Physicians often follow medical recommendations when responding to hypothetical scenarios, but may act otherwise in reality. Linder and colleagues have found, for instance, that even though medical guidelines state that antibiotics are *never* needed for acute bronchitis, they are prescribed 70 percent of the time.

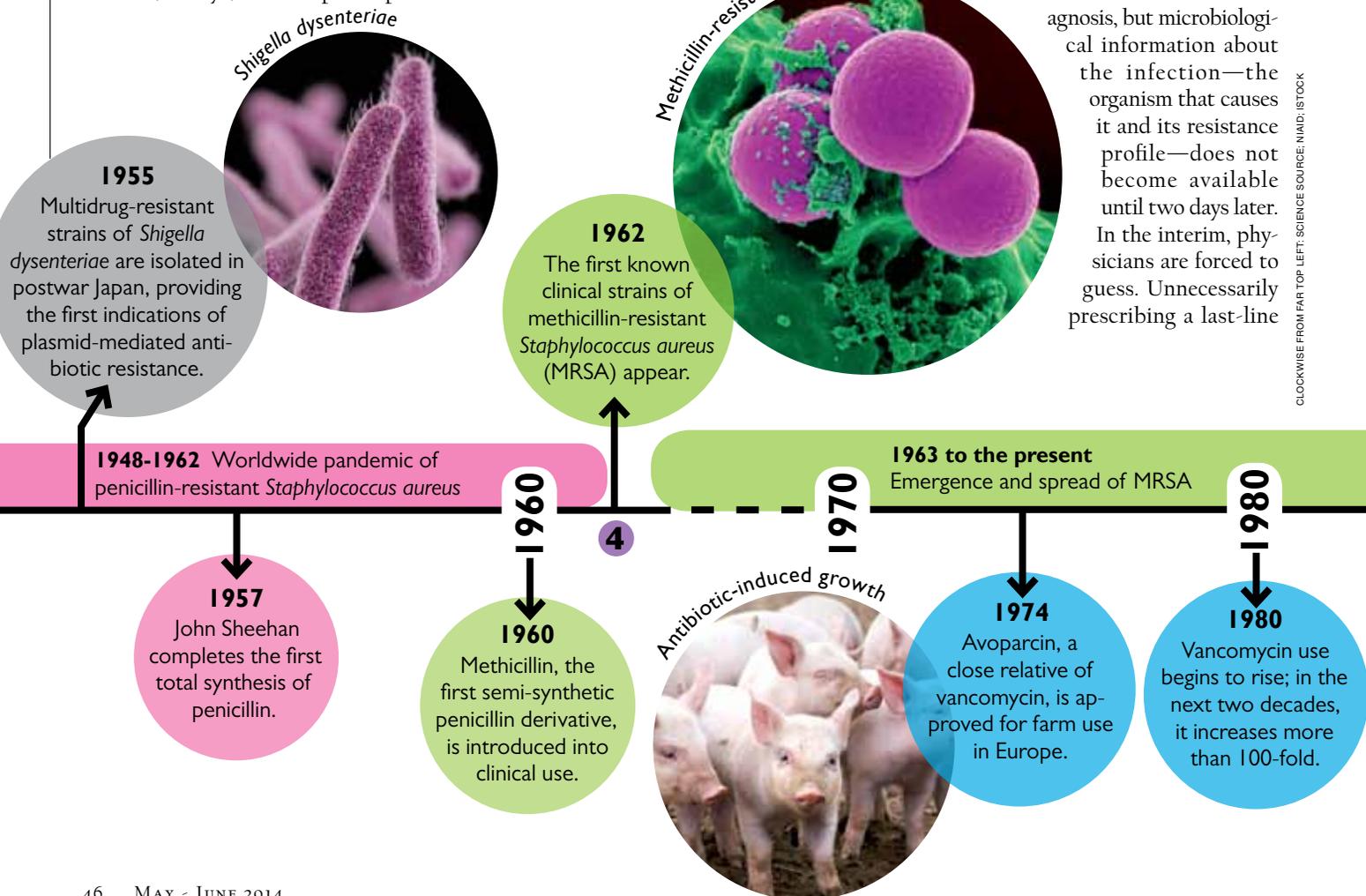
Often, he says, the over-prescription results from miscommu-

nication. Patients are often confused about when antibiotics are effective and concerned by how long symptoms last, even though one or two weeks is normal for a cold, three for a cough. Doctors, in turn, may prescribe antibiotics in hope of avoiding a patient confrontation. “I think there’s a role for educating patients” about what antibiotics can and can’t do, Linder adds. “There’s stuff doctors can do to help people feel better and get a good night’s sleep, but antibiotics won’t make the duration of a cold or cough any shorter.” In fact, their over-prescription can make patients *worse*. Antibiotic overuse has societal *and* personal side effects: diarrhea, allergic reactions, drug interactions, and unnecessary cost.

Though common ailments account for most instances of antibiotic over-prescription, the problem extends to severe infections in hospital settings as well. In the case of last-line drug vancomycin, for instance, skyrocketing usage in the 1980s likely helped spread strains of the vancomycin-resistant *Enterococcus* that had emerged on farms, creating the current epidemic. Most of this antibiotic use was unavoidable, a consequence of MRSA’s rapid spread, but public-health officials still see considerable room for improving treatment practices. According to a CDC report released in March, approximately one-third of vancomycin prescriptions include potential errors: the drug is given without proper testing or evaluation, or given longer than necessary.

The errors reflect a significant and longstanding information gap. When a hospital patient is admitted,

doctors prescribe treatment based on an initial clinical diagnosis, but microbiological information about the infection—the organism that causes it and its resistance profile—does not become available until two days later. In the interim, physicians are forced to guess. Unnecessarily prescribing a last-line



drug like vancomycin can decrease its long-term efficacy, but treating an infection with methicillin could be deadly if the pathogen turns out to be MRSA.

In response, many hospitals have set up infection-control units that track patterns of disease and resistance within their wards—critical measures for promoting responsible antibiotic use. “With few antibiotics in the pipeline, we have to be even more careful about preserving the ones we have,” says David Hooper, professor of medicine and chief of the infection-control unit at Massachusetts General Hospital, and another HWPAR researcher. “Antimicrobial stewardship is important to help doctors select the right drugs, and infection control is important to make sure we don’t amplify infections by allowing them to be passed from patient to patient.”

In northern Europe, proactive infection control and vigilant surveillance have kept MRSA rates low: less than 5 percent of staph specimens isolated in Denmark and the Netherlands are methicillin-resistant, compared to nearly 50 percent in the United States. But even in the United States, increased hospital vigilance is beginning to have an effect. Between 2005 and 2011, national MRSA rates fell by nearly one-third, with rates of hospital-acquired infections dropping by more than half, and Congress is considering an

act that would strengthen disease surveillance at a national level.

Nevertheless, MRSA continues to kill more than 11,000 Americans every year, and approximately a quarter of infections occur in the community, outside healthcare settings. Hospitals can play critical roles in curbing drug-resistant strains, but their role is limited: agriculture and the wider community remain bigger drivers of antibiotic use. By the time drug resistance reaches hospital wards, an epidemic is already under way.

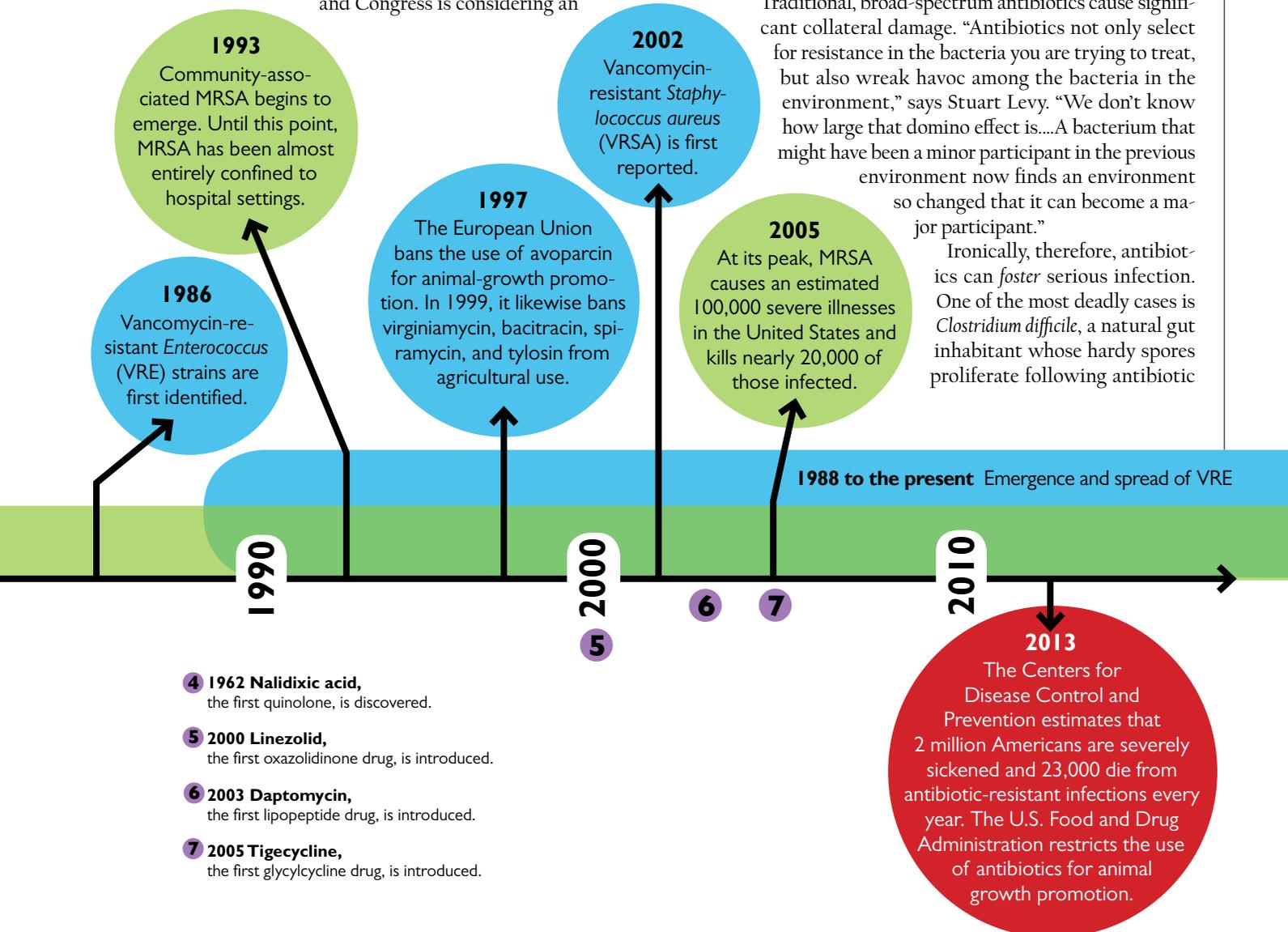
A new normal

ANTIBIOTIC RESISTANCE raises the grim specter of a return to the medicine of a century ago. Last year’s emergence of plasmid-mediated resistance to carbapenems, last-line drugs against a variety of pathogens, set off alarms throughout the public-health community. Before long, officials warned, resistance might become so common that physicians will run out of treatment options altogether.

In fact, we are already in the post-antibiotic era. It is not that drugs have lost all efficacy: the handful of truly untreatable superbugs has, so far, been contained. But decades of antibiotic use have altered, perhaps irrevocably, the relationship between humans and the microbial world.

Traditional, broad-spectrum antibiotics cause significant collateral damage. “Antibiotics not only select for resistance in the bacteria you are trying to treat, but also wreak havoc among the bacteria in the environment,” says Stuart Levy. “We don’t know how large that domino effect is....A bacterium that might have been a minor participant in the previous environment now finds an environment so changed that it can become a major participant.”

Ironically, therefore, antibiotics can foster serious infection. One of the most deadly cases is *Clostridium difficile*, a natural gut inhabitant whose hardy spores proliferate following antibiotic



Encouraging Antibiotic Innovation

ONE OF THE chief obstacles to finding new antibiotics is that many pharmaceutical companies have stopped looking. According to a report by the Infectious Diseases Society of America, just five major firms were engaged in antibiotic discovery in 2009; others, discouraged by economic and regulatory challenges, have left the field. Even worse, the report warned, “We remain concerned that the infrastructure for discovering and developing new antibacterials continues to stagnate, thereby risking the future pipeline of antibacterial drugs.”

The economics of antibiotics pose a major barrier to pharmaceutical investment. Antibiotics are no cheaper to develop than other drugs, but they bring in less revenue: unlike treatments for chronic conditions like asthma or high cholesterol, antibiotics are given in courses that typically last only a few weeks. Moreover, because resistant infections are on the rise, newly approved antibiotics are held in reserve, to be used only after more common treatments fail. To encourage antibiotic development, Congress passed an act in 2012 that granted companies an extra five-year exclusive-marketing period for new drugs that combat infectious diseases, and public-private partnerships are beginning to subsidize the cost of research and clinical trials.

Such clinical trials are a formidable second hurdle: the drug-approval process traditionally requires large, costly trials with many patients. For companies developing treatments for drug-resistant pathogens, says John Rex, head of infection development at AstraZeneca, “That means the epidemic has to have already occurred.” The European Union recently created a new, streamlined pathway for antibiotic approval; the U.S. Food and Drug Administration is considering similar guidelines. The pathway would permit smaller, more rapid trials for drugs that target resistant pathogens; they are similar in concept to guidelines for “orphan drugs” that treat rare diseases. Drugs approved under this pathway would carry a more provisional usage label, advocating their prescription only in well-defined cases in which other options have been exhausted. Such drugs might be considerably more expensive as well, reflecting their medical value. “Antibiotics save your life,” says Rex. “And on average, they give you back many *years* of life”—but they are currently among the cheapest drugs. When accounting for the years of life saved, Rex and colleagues have argued that a course of novel antibiotics given to treat an otherwise resistant infection might rationally cost \$30,000.

Together, the new policies aim to draw companies back into antibiotic development, leading to future innovation. “What I really want to see is a diverse, vibrant drug pipeline,” says Rex. “We’re not quite to that yet, but we’ve laid the groundwork.”

treatment. Without a normal microbial ecosystem to keep it in check, *C. difficile* can cause symptoms ranging from mild diarrhea to life-threatening colitis; in the United States, it now causes 14,000 deaths and at least \$1 billion in additional medical costs a year. Antibiotics may have subtler effects as well: some studies now suggest that, by altering the balance of bacteria in the body, the drugs contribute to weight gain, perhaps bulking up humans as they have long fattened livestock.

By eliminating susceptible bacteria, decades of antibiotic use have also made drug resistance more common, even in nonpathogenic species. As Levy has observed, “The antibiotic susceptibility profile of bacteria on the skin of people today, and in the environments of hospitals and homes, is very different from what it was in the pre-antibiotic era, and even 10 years ago.” In the bacterial community at large, it is no longer unusual for organisms to carry one or more resistance genes, even in the absence of obvious antibiotic exposure. Microbiologists once hoped that antibiotic-resistant bacteria—both within a single patient, and in the broader environment—would die off after drug treatment stopped. But in large swaths of the microbial world, it seems, antibiotic resistance is the new bacterial normal.

It may be time, therefore, for antibiotics themselves to evolve. Michael Gilmore draws an analogy to ecological control: “What we’re talking about now is human ecology management,” he says. “The antibiotics we first discovered were clear-cutters—they killed everything. They were broad-spectrum, they wiped everything out.” Now, he says, researchers are exploring ways to fine-tune antibiotics’ lethal potential.

A holy grail for researchers and clinicians is the development of reliable rapid diagnostics, tests that identify both the microbial cause of an infection and its drug resistance profile within hours, rather than the current standard of two days. “Patients come in with a clinical disease—a urinary tract infection, or pneumonia—but the *cause* of that infection could be one of many different things,” explains Scott Evans, senior research scientist in biostatistics at Harvard School of Public Health. “Currently, we often have to initiate treatment of clinical disease based on unknown causes and antibiotic susceptibility. If we could get rapid diagnostics, then we could better tailor patient treatment.”

In fact, rapid diagnostics are already becoming a reality. As director of the Statistics and Data Management Center for the Antibacterial Resistance Leadership Group, a nationwide clinical research network created in 2013 by the National Institutes of Health, Evans helps evaluate the effectiveness of existing tools. He and collaborators have found that some genomics-based rapid diagnostics are able to accurately detect resistance to certain drugs like penicillins, cephalosporins, and carbapenems.

“I think that rapid diagnostics are a very solvable problem, in the very near future,” says Deborah Hung. “And once we solve that, it completely changes the landscape of what we do.” Reliable rapid diagnostics would pave the way for more precise incarnations of Ehrlich’s magic bullet: narrow-spectrum drugs that target a few bacterial species, rather than the broad spectrum of bacterial diversity that current antibiotics are designed to eliminate. Such possibilities would also open new avenues of drug discovery. “If we get to the point of narrow-spectrum drugs—say we’re looking for a staph-only drug—then you have a lot more potential targets, because a drug doesn’t have to kill



...TE ADJUSTED FOR DAYS OF ANTIBIOTIC RISK
(RADAR)
PENICILLINS
AMPCILLIN
PENICILLIN COMBINATIONS
AMPCILLIN/SULBACTAM
HP/TAZO
CEPHALOSPORINES (COMBINATION)
CEFTRAXONE (IV)
Ceftazidime (IV)
Cefepime (IV)
MONOBACTAMS
AZITROMYIN
CARBAPENEMS
EPRIZINAM
EPRIZINAM
MEROPENEM

as many bacteria as possible,” says Suzanne Walker.

A more radical antibiotic future may cut back the role of antibiotics altogether by using normal bacteria to counter relatively minor infections. A growing area of research explores how to alter microbial interactions to promote human health. Fecal transplants, for instance, have occasionally proven effective against recurrent *C. difficile* infections. Such probiotic treatments that use live microbes are in their infant stages—no one knows exactly how normal gut bacteria keep *C. difficile* in check—but evidence is beginning to suggest that humans’ future with bacteria will depend, at least in part, on careful coexistence.

An epidemic begins

NEARLY 80 years after the antibiotic revolution, the human relationship with *S. aureus* is again on the verge of change. Genes for vancomycin resistance are increasingly prevalent, and on at least 12 separate occasions, they have entered MRSA to create new, vancomycin-resistant strains. Resistance to last-line drugs is brewing in many other bacterial species as well. Chance will

“What we’re talking about now is human ecology management. The antibiotics we first discovered were clear-cutters—they killed everything.”

determine when resistance finally catches on, and resistant strains spread through the bacterial population—taking the place of what has come before,

once again transforming the game of survival that humans and microbes play.

Can humans evolve first? Bacterial evolution occurs with barely imaginable rapidity. But the antibiotic revolution that transformed our ancient relationship started not with a gene, but with an idea. This idea, once harnessed and spread through society at scale—the human version, perhaps, of horizontal gene transfer—has enabled our species to remain ahead.

The pieces are in place for change. We have our own means of resistance, and they are already common in parts of the human population. Activism and awareness are ancient, while the seeds of scientific innovation are new. What has been missing is the impetus for change, the pressure that causes an idea to spread.

“How big does this problem have to get for us to do something about it?” asks Michael Gilmore. “The challenge is, there’s a lag between when we realize a problem is big enough and when we can come up with a solution.”

The cause may be a gene or an idea. But sometime soon, an epidemic will begin. ▽

Scott Evans designs clinical trials that test the efficacy of rapid diagnostics.

Katherine Xue '13 is associate editor of this magazine.