Reviving the Antibiotic Miracle?

As the development of antibiotic-resistant bacteria accelerates, research on new antibiotics lags. But a few promising lines of investigation remain open

Back in the 1940s and 50s, when the first antibiotics such as penicillin began making their way into clinical use, they were hailed as miracle drugs—and rightly so. By killing the bacteria that cause many of humankind's worst infectious diseases, such as tuberculosis and pneumonia, they saved countless lives. But not all miracles last forever.

Today, we're on the verge of a "medical disaster" that would return physicians to the pre-penicillin days when even seemingly small infections could turn lethal for lack of effective drugs, warned microbiologist Alexander Tomasz of Rockefeller University at the recent meeting of the American Association for the Advancement of Science. That gruesome prediction, which would have been scoffed at a decade ago, stems from the remarkable ability of bacteria to develop resistance to almost any antibiotic medical research has thrown at them. Given enough time, it seems, these wily microbes will learn to chew up, spit out, or shield themselves from any drug (see articles on pages 375, 382, and 388). And when one strain learns a new resistance strategy, it's not shy about sharing it with others, an ability that's played a crucial role in the rapid spread of antibiotic resistance.

That was then. But now, antibiotics, which saved many lives in World War II, are losing their punch.

Equally worrisome is the relative dearth of new antibiotics in the pipeline, particularly those with novel modes of action that would presumably be more difficult for bacteria to circumvent. Thinking that they had already won a total victory—the market after all is crowded with more than 100 antibiotics—many pharmaceutical firms all but abandoned work on new antibiotics in the eighties (see story on p. 362).

And while drug companies often don't reveal what they are doing for proprietary reasons, many academic researchers argue that they haven't changed course, even though the bacteria, pressured by the heavy use of antibiotics in farm animals and overprescription of the drugs by physicians, have continued to develop resistance. For instance, strains of *Staphylococcus*, which cause often fatal hospital infections, are now immune to all but one existing antibiotic—and that final barrier could fall at any time, caution microbiologists. "The bacteria won't give in. The drug companies will," grimly jokes microbiologist Brian Spratt of the University of Sussex in the United Kingdom.

But while Spratt may be correct about drug companies putting little emphasis now on antibiotic drug development, the research hasn't disappeared completely. Companies, for example, continue to screen soil samples, marine waters, and other sources for original bacteria-killing compounds. Investigators are also pursuing a more speculative line of attack on bacteria, exploring whether physicians actually need to kill the microbes outright or merely find ways to "disarm" them, thus preventing their host from becoming ill. And finally, the growing molecular level understanding of how bacteria evade drugs has provided hope that that information will revive the aging classics of antibiotics. "This allows you to rejuvenate the old drugs by poisoning the resistance mechanism," says Stuart Levy, director of the Center for Adaptation Genetics and Drug Resistance at Tufts University School of Medicine.

Teaching old drugs new tricks

Indeed, such "drug rejuvenation" has long been an industry strategy for staying one jump ahead of the development of resistant bacteria. Consider the *beta*-lactams, a family of antibiotics that includes the penicillins and cephalosporins, which work by disrupting the construction of the bacterial cell wall. Microbes battled back against these drugs with enzymes that destroy the *beta*-lactams. In fact, penicillin resistance by this mechanism showed up only a few years after the drug made its clinical debut in 1942.

But for decades, drug company chemists managed to keep ahead in this struggle by making slight alterations in the structures of their antibiotics, so that the destructive enzymes, called *beta*-lactamases, could not recognize and attack the drugs. But the fixes always proved temporary because the bacteria quickly mutate their *beta*-lactamases, or acquire new ones from other microbes, to match the subtly altered structures. Cephalosporins, for example, have passed through three generations, and though there's been talk for years about fourth-generation drugs, none have made their debut. That example, and similar roadblocks on other drugs, suggests that companies may be reaching their limits on chemical manipulation of existing groups of antibiotics, says George Miller, a presidential fellow at the Schering-Plough Research Institute in Kenilworth, New Jersey.

S. B. LEVY, *THE ANTIBIOTIC PARADOX: HOW MIRACLE DRUGS ARE DESTROYING THE MIRACLE*, PLENUM, N.Y., 1992.

That's one reason why a few firms, such as Pfizer Inc., SmithKline Beecham, and Lederle Laboratories, have taken a more direct tack against the *beta*-lactamases. They're marketing combination therapies in which a *beta*-lactam antibiotic is protected from destruction by a separate *beta*-lactamase inhibitor. These inhibitors were found with traditional screening methods, but back in 1986, x-ray crystallographer James Knox of the University of Connecticut in Storrs and colleagues first unveiled the three-dimensional shape of one of these *beta*-lactamases. With such images comes hope of structure-based design of new and more effective inhibitors. "If you know what the target is, you can use a broader imagination," notes George Jacoby, a *beta*-lactam expert at the Lahey Clinic in Boston.

The *beta*-lactam family is not the only class of antibiotics where there's plentiful information on resistance mechanisms to exploit. The previously popular tetracyclines, which work by inhibiting bacterial protein synthesis, have been rendered mostly ineffective, in large part because many bacteria have developed an efficient pump that removes the antibiotics before they can do any damage. But Tuft's Levy and his colleagues are trying to bring about what he calls "a renaissance of tetracyclines," by analyzing the proteins that make up these pumps and developing small molecules to block their action. Such compounds could return tetracyclines to their old glory, if delivered in concert with the antibiotics. Moreover, they would provide a test case of whether other antibiotics affected by bacterial pumps can be revived.

To some, such tinkering with existing drugs is merely a delaying tactic that won't

buy much time against clever bacteria. Current antibiotics tackle three kinds of targets: protein synthesis, cell wall construction, and DNA replication. But microbes have clearly demonstrated they can maneuver around such drugs, argues Schering-Plough's Miller. "We need to discover new classes of antibiotics," he says, adding that his company is hopeful it's actually found one such novel-acting compound.

In the early 1980s, Schering-Plough microbial ecologists collected soil from a dried lake bed in Kenya. When the samples were later analyzed, the company chanced upon a class of compounds called everninomicins, natural products produced by bacteria in the soil. The everninomicins proved to be effective microbe-killers, at least for so-called gram-positive bacteria (because their cell walls take up a special stain). Through a target that is still unclear—but definitely differs from the traditional three, says Miller—the everninomicins were found to wipe out even multi-drug resistant gram-positive bacterial strains, a group that includes killers such as *Enterococcus* and *Staphylococcus*. But because the compounds damaged the kidneys of experimental animals and there was already a glut of antibiotics on the market, Schering-Plough never followed up this lead.

That changed recently, says Miller, when strains of *Enterococcus* became resistant to vancomycin. Vancomycin resistance is a physician's worst nightmare, since this is the only antibiotic to which a number of strains of bacteria currently respond. Among them are *Staphylococcus* and pneumococcus, which causes pneumonia and ear infections. And if one microbe has developed resistance, others are likely not far behind. Laboratory experiments have shown, for example, that *Enterococcus* can transfer vancomycin resistance to *Staphylococcus*. It's only a matter of time, say researchers, before that happens in nature and creates a superbug that physicians are helpless against.

This threatening development prompted Schering-Plough to pull the everninomicins off the shelf for another look. The company has now spent four years in preclinical development, tinkering with the compounds' structure to eliminate their kidney toxicity and other side effects, while retaining their microbe-killing abilities. One such compound has made it through laboratory and animal testing and is about ready to start trials with humans. But preclinical success is no guarantee that a drug will prove safe and effective in humans and survive the FDA gauntlet. Indeed, several companies trying to develop drugs to treat sepsis, an often lethal condition that develops in some infection patients, have learned this to their dismay (see story on p. 366). Miller warns: "We have one compound and that compound could easily disappear."

And if the everninomicins fade from sight again, there's little out there to take their place. In the last year or two, peptide and steroidal antimicrobial agents found in sharks and frogs have attracted a great deal of press attention and have even given birth to a company called Magainin, Inc. (see Perspective on p. 373), but these compounds are still years from clinical trials. Moreover, peptides are traditionally difficult to turn into drugs taken orally, since the stomach's enzymes chew them up easily.

This apparent drought in novel antibiotics is exacerbated, claim some, because industry so far has shown little inclination to take advantage of the leads being provided by academic researchers. As Knox points out, his pictures of key proteins involved in antibiotic resistance could be of great aid in developing novel drugs. From the structure of these target molecules, drug designers should be able to build, atom by atom, original antibiotics or inhibitors that protect the drugs from enzymes like *beta*-lactamase. But, he says, no such "rationally"-designed antibiotic or inhibitor has yet emerged from industry. "They've had this information for some time....They're riding on the old antibacterial drugs, hoping they'll carry them through," Knox asserts.

And he's not the only researcher who's found that industry has been slow to call. Take William Jacobs, a Howard Hughes Medical Institute researcher at the Albert Einstein College of Medicine, who with his colleagues has been waging a research war on the bacteria that cause tuberculosis. Last year, they scored a crucial victory, cloning a gene that makes the microbes resistant to isoniazid, a drug of choice for the deadly disease (*Science*, 14 Jan., pp. 172 and 227). In the months that followed, the Albert Einstein group has purified the protein encoded by the gene, worked out what it does, and is now slowly revealing its three-dimensional structure. This vital information could allow biomedical firms to intelligently redesign an isoniazid—or shape a completely new drug—that would sidestep any resistance.

One might expect that Jacobs and his colleagues have been flooded with inquiries from industry. Think again. "I'm very surprised, to be honest, that the Mercks, the Bristol-Myers, the Lillys haven't called....The phone hasn't rung off the hook....The only people who have called have been small [compa-

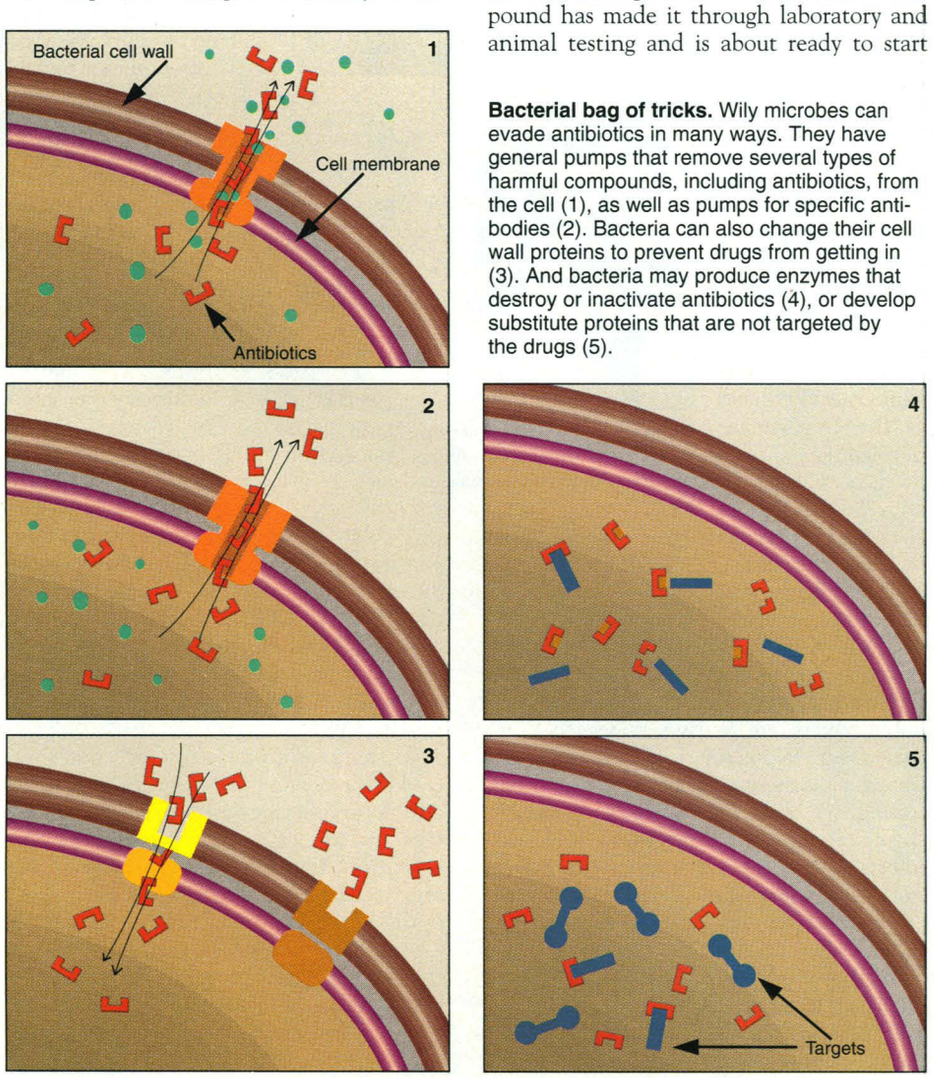


ILLUSTRATION: D. DEFRANCESCO

Bacterial bag of tricks. Wily microbes can evade antibiotics in many ways. They have general pumps that remove several types of harmful compounds, including antibiotics, from the cell (1), as well as pumps for specific antibodies (2). Bacteria can also change their cell wall proteins to prevent drugs from getting in (3). And bacteria may produce enzymes that destroy or inactivate antibiotics (4), or develop substitute proteins that are not targeted by the drugs (5).

nies]," says a perplexed Jacobs. Perhaps, he suggests, the pharmaceutical giants are following up on the advances secretly, but Jacobs worries they're simply ignoring the work.

Taming, instead of killing

The current drought of new drugs, combined with the proven ability of bacteria to develop resistance to all traditional antibiotics, has prompted some scientists to think it's time to stop concentrating exclusively on developing drugs to kill microbes and to take another approach instead: disarm, rather than kill. Aggressively pursuing that unusual agenda is Microcide Pharmaceuticals, a start-up in Mountain View, California. Microcide envisions, for instance, producing drugs that interfere with the spread of bacteria throughout the host, presumably keeping the microbe in check long enough for the patient's immune system to look. It's a novel strategy that will demand a detailed picture of the mechanisms by which microbes select, infiltrate, and destroy cells. "It's not a short fix. It's a long-term approach and it's going to be difficult....You have to understand the basics of how pathogens work," explains Stanford University microbiologist Stanley Falkow, a member of Microcide's science advisory board.

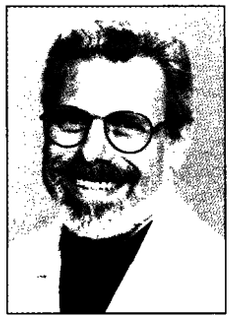
But while Microcide has locked up some of the nation's leading experts on bacterial pathogenesis, some wonder whether that will be enough; they question, for instance, the basic premise of drugs intended merely to keep the bacterial population static or weakened, especially in individuals who might already have a feeble immune system. "I want to get the bugs dead in an immunocompromised host....If you cut down on virulence, the bugs don't go away. If a couple of bugs survive, you're back to square one," says Prabhavathi Fernandes of Bristol-Myers Squibb's drug discovery unit.

Indeed, square one is how many researchers portray the overall state of antibiotics today. And the rapid rise of resistant bacteria has made many worry that even intelligently constructed antibiotics, crafted with an intimate knowledge of the target proteins in the microbe, will prove no less vulnerable than compounds found by blind screening. "Bacteria adapt to everything we do, even if it's designed rationally," says Mitchell Cohen of the Centers for Disease Control. In fact, those familiar with the life-and-death struggle against bacteria are increasingly hesitant to place their money on the continued success of medical researchers. As Julian Davies, a microbiologist at University of British Columbia in Vancouver, Canada, told *Science*: "If I'm reincarnated after death, I'd like to be a microbe. They're fantastic." Such enthusiasm for these amazing bugs, however, is quickly tempered by the knowledge of the horrors they can bring.

–John Travis

Funding Crunch Hobbles Antibiotic Resistance Research

In 1990, a disgruntled trio of physician-scientists convened a workshop on antibiotic resistance. They brought together some twenty participants to talk about research, but that wasn't their chief motive. They were trying to persuade funders to sit up and take notice of antibiotic-resistant bacteria. The organizers hoped to prod agencies such as the National Institutes of Health (NIH)—which paid for the workshop—into action. Study how bacteria become resistant, they urged. Develop new antibiotics. At the very least, prepare for and track stubborn bacterial strains, such as multi-drug resistant *Mycobacterium tuberculosis* and pneumococci.



Triumvirate: Stuart Levy (top), David Shlaes (lower left), and Gordon Archer sounded the alarm about antibiotic resistance.

Administrators listened and nodded, recalls one of the three instigators, Stuart Levy of Tufts University Medical School. But four years later, with the marked exception of new awards for TB, little of the hoped-for funding has materialized. "Everything we said then is true now—except now the problem is worse," says Levy. He and co-organizer David Shlaes of the Department of Veterans Affairs Medical Center in Cleveland argue that their field suffers from a tradition of neglect by federal agencies, and that drug companies aren't filling the gap.

Agencies such as NIH counter that in the lean, mean 1990s, almost every field of research is underfunded. But as resistant bacterial strains emerge in unexpected places, policymakers are setting aside stock responses and taking a second look at funding for antibiotic resistance research and monitoring. "We are at a very critical crossroads in this country in terms of readiness to deal with infectious diseases and antibiotic resistance from a funding standpoint," warns Gail Cassell, president of the American Society of Microbiology and a member of the advisory council of the National Institute of Allergy and Infectious Diseases (NIAID).

Estimating just how much the government spends on antibiotic resistance is tough, since research and surveillance projects may be included under any number of programs and institutes. Most researchers agree the overall federal effort is modest, especially compared with that in priority fields such as AIDS or breast cancer. In Cassell's view, the most immediate need is more money to keep tabs on resistant strains in communities, so that physicians can take steps, such as changing the drugs they prescribe, to help prevent serious outbreaks.

Unfortunately, in the past decade, many state public health departments have lost resources. Available funding is usually earmarked for specific diseases, leaving little to deal with problems that cut across disease categories, says Cassell. Indeed, in 1992, federal, state, and local governments together spent less than $55,000 on routine monitoring of resistant diseases, according to a survey done by Minnesota state epidemiologist Mike Osterholm.

The Centers for Disease Control (CDC) does have a voluntary program in which hospitals report resistant infections in their patients, but the effort isn't comprehensive and doesn't extend beyond hospitals, says Ruth Berkelman, deputy director of the National Center for Infectious Disease (NCID). As a result, she says, "Nationally, we don't even know how much pneumoccocal disease there is, much less how much of it is resistant." (See Policy Forum, p. 368.)

Better monitoring of what's out there could help prevent and manage outbreaks of antibiotic resistant disease. But most scientists, including Cassell, argue that basic research on how bacteria defy antibiotics is also needed. The government's lead agency in this area is NIAID, which in 1993 funded 24 grants for a total of $7.5 million—less than 1% of the institute's budget. Still, NIAID officials argue that their track record is reasonably good. "We have a very active and diverse program in this area. It's not as