Exploring New Strategies to Fight Drug-Resistant Microbes

"Bacteria are cleverer than men." So writes Columbia University physician Harold Neu, an antibiotics expert, in this special issue on the growing crisis in antibiotic-resistant bacteria. And he should know. At the Columbia-Presbyterian Medical Center in Manhattan where he treats patients, Neu has seen bacteria outwit doctors and their drugs time and time again. Just this summer, he had to prescribe $25,000 worth of antibiotics to a physician who contracted a new strain of multidrug-resistant tuberculosis from a patient. And a few years ago, Neu had to take the extreme step of closing an intensive care ward in his hospital to stop the spread of a deadly species of *Acinetobacter* that killed one patient and infected a half-dozen others with sepsis before he found an antibiotic that could quash it. "For me," says Neu, "drug resistance is very real."

Neu isn't alone. As documented in the series of articles beginning on page 1064, doctors in other hospitals and clinics around the world are also losing the battle against an onslaught of new drug-resistant bacterial infections, including staph, pneumonia, strep, tuberculosis, dysentery, and other diseases that are costly and difficult, if not impossible, to treat. Close behind are viruses—such as AIDS, herpes, cytomegalovirus, and influenza—and other microbes, including pathogenic fungi and the malaria parasite, that are becoming resistant to new drugs. It all adds up to one frightening conclusion: "We have an epidemic of microbial resistance," says National Institutes of Health (NIH) senior scientific adviser Richard Krause, also former director of the National Institute of Allergies and Infectious Diseases (NIAID). And the epidemic is expensive, too. Having to cycle through drug after drug to find one that will kill a patient's resistant bug adds between $100 million and $200 million a year to the nation's medical bill.

As doctors use up their arsenal of familiar antibiotics one by one, it is clear that they will have to find new ways to combat these pernicious microbes. In interviews with *Science*, infectious disease experts proposed a strategy to fight the emerging resistance on three different fronts: In research labs, scientists will need to study these deadly bugs to find ways to design better drugs "rationally" that will disarm them longer. In hospitals and clinics, doctors will have to learn to prescribe antimicrobials more selectively, so as to prevent the spread of resistance from one type of bacteria to another, and also improve sanitation so they don't spread resistant strains from patient to patient. And, in the community, worldwide surveillance systems should be put in place to detect new resistant strains early enough so that they can be contained before they spread.

But despite the threat, experts warn that neither the drug companies nor the federal granting agencies are mobilizing to the extent needed to combat the new drug-resistant bugs. Until the 1980s, drug companies were active in developing new antimicrobials, so that if a pathogen became resistant to one, there was always another that would work. But if people think that drug companies will continue to save them, they should think again, says microbiologist George Miller, a presidential fellow at the Schering-Plough Research Institute: "Drug companies are not looking for a lot of new types of antimicrobials [any more]." Figures from the Food and Drug Administration confirm that only five new antimicrobials were approved last year, and two the year before.

The main reason for the lack of interest, Miller says, is economics. With the possible exception of the *Tuberculosis bacillus*, most drug-resistant bacteria are still a bigger problem for developing nations than for developed coun-

TOP TEN DRUG-RESISTANT MICROBES

Microbes	Diseases caused	Drugs Resisted
1. *Enterobacteriaceae*	bacteremia, pneumonia, urinary tract, surgical wound infections	Aminoglycosides, Beta-Lactam antibiotics, Chloramphenicol, Trimethoprim
2. *Enterococcus*	bacteremias, urinary tract, surgical wound infections	Aminoglycosides, Beta-Lactams, Erythromycin, Vancomycin
3. *Haemophilus influenzae*	epiglotitis, meningitis, otitis media, pneumonia, sinusitis	Beta-Lactams, Chloramphenicol, Tetracycline, Trimethoprim
4. *Mycobacterium tuberculosis*	tuberculosis	Aminoglycosides, Ethambutol, Isoniazid, Pyrazinamide, Rifampin
5. *Neisseria gonorrhoeae*	gonorrhea	Beta-Lactams, Spectinomycin, Tetracycline
6. *Plasmodium falciparum*	malaria	Chloroquine
7. *Pseudomonas aeruginosa*	bacteremia, pneumonia, urinary tract infections	Aminoglycosides, Beta-Lactams, Chloramphenicol, Ciprofloxacin, Tetracycline, Sulfonamides
8. *Shigella dysenteriae*	severe diarrhea	Ampicillin, Trimethoprim-Sulfamethoxazole, Chloramphenicol, Tetracycline
9. *Staphylococcus aureus*	bacteremia, pneumonias, surgical wound infections	Chloramphenicol, Ciprofloxacin, Clindamycin, Erythromycin, Beta-Lactams, Rifampin, Tetracycline, Trimethoprim
10. *Streptococcus pneumoniae*	meningitis, pneumonia	Aminoglycosides, Chloramphenicol, Erythomycin, Penicillin

Source: George Jacoby

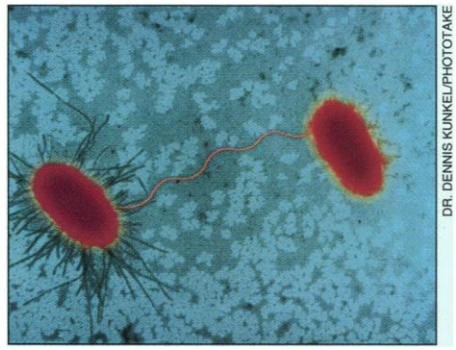
tries like the United States, where doctors can still usually find at least one antibiotic that will work—even though the patient's health may deteriorate and his bills escalate as doctors search for an effective drug. Since it costs about $200 million to bring a drug to market, Miller explains, a company can't expect to make a profit on a drug that will be needed mainly by citizens of developing nations who can't afford the new drugs.

And the government doesn't seem to be investing much in the research end of the pipeline either. NIH funding for infectious disease research dwindled until the mid-1980s, and though it is now rising, most of the new funds are aimed at finding drugs to treat AIDS. The budget is inadequate to address the scientific challenges of increasing drug resistance, says internist George Jacoby, a specialist in infectious diseases at Harvard's Massachusetts General Hospital. NIAID spent only $8.8 million last year on research related to drug resistance (excluding AIDS)—and last year the institute turned down a formal proposal by infectious disease experts to increase funding for antibiotic research.

Still, some dire emergencies have spurred the research funding agencies to action. The emergence of a strain of *Tuberculosis bacillus* resistant to one or more drugs—identified in 36 states last year including New York, where it accounted for 42% of hospitalized TB cases—has helped NIAID win more funding for TB research, albeit only a $200,000 increase in the proposed budget for 1993. And the World Health Organization recently initiated a new TB program that includes $4.3 million for disease control and about $2 million for research this year. This new wave of interest in TB seems to be paying off already: Last week, a team of British and French researchers announced that they had discovered one cause of drug-resistance in the TB bacillus (see story on page 1038).

Not even for TB. In the excitement following the discovery, *The New York Times* said the new TB research breakthrough would "pave the way for new medicines." But that may be overly optimistic: Even TB isn't attracting much interest from the drug companies, says Miller. The drug companies are mobilizing, however, in response to another crisis, AIDS.

With the surge in AIDS, Miller says, many companies' viral research divisions have been given an infusion of money. The dollar amount is unavailable, but a survey by the Pharmaceutical Manufacturers Association shows they now have 96 research projects in the works to develop medicines to treat AIDS and related disorders. This emphasis on AIDS has benefits for understanding infectious disease mechanisms in general, including drug resistance: Drug company researchers are among those trying to figure out how the AIDS virus has developed resistance to AZT, the principal drug used to treat the disease.



DR. DENNIS KUNKEL/PHOTOTAKE

In flagrante delicto. *Escherichia coli* bacteria caught exchanging genetic material.

And the beginnings of a broader assault on the problem of drug resistance are beginning to take shape in pharmaceutical research labs. While the efforts are still in their early stages, some companies are beginning to use "rational drug design" to design new drugs that can use selective mechanisms to destroy a specific microbe. Until recently, says University of California, San Francisco, chemist Irwin Kuntz, drug companies relied heavily on screening to find new antibiotics that work just like the old, tried-and-true antibiotics, such as penicillin—but that are different enough to fool bacteria, at least for a while.

"Bugs are always figuring out ways to get around the antibiotics we throw at them."

–George Jacoby

A better approach, says Kuntz, is to learn how bacteria become resistant to drugs, and then design new drugs that could prevent that from happening. An example of the kind of work that Jacoby, for one, would like to see more of is the development of a replacement for kanamycin, an antibiotic used to treat staph and gram-negative infections, such as enterobacterial infections that are common in hospital patients. These bacteria became resistant to kanamycin by making enzymes that destroy the drug. Researchers at Bristol Banyu Research Institute in Tokyo, a division of Bristol-Myers Squibb Co., learned how to counteract the enzymes by figuring out what part of the kanamycin they bind to, and then attaching a side chain to that site that would prevent the destructive enzymes from binding there and at neighboring sites. The result was a new drug—amikacin—that is resistant to the staphylococci enzymes and should be able to keep bacteria at bay longer than most drugs.

Another "rational" approach some companies are taking is combination therapy—using two drugs that work together to stop bacteria. That strategy is giving new life to a class of antibiotics known as broad-spectrum beta-lactams that were launched in the early 1980s to kill microbes, including those that cause pneumonia and gonorrhea, that had become resistant to penicillins and earlier cephalosporins. Shortly after penicillin was introduced in the early 1940s, these bugs began pumping out an enzyme called beta-lactamase, which destroyed penicillin and other antibiotics like it. So, the drug industry responded by developing the broad-spectrum beta-lactams, which were resistant to the beta-lactamase enzyme. But "surprise, surprise," says Jacoby, the wily bacteria responded by mutating the gene encoding its beta-lactamase enzyme so that it could "still chew up these antibiotics."

One way around this problem, says Jacoby, may be to use a new class of drugs, called beta-lactamase inhibitors, in conjunction with the broad-spectrum beta-lactam antibiotics. These inhibitors, including clavulanic acid, developed by SmithKline Beecham, or sulbactam, by Pfizer Inc., bind tightly to the active site on the beta-lactamase enzyme, preventing the enzyme from binding with the antibiotics and destroying them. "This is an example of how our knowledge of the mechanisms of resistance allowed the development of a rational strategy," says Jacoby.

It is obvious, however, that waiting for new drugs to save the day won't be enough. "So far, we've kept ahead of the game," says Miller of Schering-Plough. "But I think there's a good possibility that will change. Not tomorrow, but in a decade." That's why doctors—and patients—will have to take matters into their own hands—literally. One thing that's needed, says University of Iowa College of Medicine physician Bradley Doebbeling, is more attention to good, basic sanitation practices to cut down the spread of bacteria in the first place. In the 9 July issue of the *New England Journal of Medicine*, Doebbeling reported that when health care workers used a soap and an antiseptic to wash their hands, their patients showed about one-quarter fewer bacterial infections than those of their colleagues who washed with soap alone or with alcohol. Neu, for one, knows the importance of strict sanitation: The sepsis infection at Columbia-Presbyterian Medical Center was spread by a health care worker who forgot to change his gloves when he was checking patients' respirators.

But even more important, says Center for Disease Control (CDC) epidemiologist Mitchell Cohen, is educating doctors to prescribe the right antibiotics for a disease—particularly in hospitals, where one-third of the patients are on antibiotics and where the selection pressure leading to the development of resistant microbes is highest. All too

Genetic Basis Found for Resistance to TB Drug

Of all the bacterial diseases that are developing resistance to the antibiotics used to treat them, few are more worrisome than tuberculosis, which not only can be spread by casual contact but is also often fatal. That's why a paper in last week's *Nature* sent a wave of excitement through the TB research community. In it, a team from London's Hammersmith Hospital and the Pasteur Institute in Paris describes the identification of a mutation that makes *Mycobacterium tuberculosis*, the bacterium that causes TB, resistant to isoniazid, the main drug used to treat the disease—the first time anyone had found a genetic basis for TB drug resistance. In terms of basic research, "it's a very important paper," says Joseph Bates, a bacterial geneticist from the University of Arkansas at Little Rock—and there's good reason for clinicians to sit up and take notice as well.

Although it's not yet known what proportion of drug-resistant TB cases are due to the mutation identified by the Anglo-French team—the deletion of the gene that codes for an enzyme called catalase—the discovery could be the first step in the long hike to develop new drugs to tackle isoniazid-resistant TB. The working theory is that isoniazid is toxic to M. *tuberculosis* only after it's been converted to another compound by the catalase enzyme, explains molecular biologist Douglas Young, who led the Hammersmith group. So it may be possible, he says, to design drugs to bypass this "catalase step."

The new results should also lead to improved diagnosis of drug-resistant TB. At present, it can take up to 3 months to find out whether a patient is infected with a resistant M. *tuberculosis* strain, says clinical epidemiologist Paul Nunn from the London School of Hygiene and Tropical Medicine, "by which time this patient could have infected heaven knows how many people." Stewart Cole, who heads the Pasteur arm of the Anglo-French collaboration, is already trying to develop a diagnostic test based on the polymerase chain reaction that will let clinicians find out rapidly if a sample of sputum from a TB patient contains M. *tuberculosis* with a missing or defective catalase gene.

Young says that this gene, called *kat*G, was an obvious place to start looking for mutations that confer isoniazid resistance. As early as the 1950s, researchers found that most resistant M. *tuberculosis* strains produce little or no catalase. In the current work, which started about 8 months ago, the team began by confirming that the catalase was in fact a key to the activity of the drug. The researchers first found that a highly isoniazid-resistant strain of a related bacterium, M. *smegmatis*, could be made sensitive to isoniazid by adding into its genome a stretch of M. *tuberculosis* DNA, containing *kat*G. Then they found that this gene was missing in two out of eight drug-resistant M. *tuberculosis* strains.

So if the breakthrough came so quickly after the work was under way, why have TB researchers had to wait so long to get started? The main reasons, says Young, are a dearth of funding and the reluctance of bacterial geneticists to work with an organism that grows very slowly in culture.

But now that geneticists are beginning to pay attention to M. *tuberculosis*, it shouldn't be long before other mechanisms underlying isoniazid resistance are uncovered. Indeed, molecular geneticist Bill Jacobs, from New York's Albert Einstein College of Medicine, has already mapped a second gene that also seems to be involved in resistance, and he's now working to discover this gene's function. Still, knowing how the TB bacterium resists isoniazid will be only one step toward defeating drug-resistant TB, warns Jacobs' colleague at Albert Einstein, Barry Bloom. "We have patients in New York who are resistant to eight drugs."

–Peter Aldhous

often, says Neu, a doctor will prescribe a broad spectrum antibiotic, which works against many different kinds of bacteria, when a more specific one, which acts only against staphylococcus or pneumococcus or whatever the particular problem is, will do. As he puts it: "You don't need a Cadillac when you can get away with a Volkswagen." The problem is that bacteria, even of different species, can exchange genetic material, including the genes for antibiotic resistance. So if one bacterial species becomes resistant to a broad-spectrum antibiotic, it can transfer that resistance to other bacteria as well.

Patients also have to wise up. They should always finish a treatment of antibiotics to be sure they wipe out all the infecting bacteria. The evolution of the drug-resistant TB strain has been accelerated by TB patients who failed to complete their 6- to 12-month regimen of antibiotics, says Barry Bloom of the Albert Einstein College of Medicine. And, on the other end of the spectrum, patients need to stop sharing their old antibiotics with friends and family, and pressuring their doctors to prescribe antibiotics for viral infections that are invulnerable to antibiotics, says Cohen. That's because the more exposure different bacteria get to different antimicrobials, the more likely they will evolve a new defense against it. And a 1989 report from an Institute of Medicine and the National Academy of Sciences panel calls for similar discretion in giving antibiotics to livestock.

The early identification of reservoirs of drug-resistant strains of microbes will also be critical for trying to contain the spread of the organisms. That will take global surveillance programs, some of which are already being put in place, such as the WHONET program from the Microbiology and Immunology Support Services of the World Health Organization.

Surveillance network. WHONET's goal, says its coordinator, Thomas O'Brien of Harvard Medical School, is to link a minimum of several hundred microbiology labs around the world so that information about drug-resistant strains of bacteria and viruses identified in any particular lab could be shared rapidly. "If you could see the emergence of resistance genes in bacteria early, you might be able to head off the spread early," says O'Brien, who is head of microbiology at Brigham and Women's Hospital. O'Brien is persuading doctors to join the network by providing free record-keeping software, written by his postdoc John Stelling, for keeping track of infectious diseases and drug susceptibility. Once the new recruits are dependent on the software, they mail, FAX, or hand-carry the data to O'Brien and Stelling, who then incorporate the information into their database. Although this 4-year-old computer network is operating on a shoestring budget of $3,500 a year and volunteer labor, it already has linked two dozen labs in South and Central America and a dozen in Asia, including China, says O'Brien.

Hospitals within the United States also need to improve the communication between labs, says Cohen. The CDC's current program tracks diseases—not specifically drug resistance. And state and local governments also need to restore some of the public health programs, cut during tough budget times, that used to follow up patients with TB and other drug-resistant organisms. Laments Cohen: "We're seeing a breakdown in some of our societal accomplishments. We're not preventing and controlling disease as well," he says.

In the end, a successful strategy will require a combination of all these approaches. "There's no magic bullet," sighs Jacoby. "Bugs are always figuring out ways to get around the antibiotics we throw at them. They adapt, and come roaring back."

–Ann Gibbons