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.

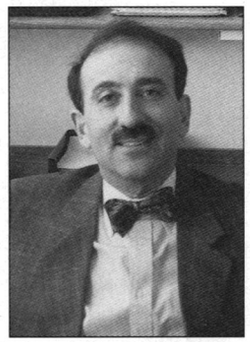
Indeed, square one is how many researchers portray the overall state of antibiotics today. And the rapid rise of resistant bacteria has made many worry that even intelligently constructed antibiotics, crafted with an intimate knowledge of the target proteins in the microbe, will prove no less vulnerable 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.

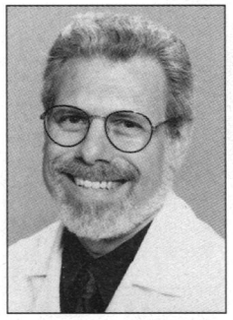
–John Travis

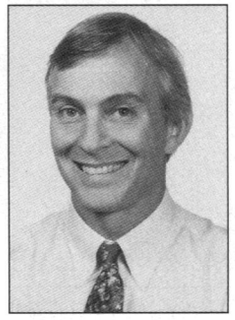
SCIENCE POLICY

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

though we're not doing anything," says John La Montagne, director of microbiology and infectious diseases at NIAID, noting that antibacterial research funds doubled from 1983 to 1993.

He also points out that basic research may not solve today's clinical problems, and adds that NIAID may consider funding more studies aimed at curbing unnecessary antibiotic use, in hopes of slowing the evolution of resistance.

Budgets are tight, and may remain so, but those campaigning for more funds have won at least one battle, in TB research. Indeed, a large part—about three-quarters—of the increase in antibacterial funding between 1983 and 1993 was earmarked for TB research. Elsewhere at NIH, TB projects are also faring well, as the agency strives to avert the public health disaster of rampant multi-drug resistant TB. In 1994, NIH as a whole will devote an estimated $47 million to TB, up from a mere $4.3 million in 1991. Of this, $27.9 million will be spent by NIAID on basic bacteriology, new diagnostics, drugs and vaccines, and public education and training.

But researchers like Shlaes say drug resistance in other bacteria may become just as grave a threat as resistant TB is now. If they're right, current funding lags behind what may be needed, since the 1994 budget for non-TB bacterial research looks even bleaker than last year's. The overall budgets of NIH and NIAID rose in 1994, but the extra dollars were steered into a few programs, including AIDS and breast cancer. Other areas faced mandatory cuts, and since AIDS research takes half of NIAID's budget, the ax fell heavily on the institute's non-AIDS research. Specifically, funds for all non-AIDS, non-TB research will drop 7.5% in 1994, according to the NIAID Council; this translates into roughly 86 lost grants and 30 lost training positions, says Cassell.

So even established scientists are turning elsewhere for funding. For example, George Jacoby, a leading researcher in mechanisms of resistance, lost his NIH funding a few years ago and last year moved his lab from Massachusetts General Hospital to a smaller institution with lower overhead costs, the Lahey Clinic in Boston. He's now funded by pharmaceutical companies and hopes for funding from the Veterans Administration.

The VA has served as a white knight for other resistance researchers, too. "If it weren't for the VA, I'd be in practice instead of research," says Shlaes, who has been awarded $220,000 annually for his work. VA officials have no grand plan to fund specific fields, however, and can't even say how much goes to resistance-related projects.

Beyond basic science, some researchers argue that new antibacterial compounds need more attention. NIH has funded the discovery of new antiviral and anticancer drugs but has left antibiotic discovery programs to private industry. "It's our perception that the drug industry does a superb job at that [discovering new drugs] and has the resources to do it...and is still doing it extremely well. They're still producing drugs at a reasonable clip," says La Montagne.

Not everyone agrees with him. The pipeline may be drying up, and innovative drugs are already in short supply, counters George Miller, presidential fellow and director of preclinical infectious disease research at Schering-Plough. Nine new antibiotics were approved in 1992 and 1993, according to the Food and Drug Administration, but all were members of existing classes of antibiotics and none had new mechanisms of action, says FDA medical reviewer Philip Coyne.

Miller attributes this apparent lack of innovation to the fact that in the mid-'80s, many drug companies (including his own) decided to shift resources from antibiotic to antifungal and antiviral compounds. "Perhaps we are equipped to do it [antibiotic discovery]. We certainly have done it in the past. But few of us are doing it now," says Miller. Agrees Jacoby, who often consults for drug companies, "Development of antibiotics is way down in this country. Most of the new agents I know of are coming from Japan."

The companies, of course, are following simple market logic. There are already more than 100 drugs listed as approved antibiotics, compared to about 20 antiviral drugs. New antibiotics must therefore fight for a small share of a crowded market, while a new antiviral could capture a huge, untapped market, explains Miller. And while a few researchers are sounding the alarm, lack of surveillance data makes it tough to persuade companies—and physicians—of the danger.

Indeed, physicians can still pull an existing antibiotic from the shelf to treat the vast majority of infections. But just four years after the workshop, some bacteria, such as strains of *M. tuberculosis* and *Enterococcus*, resist all known antibiotics, and an increasing number of strains are vulnerable to just one drug. Are these developments worrisome enough to justify a major counterattack? That's the question funding agencies—and the U.S. Congress—will have to ponder.

–Elizabeth Culotta

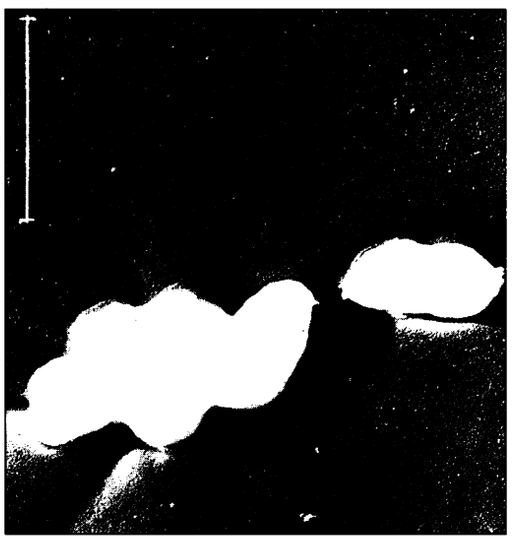
INTERNATIONAL

Resistance a European Problem, Too

LONDON—During the past few years, microbiologists in Europe, like their counterparts in the United States, have been grappling with hard-to-treat infections, as more and more pathogenic bacteria become resistant to antibiotics that formerly killed the pathogens with ease. "The rising level of antibiotic resistance is a real cause for concern. Reports from around Europe show that severe problems already exist in some countries," says Alan Johnson, clinical scientist with the Antibiotic Reference Unit at the Central Public Health Laboratory in Colindale, north London. The patterns of drug resistance are different on each side of the Atlantic, however, in part because of different patterns of antibiotic use. Some types of resistant bacteria are more common in Europe than in the United States, while others, including multi-drug resistant *Mycobacterium tuberculosis*, are less of a problem here.

Among the most common of the resistant bacteria in Europe are penicillin-resistant pneumococci, which cause a range of infections, including pneumonia and the often-fatal blood infection septicemia. The problem is particularly acute, Johnson says, in Spain and Hungary. These two countries have a history of heavy use of penicillin and other antibiotics that would provide strong selective pressure for the evolution of resistant strains.

In Spain, for example, according to a review in 1992 by Peter Appelbaum of the Hershey Medical Center in Pennsylvania, only 6% of pneumococcus isolates were penicillin-resistant in 1979, but by 1989, the proportion had shot up to 44%. And in Hungary, at least 50% of pneumococcus isolates were resistant to penicillin in 1988 and 1989, although recent data suggest that percentage may be dropping as physicians switch to other



A. TOMASZ, ROCKEFELLER UNIV.

Dangerous acquisition. Here a pneumococcus bacterium is taking up a DNA strand—one way of acquiring antibiotic resistance genes. (Bar equals 1 micron.)