

THE ABUSE OF ANTIBIOTICS

SEARCHING FOR A NEW CURE

Budget Cuts Slow Agencies Fighting New Bacteria Strains

Calvin Day

Second of two articles

By Kathleen Day

Washington Post Staff Writer

ATLANTA

The carpets are frayed, much of the lab equipment is old, and the hallways are crowded with refrigerators filled with medical specimens at Ruth Berkelman's facility in Atlanta. But it's the best the Centers for Disease Control has been able to muster so far to fight what some experts call the worst medical threat since

AIDS—the spread of new strains of bacteria that resist the antibiotics that cure so many diseases.

In three aging buildings at the center, Berkelman and a staff of 50 medical sleuths work long hours to track the bugs. They seek out patterns among the microbes hospitals have encountered; they put out bulletins to doctors. But, looking at the limitations of equipment and resources they face, they worry that lawmakers in Washington don't understand the dangers society may face.

Last year, about 25,000 people between the ages of 3 and 49 died of unexplained causes in the United

States—but with symptoms that suggested microbial infections. The center, theoretically the world clearinghouse for such information, would like to send people into the field to investigate. But it lacks the money.

Hiring freezes and budget cuts have prevented the CDC from getting a reliable picture of the superbugs, let alone doing much to fight them, Berkelman said. The agency must rely on state governments to track where the microbes crop up, and most states simply don't. The federal government doesn't even have a

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central computer library on infections, meaning that many researchers can't get at what information exists, she said.

"If we continue to let this get out of hand, we're setting ourselves up for a major catastrophe," said Berkelman, a deputy director at the agency, in an interview in her office here. "I'm talking about going in for a routine operation and dying from an infection."

Said Robert E. Shope, professor of epidemiology at Yale medical school: "If we don't gear up to bring matters under control, we could face new crises similar to the AIDS epidemic or the influenza epidemic that killed 20 million people worldwide" in 1918 and 1919.

Across the medical community, people such as Berkelman and Shope are sounding the alarm about resistant germs, which threaten to bring back the days when Americans routinely died of such illnesses as tuberculosis, pneumonia and complications of common ear infections.

Their efforts have sparked some new drug research, speeches at medical conventions and changes in how some doctors use existing antibiotics. But by and large, many scientists and other experts believe, the response to the new antibiotic-resistant bugs doesn't measure up to the threat.

"Our public health capacity may be fraying at the edges at a time when we face some frightening challenges," said Sen. Nancy L. Kassebaum (R-Kan.), chairman of the Senate subcommittee that oversees medical research funding and one of the few people in Congress to take up the issue. "We've taken our health care system for granted. Suddenly we have to realize we can be very vulnerable."

At times, people sounding the alarm almost wish they had a crisis to point to. The AIDS epidemic has drawn billions of dollars in research money; the Ebola virus in Africa has captured the public's attention. But resistant bugs do their work quietly—for now—mainly making themselves known through an occasional infection-related death and through children who keep coughing while they're taking a once-reliable drug.

Even in the most optimistic scenarios, new drugs won't appear on the market for at least five to seven years. The hope among people such

as Berkelman and Shope is that the lid will remain on until then, that resistant bugs will remain isolated curiosities, not things that kill on a widespread scale.

Budget Battle at the CDC

It's a bad time, of course, to be seeking extra money from the federal government. The Republican-dominated Congress, seeking to cut the budget deficit, is looking for savings everywhere, including medical programs.

The CDC, a sort of emergency line for the health care system, wants \$125 million a year to implement a plan to detect and fight drug-resistant bacteria and other emerging infections. But for the current fiscal year, Congress approved only \$7.7 million for the plan, with the Senate defeating House efforts to cut that by \$3 million. For the fiscal year that begins in October, the White House has proposed spending \$16.5 million.

Kassebaum is leading the fight for the CDC, saying \$125 million is hardly large in view of the \$550 million it already spends annually on AIDS. It's an uphill struggle, she said, but she expressed hope that some of the budget cutters in Congress will conclude that government-supported research and monitoring is key to avoiding a medical crisis.

The CDC proposes to open several new outposts in strategic regions throughout the country to comb for germ outbreaks. The agency also would create a comprehensive, interactive computer data base that would help health care professionals throughout the nation share information about infections. The Institute of Medicine has cited the lack of such a data bank as one of the key weaknesses of the U.S. health system.

The cornerstone of the plan, however, is to improve the country's impoverished surveillance program. If new drugs are to be developed, experts agree, researchers must first know what the target is—what bugs are out there and what they can do to combat them.

In the United States, field research of this kind is the responsibility of the states—and very limited. There is no federal law requiring that drug-resistant strains of diseases be reported to the CDC. Information from states is so scanty that the agency doesn't even have a firm grip on which state reports what diseas-

es.

As evidence of how haphazard the system is, Berkelman cites a 1993 episode in Washington state and Nevada where *E. coli* bacteria in fast-food hamburgers caused a food-poi-

soning outbreak that sickened at least 600 people and killed four children.

Washington state's well-run department of epidemiology detected the outbreak and contained the source within weeks. Nevada, by comparison, identified its outbreak—which began weeks earlier than Washington's—only after a mother of a sick child read about the Washington cases in the news and contacted health officials, Berkelman said.

Although the bacteria isn't drug-resistant, Berkelman and others say it's proof of how little actually gets reported even when the sickness is dramatic. To track drug-resistant illnesses, which are far less obvious, all states combined were spending only \$55,000 a year, a study found in 1992.

Locally, Maryland, with the help of the CDC and Johns Hopkins University, is trying to expand the list of germs it tracks to include drug-resistant ones.

Virginia does not track drug-resistant bacteria on a regular basis. But last year, state officials surveyed all microbiology labs in the state for evidence of penicillin-resistant *Streptococcus pneumoniae*, the bacteria that is a common cause of pneumonia and of children's ear infections and meningitis.

"We found it's everywhere in the state," said state epidemiologist Elizabeth Turf. Her office sent out a cautionary bulletin to the health care community warning about the problem and suggesting other antibiotics be used.

The District does not track the bugs, for lack of personnel. In a recent incident, 30 elderly patients at a District nursing home came down with a respiratory illness that hospitalized 10 of them and killed one. (D.C. chief epidemiologist Martin Levy won't identify the home for fear that would deter reporting of outbreaks by other local health facilities.) Lack of staff and testing supplies prevented the District from ever identifying the germ or whether it may have been a drug-resistant bacteria.

But despite budget cuts at their level, many state officials are willing

to upgrade cooperation with the CDC. In December, state health officials held a conference in Atlanta to discuss how to update and bring coherence to the state-based reporting system. A measure of how much work remains to be done: It was the first such meeting in 40 years.

A ballot on what to do was sent out in January and by summer the tab should be in, said Richard E. Hoffman, chief epidemiologist for Colorado and president of the Council of State and Territorial Epidemiologists. As for whether everyone can afford to comply with what's voted on—"that's another question," Hoffman said. "Drug resistance is alarming and we're not prepared."

In other government agencies, money also is tight. The National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health in Bethesda, devotes only \$10 million, or 3.7 percent of its funding, directly to drug resistance. That's only \$4 million more than in the late 1980s, though the agency also funds basic research that is helpful to all fields of medicine.

At the Department of Defense, budget cuts are threatening the survival of a half-dozen medical research labs around the world. Officials are taking low-cost steps, however: This year the CDC, the Pentagon and other federal agencies hatched new procedures for coordinating efforts in the event of "emergency outbreaks" of killer microbes.

Industry Seeks Solutions

Many experts say that the main long-term hope lies with private industry and development of new drugs. In the last several years, the drug industry has started to spend more money on antibiotic research after cutting back in pursuit of other drugs in the 1970s and 80s, as many doctors wanted them to.

The drug industry also has entered into a number of collaborations with government and nonprofit labs, as well. American Cyanamid Co., for example, has joined with the University of Iowa to devise a tracking system; the nonprofit Public Health Research Institute of New York has a \$1 million grant from Pfizer Inc., Lederle Laboratories and F. Hoffmann La Roche & Co. to study drug-resistant tuberculosis.

Industry executives talk optimistically of major discoveries and breakthroughs in the next five to seven years. The Pharmaceutical Research

and Manufacturers of America, the drug companies' Washington-based trade group, said that members now have 79 anti-infectious disease medicines in various stages of development.

Pfizer, based in Groton, Conn., and Eli Lilly and Co. of Indianapolis are among the big companies that are expressing new interest. Lilly recruited Barry Eisenstadt 2½ years ago from his job as chairman of microbiology at the University of Mich-

igan and put him to work rejuvenating anti-microbial research.

"Incremental improvements in antibiotics are no longer acceptable economically or medically," he said. And he is optimistic: "Just as drug resistance has emerged . . . scientists now have the molecular and genetic tools" to combat the problem.

In the past, research methods consisted of taking samples of chemicals secreted from organisms in nature and, through trial and error, determining if the substances showed promise in killing bacteria and whether they could be mass produced or replicated chemically.

Today, drug researchers often work by modeling new compounds on computer screens and simulating their interaction with other compounds. These techniques let scientists study many more substances and, ultimately, create drugs that are chemically more refined.

But the best hope for true breakthroughs, many scientists say, is biotechnology, the manipulation of hereditary material in living cells. Scientists at biotech firms hope to create cells that produce germ-killing substances—that is, a new generation of genetically engineered antibiotics.

Other biotech research aims at drugs that would alter the genetic material of the invading bug itself. Doctors would inject drugs into a patient that would seek out any resistant bacteria and alter their genetic content so that they would lose their resistance—and be killed by conventional antibiotics.

Still other biotech products might be new vaccines that would stimulate a person's immune system to produce a stronger response to an infection.

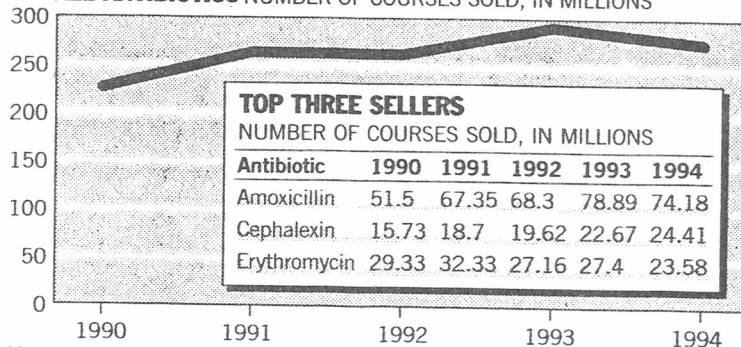
Big biotech firms are looking at these techniques, but much of the work occurs at small, start-up companies such as Medimmune Inc. of Gaithersburg, Martek Biosciences Corp. of Columbia, Univax Biologics Inc. of Rockville and Microcide Pharmaceuticals Inc. of Mountain View, Calif. Univax, for example, is

ANTIBIOTICS IN DEMAND

NUMBER OF COURSES* SOLD IN U.S. RETAIL PHARMACIES, 1990-94

CDC experts theorize that more courses were sold in 1993 than in 1994 because the 1992-93 winter influenza season peaked late, while the 1993-94 season got off to an early start. Although influenza is a virus, flu victims can also develop bacterial infections—and some doctors mistakenly prescribe antibiotics to treat flu symptoms.

ALL ANTIBIOTICS NUMBER OF COURSES SOLD, IN MILLIONS



*A course of treatment consists of the amount of medication needed to treat an infection.

SOURCE: IMS America Ltd., a pharmaceutical market research firm

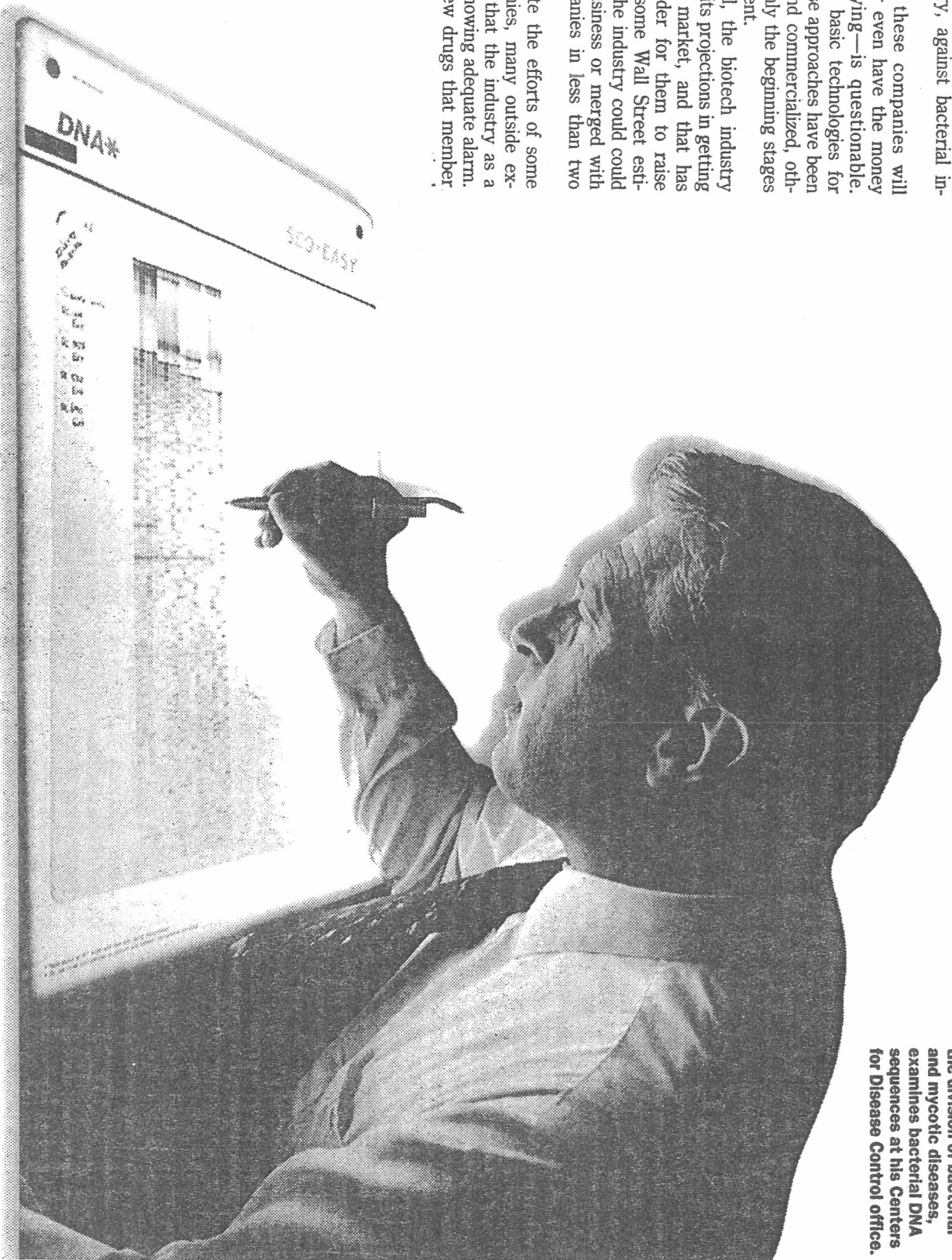
focusing efforts on vaccines, including some that would guard high-risk patients, such as people recovering from surgery, against bacterial infections.

Whether these companies will succeed—or even have the money to keep trying—is questionable. Though the basic technologies for some of these approaches have been developed and commercialized, others are in only the beginning stages of development.

In general, the biotech industry has not met its projections in getting products to market, and that has made it harder for them to raise money. By some Wall Street estimates, half the industry could be out of business or merged with larger companies in less than two years.

And despite the efforts of some drug companies, many outside experts worry that the industry as a whole isn't showing adequate alarm. Of the 79 new drugs that member

Mitchell Cohen, director of the division of bacterial and mycotic diseases, examines bacterial DNA sequences at his Centers for Disease Control office.



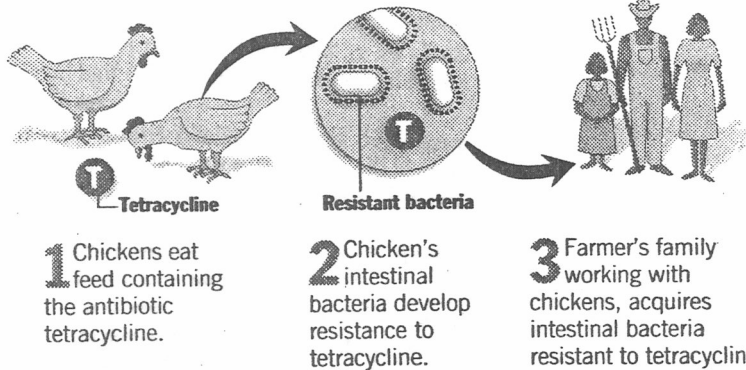
BY ERIK S. LESSER FOR THE WASHINGTON POST

BARNYARD ANTIBIOTICS

Antibiotics are given to farm animals not only to fight specific infections but as nonspecific "growth promoters." Consequently, animals constitute a large reservoir in which microbes can evolve and exchange resistance genes. Whether this contributes to disease in human is unknown, but people can clearly acquire resistant microbes from animals.

Stuart B. Levy, of Tufts University School of Medicine, gave chickens on a Massachusetts farm feed supplemented with the antibiotic tetracycline. Tetracycline-resistant intestinal bacteria quickly appeared in the birds. Within six months, seven of 11 members of the farm's household carried large numbers of bacteria resistant to tetracycline, and some had microbes resistant to more than four antibiotics.

PASSING RESISTANCE FROM ANIMALS TO PEOPLE



THE WASHINGTON POST

companies of the Pharmaceutical Research and Manufacturers of America trade group are working on, many may not be ready on time. Even if they are, most would be mere "me-too" drugs that offer only incremental advantages over existing drugs.

More questions about drug companies' commitment arose at a meeting last fall at which Food and Drug Administration officials asked

company representatives for voluntary cooperation in tracking cases of drug resistance.

According to a transcript of the meeting, several industry executives said that a national surveillance system is needed. But some cautioned against its being used to remove antibiotics from the market, saying the decision to stop using a drug should be left to doctors and patients. Some expressed concern that a national system could give trade secrets to competitors or that it would add to the red tape the drug industry already faces.

"I believe that the extent of the problem is far less ubiquitous and dangerous than the so-called scientific reviews and the media try to portray," said Victor Lorian, a doctor at the Bronx Lebanon Hospital in New York. In his testimony, he said

his trip to the hearing was paid for by Bayer Corp.'s West Haven, Conn.-based pharmaceutical division, which makes Cipro, a common antibiotic. A Bayer spokesman confirmed the company paid for the trip.

Eight months later, the FDA still has no program in place—or even a proposed plan—to track such incidents.

Firms Promote the Drugs

One important way to slow down any new bug's emergence is, paradoxically, to get doctors, patients and drug companies to drop their romance with antibiotics as a cure-all. Today, such drugs are routinely prescribed for even minor illnesses. The more antibiotics that circulate in the world's bloodstreams, the faster bugs evolve ways to resist them.

Critics of the drug companies say they bear part of the blame for that. They continue to pass out free samples and make pitches for antibiotics, a practice that critics say encourages doctors and patients to keep using them, even when they may not be needed.

The industry argues that the drugs are strictly controlled and that marketing techniques are not part of the problem, so they don't need to be changed. Doctors don't blindly

prescribe drugs based on what companies tell them, said Mark Grayson, vice president at the pharmaceutical trade group. "They are smarter than that."

But a few advocacy groups disagree, and they are organizing protests on this issue. Last summer, some pediatricians and consumer groups criticized the Department of Health, saying it allowed drug companies excessive influence in wording federal practice guidelines on how to treat common childhood ear infections, an illness that appears to be growing in part because of a well-documented increase in drug resistant strains of bacteria.

The agency's draft guidelines, which stressed the use of antibiotics, were subsequently changed to say that waiting for natural improvement and prescription of antibiotics are *both* viable treatment options.

"Has the drug industry oversold their drugs? I don't think there's any doubt about it," said Courtney Fletcher, professor of pharmacy at the University of Minnesota. "I wouldn't place the problem solely at their doorstep, but they have played a part."

Doctors also are facing some criticism for overprescribing antibiotics.

To be sure, doctors now are more aware of the problem. Medical and scientific journals are giving it increased coverage. Science magazine, for example, has devoted two full issues to it since 1992. And some doctors, such as Tufts University professor of medicine Stuart Levy, are encouraging medical

schools to make problems of drug resistance a major issue in medical education.

The CDC has joined in this crusade, too: Last spring, in its first such move ever, the agency put a notice in the Federal Register warning doctors that overuse of the antibiotic Vancomycin—one of the last effective antibiotics for some infections—could reduce the drug's effectiveness.

Still, there is little evidence that these moves are cutting the number of prescriptions. Doctors continue to prescribe them widely. For an individual patient, a course of antibiotics generally can't hurt, regardless of what the illness is. In the event of a malpractice lawsuit, it can help the doctor's case to have done everything possible.

Experts say some blame also