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**

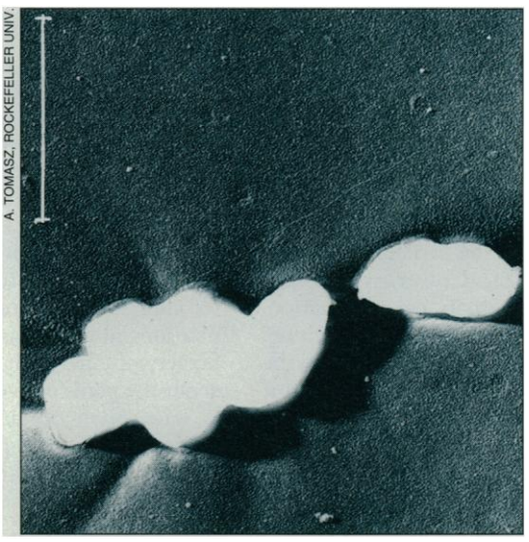
INTERNATIONAL

# 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




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

antibiotics (see box below). Comparison figures for the United States are hard to come by, but probably no more than 10% of pneumococci are penicillin-resistant, except in rare outbreaks.

In another resistance area—multi-drug resistant tuberculosis—Europe seems to be faring much better than the United States—at least for now. In some areas of the United States, especially large cities, isolates of *M. tuberculosis* that are resistant to both isoniazid and rifampicin, the two major drugs for treating TB, are becoming common. For example, almost 20% of the isolates tested in New York City in 1992 were resistant to both drugs, according to data compiled by the World Health Organization. But isolates resistant to two or more drugs are still rare in England and Wales, constituting only 0.6% of all isolates made there between 1982 and 1991. Says Tony Jenkins, microbiologist at the Mycobacterium Reference Unit of the Cardiff Regional Public Health Labor Laboratory: "Without wishing to sound blasé, I can't see drug-resistant tuberculosis as being a threat in England and Wales at the moment."

He attributes the success in controlling the problem here to the ongoing tuberculosis control program, which includes tracing the contacts of infected individuals and well-trained physicians who continue to have a good understanding of how to treat the disease. "We were fortunate in that, unlike the United States, we did not dismantle our TB services. And we don't have the same inner-city problems on the same scale as in some cities in the U.S., where high levels of drug abuse, alcohol problems, and homelessness lead people not to take their drugs or to take them inadequately. These are the breeding grounds for drug resistance." Indeed, the importance of public health measures in controlling tuberculosis is underscored by recent findings that the number of new cases in New York City dropped last year by 15%, the first major decrease there since the late 1970s. A major factor in the decline, according to city health officials, was their stepped-up efforts to identify patients and ensure that they take their medicine.

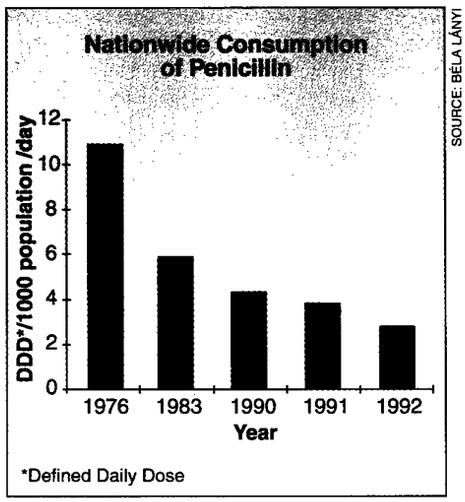
Rates of multi-drug resistant tuberculosis are similarly low in France, where only 0.5% of isolates were resistant to both isoniazid

## Hungary Sees an Improvement in Penicillin Resistance

Childbirth is a gamble with death. Dental surgery, potentially disabling. Even a facial boil can end in a trip to the morgue. Such is the forecast of the postantibiotic era, an era in which antibiotics are powerless against the new drug-resistant strains of bacteria.

Sound fanciful? Maybe not: Take a look at what was happening in Hungary in the 1980s. At the time, the country was highly dependent on penicillin for treating infections. So when bacteria such as pneumococcus, a frequent cause of ear and sinus infections in children, became resistant to the antibiotic, Hungarian physicians all too often saw these simple infections turn into life-threatening pneumonia, or, in rare instances, even meningitis.

But Hungary provides a ray of hope as well as a preview of medicine without effective antibiotics. In a surprise turnabout, by 1992 the levels of penicillin-resistant pneumococcus infections had fallen from a high of 50% to 34%. Still not good—for comparison, although there is little surveillance data, in the United States the incidence of penicillin-resistant pneumococcus is thought rarely to exceed 5%—but a shift in the right direction nonetheless.




**Down, down, down.** Faced with penicillin-resistant pneumococcus, Hungary's penicillin use fell.

The decrease may have been partly caused by what Anna Marton, a microbiologist at the Heim Pál Children's Hospital in Budapest, describes as a "sharp reduction" in penicillin use as Hungarian physicians became aware of the resistance problem and switched to other antibiotics, thereby relieving the selective pressure that drove the development of the penicillin-resistant strains. And that, says Stuart Levy of Tufts University School of Medicine, who in 1981 cofounded an international organization, the Alliance for the Prudent Use of Antibiotics, is "very exciting. It offers hope that the more careful use of antibiotics can turn the tide. We've seen it before in hospitals, but we've never seen it across a country. If we can get it down to 5 or 10%, we're in great shape." Levy cautions, however, that the link between falling penicillin use and the reduction in resistance to the antibiotic must be confirmed.

The eventual discovery of the changing fortunes of penicillin depended, in part, on Hungary's remarkably sophisticated surveillance system for antibiotic resistance. Since 1974, the country's National Institute of Public Health in Budapest has collated data on bacterial resistance to upwards of 20 different drugs from 23 microbiological laboratories in all 19 counties. "Hungary has a beautiful surveillance system. It's really unique," says Alexander Tomasz of Rockefeller University, an expert on antibiotic resistance.

Yet the surveillance data, which has been published annually for the past 20 years, did little to avert the crisis in penicillin resistance. Indeed, says Marton, during the 1980s, Hungarians used even more penicillin—and more antibiotics generally—per capita than people from Spain, a country that is infamous for its high antibiotic consumption. Consumption was high, says Béla Lányi of the National Institute of Hygiene, who set up the nationwide surveillance system, because penicillin was cheap and patients demanded it.

But by the late-1980s physicians began to change their prescribing practices because of what was happening in the clinic. By that time, says Marton, "penicillin was useless" against most common sinus and ear infections. A simple sinus infection in a child, for example, would develop into a very long and painful illness.

To avoid more such clinical failures Hungary's pediatricians are now relying more heavily on other antibiotics such as the non-*beta*-lactam antibiotics, a trend that might be behind the recent decline in penicillin resistance. And to prevent the new antibiotics' clinical effectiveness going the same way as penicillin's, organizations like Hungary's Society of Infectious Diseases and the Society of Chemotherapy are attempting to educate physicians about the perils of overusing antibiotics.

Lányi predicts that the drive to prevent the misuse of the new antibiotics should be more successful than the drive to stop penicillin abuse. "The new antibiotics are more expensive," he explains.

–Rachel Nowak

and rifampicin. In Europe, however, just as in the United States, drug resistant TB is more of a problem in AIDS patients than in the general population.

Still, Jenkins says, the better performance on this side of the Atlantic so far "doesn't mean we can afford to be complacent. [Multi-drug resistant TB] will need constant vigilance because it can creep up on you very quickly." With this in mind, the Communicable Disease Surveillance Centre in north London is tightening up its surveillance methods by introducing a computerized notification system for all cases of drug-resistant tuberculosis in each of the six regional centers for tuberculosis bacteriology.

But even though some drug-resistance patterns vary, one serious worry can be shared equally by health officials on both sides of the Atlantic. That's the emergence of vancomycin-resistant strains of *Enterococci*, which cause urinary tract and wound infections and, occasionally, meningitis, which is rapidly fatal unless checked by antibiotic treatment. "Vancomycin resistance in these bacteria was negligible up to the mid-1980s, but it's taken off in a big way since then," Johnson says. He cites the increase in the number of hospitals in England and Wales that have sent vancomycin-resistant samples to the Antibiotic Reference Unit as an indication of the scale of the problem.

In 1988, only one hospital made such a report, but by 1993 the number had risen to 18. And that's probably just the tip of the iceberg, Johnson notes: "Other laboratories are undoubtedly picking up these strains and not reporting them to us, so the incidence of this type of resistance is probably considerably greater than these figures suggest."

The emergence of the vancomycin-resistant *Enterococci* is worrisome because these bacteria are themselves a significant cause of hospital infections. But even more alarming is the possibility that *Enterococci* will spread vancomycin resistance to other genera of bacteria. Researchers think this will eventually happen because bacteria are very adept at exchanging their antibiotic resistance genes. A particular nightmare is that methicillin-resistant *Staphylococcus aureus* (MRSA), a common cause of hospital infections, will acquire resistance to vancomycin—currently one of the few antibiotics to which MRSA infections will reliably respond. "If the vancomycin resistance gene got into MRSA, that could be potentially disastrous," Johnson says. "You could end up with infections that may be virtually untreatable, and that is a real cause for concern for the future."

**–Sharon Kingman**

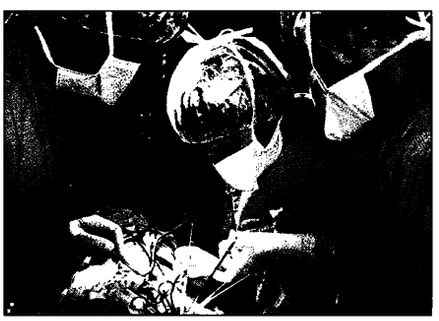
*Sharon Kingman is a freelance writer based in London.*

DRUG DEVELOPMENT

# Search for Sepsis Drugs Goes On Despite Past Failures

Row after row of stainless-steel vats fill the cavernous halls of Synergen Inc.'s protein manufacturing plant in Boulder, Colorado. The colossal, 82,000-square-foot plant was built to churn out a protein called Antril, which Synergen hoped would be the first successful drug for treating sepsis syndrome, a serious medical condition in which the body's immune system overreacts to an infection and goes haywire (see box, p. 366).

But for now Synergen's gleaming fermenters lie fallow much of the time, because the company encountered a major roadblock in its efforts to bring a potential blockbuster drug to market. To get approval for Antril from the U.S. Food and Drug Administration, Synergen needed good results from a large-scale clinical trial. However, when the trial was completed in February 1993, the news was bad: Antril worked less effectively than smaller, preliminary trials had led company executives to expect. "The failure of the trial was a shock," says Larry Soll, Synergen's chief executive officer. And company officials presumably found it small comfort that Synergen was not alone in its misery. In the previous year, two other firms, Centocor, Inc. of Malvern, Pennsylvania, and Xoma Corp. of Berkeley, California, had seen promising sepsis drugs falter in clinical trials.



MITCH KEZAR/PHOTOTAKE

**A risk.** Surgery patients and others with wounds are among those likely to get sepsis.

But these failures don't mean the search for an antisepsis drug is over. Far from it. Today, many biotech companies are in hot pursuit of just such drugs—with good reason. "It's not just about money—a lot of people die," says molecular biologist Larry Gold, a Synergen founder who has formed a new company, Boulder-based Nexagen, that's also looking for new sepsis drugs. Gold speaks the truth. Every year in the United States, some 500,000 people come down with sepsis and 175,000 of them die. And, of course, numbers like those translate into other numbers that make the biotechs salivate: The market for a successful antisepsis drug could be $500 million a year, says Jeffrey Casdin, a biotech analyst at Oppenheimer & Co. Inc., of New York City.

What's more, that market may be growing. According to the Centers for Disease Control and Prevention, the number of sepsis cases linked to microbial infections in hospital patients tripled from 1979 to 1992—partly because of the increased vulnerability of the patient population, which includes more older patients and more AIDS patients. Both groups have weakened immune systems that predispose them to sepsis.

This burgeoning market could be a pot of gold for the 20 or so companies now developing possible antisepsis drugs. But, as the experiences of Synergen, Centocor, and Xoma show, the route to this prize is neither straight nor easy. "Even though sepsis is a relatively attractive target for a biotech company, it's also one that everyone has tripped over," says Richard Rose, vice president of drug development for Cytel Pharmaceuticals of San Diego, which currently doesn't have sepsis in its sights. Yet the prize is attractive enough that, no matter how many runners trip, others are there to vie for the inside track.

**Preying on the weak.** Like a wolf stalking the sickly members of a herd of elk, sepsis finds its victims among the weak, particularly among patients in hospital intensive-care units who come down with infections. All told, about 95% of sepsis cases are caused by infections of some kind; most of the remaining 5% occur, for reasons that are poorly understood, in people with severe injuries but no signs of infection.

Even among the cases caused by infection, there's plenty of variety. While most used to be caused by *Escherichia coli* and other gram-negative bacteria (so-called because they fail to absorb a particular stain), an increasing proportion—now 55% of the total—are triggered by gram-positive bacteria and fungi. "There's been a dramatic shift recently in the pathogens that cause sepsis," says sepsis researcher Roger Bone of the Medical College of Ohio in Toledo.

Despite the dizzying array of microbes that trigger sepsis, researchers in the past decade have learned enough about the molecular biology of the initiating pathogens as well as the immune cascade that causes sepsis to begin identifying targets for antisepsis drugs. "The clinical research done so far has put us