Penicillin-Resistant Gonorrhea: New Strain Spreading Worldwide

In June 1975, at a meeting in London on "sexually transmitted diseases," Stanley Falkow of the University of Washington predicted the appearance of a novel strain of *Neisseria gonorrhoeae*, the gonorrhea bacteria, that would be utterly resistant to penicillin. Falkow speculated that there would emerge a strain of gonococcus able to produce an enzyme, known as a penicillinase, that thrives by splitting penicillin molecules apart, thereby rendering them useless as antibiotics.

To those familiar with the phenomenon of antibiotic resistance, on which Falkow is a recognized authority, it was a predictable prediction. And within a year—sooner than he would have guessed—Falkow was proved to be dead right. There is now a penicillinase-producing strain of *N. gonorrhoeae* spreading slowly but surely around the world, creating problems medically, epidemiologically, and diplomatically.

According to Paul J. Wiesner of the Center for Disease Control (CDC) in Atlanta, "We can say with confidence that there never were any penicillinase producers in the United States before February 1976 at the earliest." Now CDC officials have confirmed 41 cases of penicillin-resistant gonorrhea and anticipate finding more; how many more they cannot estimate.

The first case in the United States was identified last spring in a man from St. Mary's County, Maryland. A civilian employee of the U.S. Navy, he had just returned home after a tour of duty in the Philippines when, noticing discharge and other early symptoms of venereal disease (VD), he reported to the local VD clinic. By laboratory culture, his problem was diagnosed as gonorrhea. Health officers asked a series of standard questions. Where had he been? The Philippines. Had he had sex? Yes, with a local prostitute. Had he had sex with anyone since coming home, a so-called "contact?" Yes. One person. He gave a name. According to William Marek, who is both state and county health officer, the patient was given the standard CDC-recommended regimen of drugs, which means a "whopping" dose of penicillin, and sent on his way.

A couple of weeks later the man was back—uncured. Marek considered the possibility of a resistant strain and had cultures sent to the state laboratory and to CDC for examination. Meanwhile, he treated the original patient and his "contact" with spectinomycin, the antibiotic to which one turns when penicillin fails in gonorrhea. And down in Atlanta, CDC officials were coming to the conclusion that they had on their hands a resistant strain that is unlike any others.

Penicillin-resistant gonorrhea is not an entirely new phenomenon. It has been around at least since 1958 and had been handled by-and-large with ever increasing dosages of penicillin. Thus, the recommended dosage today is a staggering 4.8 million units of penicillin; there was a time when 200,000 units did the trick.

Antibiotic resistance occurs through a variety of mechanisms. Occasionally, through spontaneous mutation, a bacterial cell will become impermeable to a drug that must pass across the cell wall in order to be effective; that is, bacteriocidal. Sometimes antibiotic resistance develops because bacteria acquire the wherewithal to produce an enzyme that attacks the drug molecules head-on, converting them to an inactive form. It is known that this is what happens in some cases of staphylococcal penicillin resistance. But until now, gonococcal bacteria were not able to mount such a frontal approach to evading penicillin. This is what makes the penicillinase-producing gonococci so "new" and dangerous. No amount of penicillin can do it in.

Marek believes that by acting promptly they have "put the lid on" the new strain in St. Mary's County, but the disease is cropping up elsewhere—CDC knows for sure that it is present in 13 states already—brought to this country primarily by men who have picked it up in the Far East. It is present in Europe, too, and is being transmitted worldwide in a kind of great international exchange that nobody needs.

Identifying the geographic source of penicillinase-producing gonococci is a major epidemiological challenge which is proving to be something of a diplomatic challenge as well. For what country wants to be known as the seedbed of a new strain of VD? It is bad for one's national image and bad for tourism. Although there are those in official military and government positions who have taken to referring to countries of origin as country A, country B, and so forth, others are frank to say that the resistant bacteria have been found in Hong Kong, Korea, Japan, Singapore, the Philippines, New Zealand, and Australia in the East; and in Britain, Norway, and Canada, in addition to the United States, in the West. So far, cases have not been reported in South America or Africa, but officials expect that it is only a matter of time.

Most of the cases that have been confirmed by the CDC can be traced to the Philippines where large numbers of U.S. personnel are affiliated with Clark Air Force Base and Subic Bay Naval station, each within proximity to Manila, and where prostitutes in legalized brothels are known to take low dosages of antibiotics prophylactically to keep themselves "clean." Falkow speculates that by continually dosing themselves with low concentrations of antibiotics, the women created a situation that is biologically ideal for the growth of resistant organisms. Those that are susceptible are kept in check, but those that are resistant grow preferentially in the gonococci's version of survival of the fittest.

When the St. Mary's County case was first identified, followed soon thereafter by cases at the Travis Air Force Base in California, CDC officials, through the World Health Organization, went to the Philippines to try to determine how widespread the disease was there. "The first question we have to ask," says Wiesner, "is, 'Is this rare?' " A good many of the incidence figures are still in the hands of the Philippine government, but CDC officials do know that this phenomenon is anything but rare. An estimated 20 to 40 percent of prostitutes in the Philippines who contract gonorrhea have the penicillinase-producing kind. Indications are that not much is being done to eradicate the disease there and that the Philippine government is losing interest in cooperating with either CDC or American military physicians who are trying to track it down. A Philippine health officer, Ponciano Malonzo, from the town of Angeles near Clark Air base, is quoted in the Washington *Post* as saying that he has instructions from the Philippine secretary of health not to let anyone make any more studies and not to send any reports to officials at Clark (who are said to have shown more immediate concern about the problem than their counterparts at Subic Bay). The matter is all the more sensitive in view of the fact that the

United States is in the process of renegotiating agreements about continued use of the military bases, with the Philippines taking a hard line as it is.

Although it is evident that there is a high concentration of penicillinase-producing gonococci in the Philippines (and speculation that they may have been introduced there from South Vietnam), the Philippines is not the only source. A small force of the new bugs is present also in Liverpool, England, where about 9 percent of all persons known to be affected by gonorrhea have this new resistant form. Oddly, there is as yet no direct "contact" evidence that the Liverpool organisms came from the Far East and, indeed, microbiological data indicate the British bacteria may be a bit different from the Far Eastern ones. As yet, no patients in the United States have reported "contacts" in Liverpool.

Just how far this new strain of gonorrhea will spread in the United States is anybody's guess—fortunately, it seems to be spreading slowly for now—but it is gaining momentum, and it is certainly possible that it will be widely disseminated. If it is, the cost in terms of public health and public money will be great.

We tend to think of gonorrhea, if we think of it at all, as being no more serious than a mild cold and easily curable with that good stiff dose of penicillin. Indeed, purveyors of official information, including the National Institutes of Health and World Health Organization, in publications dated 1976, put gonorrhea down as a highly curable disease. And as long as it is curable, it is true that its long-range effects are not too serious. But gonorrhea can be a very serious disease indeed. In men, narrowing or blockage of the urethra can occur, requiring mechanical stretching to permit urination. In women, bacteria may spread upward through the reproductive tract causing pelvic inflammatory disease. If a pregnant woman has gonorrhea, her baby is likely to be aborted, or be born prematurely, or blind, or dead. In both sexes gonorrhea can cause sterility. If gonorrhea becomes disseminated throughout the body, it can cause arthritis, which manifests itself suddenly, with chills, fever, and joint pains. It is also possible for gonococci to penetrate the brain, causing meningitis, or the heart, causing endocarditis, though these complications are not seen frequently.

Every year in the United States there are about a million reported cases of gonorrhea, known colloquially as the "clap," and probably another million or more cases that private physicians somehow manage to forget to mention to public health officials. It is present in near-epidemic proportions and is passed around not only in brothels and cheap hotels but even in the best of high schools and colleges. Health officials really do not know what to do about it. Reasoning that they cannot stop its spread, because they cannot stop people from having sex, they are feeling something that could develop into panic if they had to cope with large numbers of resistant cases.

For the moment, spectinomycin is adequate as an antibiotic of second resort. But it poses two problems. The first is economic. Sold only by Upjohn under the brand name Trobicin, spectinomycin is far more expensive than penicillin. Therefore, a cure that used to cost 50 cents for penicillin costs $3.50 or $4 for spectinomycin, not because it is inherently more expensive to manufacture, but because it is protected by a patent and cannot be made and sold under its generic name. In this country, treatment in public VD clinics is usually free, so it is the taxpayer who would bear the burden should it be necessary to buy lots of spectinomycin. In many countries abroad, the drug simply would not be purchased. The Philippines, for example, apparently is not ready to launch a campaign to eliminate the resistant strain from its prostitutes, so the pool of penicillinase-producing gonococci will continue to spread.

The second problem is biological. It is not only likely but probable that the clever gonococci will develop resistance to spectinomycin as well, (a few spectinomycin-resistant cases have been reported recently in England) establishing the need for yet other antibiotics to

Drug Resistance Growing Worse

The problem of antibiotic resistance, graphically illustrated by the case of penicillin-resistant gonorrhea, is confounding scientists who fear that resistant gonococci will soon spread their newfound anti-penicillin enzymes to other organisms as well. University of Washington microbiologist Stanley Falkow, who accurately predicted the emergence of penicillinase-producing gonococci, now predicts that selected strains of meningococci, those that cause meningitis in adults, will be the next to go as the gene for penicillinase is passed from one type of organisms to another. If Falkow is right, public health officials could be faced with a serious epidemic of drug-resistant meningitis. The meningitis bugs already are resistant to the sulfa drugs that used to work so well against them and penicillin is among the drugs of last resort even now.

Antibiotic resistance has been around for quite some time. It was first observed by Japanese scientists in 1955 and since then researchers worldwide have learned a good deal about how it works. Resistance is transferred from organism to organism, within and across species lines, by packages of genes, designated R-factors, that reside on plasmids—units of DNA that exist apart from a cell's chromosomes where most of its genetic material is located. By a process of conjugation, or mating, R-factors pass from bacterium to bacterium, transferring genetic information in a classic, natural case of recombinant DNA. (Because of the known hazards of R-factor transfer, experiments with this class of plasmids have been restricted under the NIH recombinant DNA guidelines.)

The penicillinase produced by the new gonococcus, which is known technically as beta-lactamase, has been present at least since 1974 in another type of bacteria, the *Haemophilus influenzae*, which causes meningitis in infants and very young children at the rate of some 40,000 cases a year, according to Falkow. As a result, chloramphenicol, a potent antibiotic that can damage bone marrow, is now the "drug of choice" for these children. *H. influenzae* are present in the upper respiratory tract of many persons and there is speculation that an increase in the practice of oral sex provided the meeting ground for the influenzae and gonococci that now have penicillin resistance in common.

Although there is probably nothing that researchers can do to wipe out the phenomenon of antibiotic resistance altogether, one school of thought firmly holds that things would improve measurably if only antibiotic usage could be limited severely. That is to say, Falkow and others would like to see physicians put an end to the random prescribing of antibiotics for such passing maladies as the common cold, though there is little reason to expect that to happen.—B.J.C.

which it will only become resistant in turn. Such is the nature of antibiotic resistance, which can be infectious among bacteria just as bacteria can be infectious among human beings.

For several years, drug companies have invested considerable energy trying to find new drugs to replace those that fall by the wayside as bugs learn to outwit antibiotics, and it is at least theoretically possible that they can keep up with, if not ahead of, the challenge. Clearly, they are working on ways around the problem of penicillin resistance, although most companies are reluctant to talk too specifically about what they are doing, not only to the press, but also to academic researchers. Nevertheless, it is possible to establish what kinds of approaches are being taken. One that seems promising to some researchers lies in the development of an agent that itself is a penicillinase inhibitor. Were it to work, it could be given before or along with penicillin, restoring penicillin's usefulness by binding the bacterial enzyme that destroys it. Investigators at Beecham Laboratories' British plant are working along these lines, as, most probably, are other scientists.

The National Institutes of Health (NIH), through the National Institute of Allergy and Infectious Diseases (NIAID), spends about $3.5 million a year to study "sexually transmitted diseases," or STD. (It should be pointed out that at the London meeting a year and a half ago, scientists agreed to stop talking about VD and refer to STD instead. The May 1975 issue of *World Health*, the magazine of the World Health Organization (WHO), explains why: "Ignorance and feelings of guilt are in fact the two staunchest allies of a whole group of infections hitherto known as 'venereal diseases.' In the hope of making patients feel guilty, scientists from all over the world recently agreed to give them another name and chose the term 'sexually transmitted disease'. . . ." So it comes to this—only a couple of years after a major national campaign to make VD a term you could use in the living room.

The NIAID research, all of which is "extramural," is coordinated by Milton Puziss. Puziss says he hopes to have new money to fund grant and contract research on the new resistant organism in particular but that, at present, research is directed at understanding the gonorrhea bug in general. One thing that distinguishes gonorrhea, and other VDs or STDs, from other infectious diseases, is that people do not develop any effective natural immunity to the disease after they have had it once. No one is certain why this is so, but there are several hypotheses. One has it that people may be reinfected with an antigenically different strain of the organism, so that when they get gonorrhea a second time around it is not precisely the same condition, although the symptoms are the same. Another bet is that there would be immunity were the bugs not eradicated so swiftly with penicillin; in other words, there has not been time for an immune reaction to take place. (A rash of untreatable disease could provide an unfortunate test of that hypothesis.) A third possibility is that there is no permanent, systemic immune response because the antibody-antigen reaction that is known to take place is limited to mucosal tissues at the site of infection and does not involve the bloodstream.

Puziss observes that one way to get around the immune problem as well as the matter of drug resistance would be to develop a vaccine to prevent people from getting gonorrhea at all. Research toward this end is under way, grounded in part in studies of the relationship between gonococci and the immune system, although Puziss cautions that development of a vaccine is not exactly imminent.

But suppose there were a vaccine. What then? The problems of testing it without stigmatizing individuals and invading privacy would be enormous. The problems of distributing it to the population at large would be horrendous. Imagine, for instance, the reaction of church leaders and parents groups to a recommendation from the Secretary of Health, Education, and Welfare that all high school freshmen be vaccinated against the clap!

Lacking a satisfactory medical solution to the problem of a potential epidemic of resistant gonorrhea, health officials are trying to decide what is the best thing to do. There is debate, for example, over whether the CDC-recommended therapeutic regimen should be altered. Wiesner says that for now, CDC is recommending treatment as usual, with resort to spectinomycin only after a patient has proved resistant to penicillin (there is no simple way to test a patient in advance of therapy to find out inexpensively and quickly whether the resistant strain is present). The reasoning is that broad-scale switch to spectinomycin would only hasten evolution of spectinomycin-resistant bugs. But others believe penicillin has already outlived its usefulness. Says epidemiologist King Holmes of the STD center at the University of Washington, "I think penicillin is no longer the drug of choice, even though I developed the drug regimen that CDC now recommends."

The best bet for keeping the lid on the new gonorrhea is to turn to familiar public health measures: early identification of patients, perhaps aided by an educational campaign to get people to seek treatment; and identification and treatment of "contacts," though it can be hellishly difficult to get VD patients to tell whom they've had sex with. This is not an ideal or sure path to success. But for now, that is all there is.

—BARBARA J. CULLITON

Repression in Argentina: Scientists Caught Up in Tide of Terror

The scientific community in Argentina is under severe stress as a result of the present state of civil unrest. Hundreds of scientists have been fired from jobs in government research institutes and universities, many have been arrested without being charged with any offense, and others have chosen to leave the country.

Scientists do not seem to be a particular target of repression, but along with other professionals have been caught up in the violent tides of terror and counterterror that now prevail in Argentina. More than a thousand people are thought to have died this year in political assassinations, whether by the rightist vigilante groups that seem to have the unofficial support of the government or by the urban guerillas who include the Monteneros and the leftist wing of the Peronist movement. Since 24 March this year, when the government of Juan Peron's widow was toppled by the seventh military coup in 21 years, there has been a further deterioration in all forms of hu-