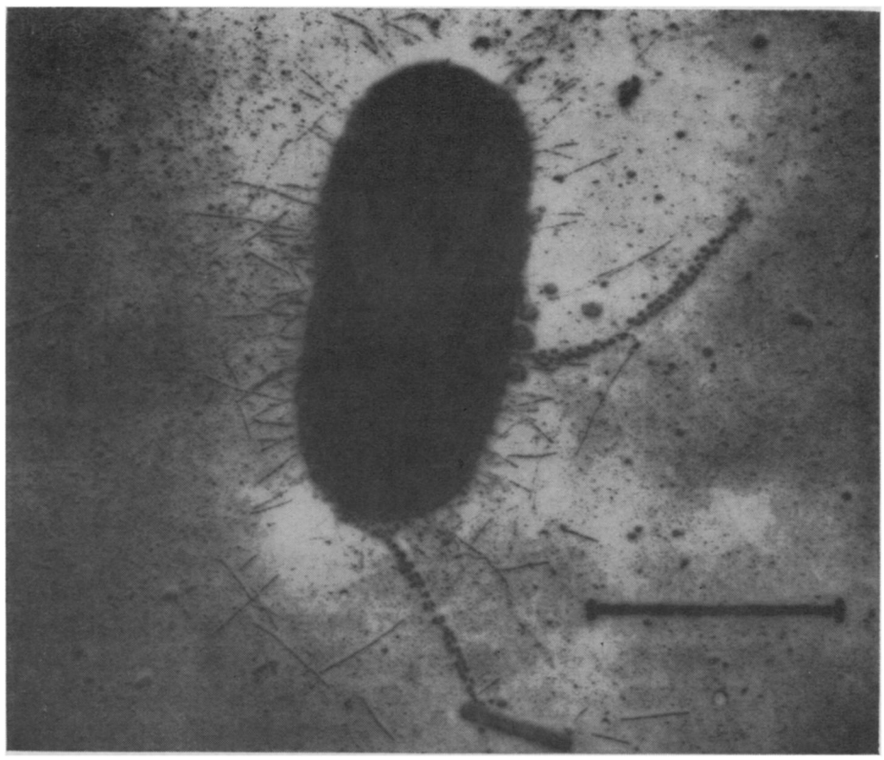
Bacteria Ganging Up on Drugs

Drug resistance is concerning more and more scientists; its magnitude remains unmeasured.



R factors move from germ to germ through the thread-like pili of the 'male.'

With the discovery of sulfa drugs and antibiotics came man's confidence in his ability to control infectious diseases.

But now, that confidence is being shaken by once defenseless germs that have learned to outwit man and thrive in the face of his wonder drugs.

Bacterial resistance to drugs is nothing new—some microorganisms have always managed to go unscathed by drugs designed to wipe them out—but it is on the rise. During the last decade, more and more resistant bacteria have turned up, making typhoid, dysentery, infant diarrhea and other infections more difficult to treat.

And the problem is complicated by the fact that one resistant bacterium can pass its resistant genes on to others, thus spreading multiple drug immunity like an infection through whole populations of intestinal bacteria.

At a recent symposium on "Infectious Multiple Drug Resistance," jointly sponsored by Georgetown University, Washington, D.C., and the U.S. Food and Drug Administration, microbiologists, geneticists, clinicians and others met to examine the potential threat of widespread drug resistance. The subject is attracting the attention of a growing number of scientists.

According to Dr. Fred Gill of Cornell Medical Center, New York, for example, of 254 salmonella strains tested during a four-month period, 14 percent were resistant to antibiotics—particularly streptomycin, tetracycline and sulfisoxazole—and 71 percent of the resistant strains transferred their resistance to others. Salmonella can be found in dried milk, eggs and other foods.

From Children's Hospital, Washington, Dr. Sydney Ross reports an increase in resistant cases of children's diarrhea. Shigella, rod-shaped bacteria that cause dysentery, salmonella and another disease-causing bacteria called E. coli were all immune to several drugs, he says. But treatment is not impossible and the magnitude of the threat cannot be measured yet.

Resistance is transferred from one bacterium to another by the resistance factor or R factor, first identified in 1959 by Dr. Tsutomu Watanabe of Keio University, Tokyo.

The R factor itself is a virus-like piece of genetic material that apparently consists only of DNA or deoxyribonucleic acid. It is made up of resistance transfer factor and a pool of resistance genes that number 100 or so. Each R factor carries genes resistant to more than one drug, though individual genes are specific only for a particular antibiotic.

The first R factors to be identified came prepackaged with genes resistant to sulfonamid, streptomycin, tetracycline and chloramphenicol, according to microbiologist Dr. Stanley Falkow of Georgetown.

"The best defense against R factor transfer is a normal intestinal tract," Dr. Falkow says, "because normal bile salts keep bacterial cells from coming into contact with each other." R factor transfer occurs when one cell wall touches another, and when antibiotics get into the intestines, upsetting normal activity, cell-to-cell contact can take place, he explains.

Although the precise mechanism of transfer is still unclear, scientists believe R factor gets into a recipient or "female" bacterial cell through pili, long thread-like antennae on the surface of a donor cell. When the two come in contact, R factor release is triggered somehow.

Promiscuous "male" bacteria can transfer their resistance genes to almost all intestinal bacteria, so that R-factor-mating is as likely between E. coli and salmonella, for example, as it is between two strains of E. coli. Transfer takes only about four minutes, Dr. Falkow says.

At present, major questions about R factors remain unanswered. Research scientists still want to know where they came from and clinicians want to know what to do about them.

The only thing that can be said with certainty about R factor's origin is that they were around long before antibiotics, thus eliminating antibacterial drugs as the cause of the trouble. R factors resistant to streptomycin have been identified in bacteria isolated before the introduction of this antibiotic, according to Dr. David H. Smith of Harvard Medical School, Boston. Furthermore, he says, R factors in 11 bacterial strains used in experimental study have proved resistant to two antibiotics not yet commercially available. In other words, some may be immune to some

drugs that haven't even been discovered yet.

In spite of the fact their origin is indiscernible just now, research in this direction is moving quickly because scientists have been able to get extremely pure isolates of R factor DNA, Dr. Falkow says. "Quickly" to a microbiologist means answers any time in the next 10 years.

Clinicians probably are not much closer to an answer to their question.

One way to cut down on drug resistance transfer is to stop prescribing antibiotics almost indiscriminately, but that is not an altogether workable solution, they agree.

Another thought is to eliminate, or at least greatly reduce, the use of antibiotics in animal feeds, thereby precluding transfer of antibiotics from animal to man as residues in meat. But antibiotics stimulate animal growth and increased protein manufacture—both desirable side effects.

Furthermore, there is little evidence to date to support the hypothesis that there is any real danger of R factor transfer from animal to man by this route, according to symposium scientists. Although they agree that more studies are in order, most see no reason for any new regulations of antibiotics in feeds.

This issue is being explored further at a second symposium this week in Washington, sponsored by the National Academy of Sciences and FDA.

A third answer to drug resistance lies in the development of drugs that would either inhibit transfer or clear infected genes of R factors before administration of antibiotics. Drug companies have been working in this direction—one has a patent application pending to combine acridine with tetracycline—but symposium scientists were skeptical of any immediate or wide-spread solution in this area.

ESRO's First Satellite

The language problems were formidable. A British contractor and a French subcontractor had to get along with German computer engineers, U.S. rocket scientists, Dutch astronomers and consultants from Belgium, Denmark, Italy, Spain, Sweden and Switzerland. Even among the central project group, documents had to be translated into four languages.

"It gets a little puzzling," admits Germany's Dr. Heinz Busch, "when an item or a system in one company is called a particular name, and in the very next company the same thing is called by another name." But overcoming such obstacles is standard operating procedure for the European Space Research Organization, whose first satellite was launched last week from Vandenberg Air Force Base in California.

It was a "textbook launch" in all ways—until the fourth stage of the U.S.-built Scout rocket failed to ignite. As downrange tracking stations waited in vain for a blip to appear on their radar screens, "indications of tumbling" were received from telemetry equipment on the satellite. It never got into orbit.

ESRO came into being with 10 member-nations on March 20, 1964, largely out of economic necessity. For any but the richest European countries to consider running their own individual space programs was virtually out of the question. The brain drain was making itself felt, as more and more European scientists were crossing the ocean to the extensive and lucrative U.S. space program, already past Project Mercury. "Our scientists must have their own satellites to work on, if we are to keep technically current," says Dr. Busch, ESRO's director of satellite projects.

With European satellites, even the construction itself is usually bid for by consortia, instead of by individual companies as in the U.S. One such was the European Satellite Team, formed last year to seek the contract to build a pair of ESRO satellites called TD-1 and TD-2, to be launched in 1969. The EST's members were companies from England, France, the Netherlands, Sweden and Italy, with General Electric retained as a consultant in the U.S.

ESRO's first satellite, which was actually ESRO II because ESRO I's observation schedule requires that it be held up until this fall, was built by a consortium including Hawker Siddeley Dynamics of England, Engins Matra of France and, as consultant, TRW Inc. of the U.S.

ESRO I's restricted launch date is planned to coincide with the long night over the North Pole. The satellite will be placed, also by a Scout rocket, into a polar orbit to study auroral phenomena at their fall peak.

Following the September launch of ESRO I, the organization's focus will shift to a pair of Highly Eccentric Orbiting Satellites called HEOS, which will come as close as a few hundred miles to earth, then swing out to almost 190,000 miles. Then come TD-1 and TD-2, to study stellar and solar astronomy, X-ray and gamma radiation. The last item presently on ESRO's schedule is LAS, a Large Astronomical Observatory weighing more than 1,800 pounds that may well be the first all-European satellite program, including the launch vehicle.

At present, ESRO has no plans to construct its own Cape Kennedy launch facility, though it does envision its own global tracking network. However, other sites than the U.S. may become available for launches in the future, including a French one now being built in French Guiana and the Italian floating platform off the coast of Kenya from which Italy's second San Marco satellite was launched.

There is even a multilateral European Launcher Development Organization at work on a booster called the Europa, but ESRO's satellite, which represents the goal of such a broad effort, has been stealing the publicity in a way that caused some wonder as to whether ELDO might not have vanished in a puff of smoke. Arnold Frutkin, the National Aeronautics and Space Administration's head of international affairs, is reassuring: "ELDO," he says, "like Bette Davis, is still around."

FROM CANADA

Measuring Quasars

Ever since quasars were discovered, astronomers have been puzzled as to their distance and the source of their tremendous energy.

Now Canadian radio astronomers have developed a refined technique for measuring the size of those baffling quasistellar radio sources. The method lets astronomers measure the angular diameter of quasars with unprecedented resolving power.

Details of the technique were reported to the annual spring meeting of the International Scientific Radio Union in Ottawa by Dr. J. L. Yen of the University of Toronto. The method is said to be so powerful that it could measure from the earth a source of radio waves the size of a man on the moon.

The size of a quasar radio source, a clue to its energy, can be measured by special equipment called a radio interferometer. Two antennas receive signals from the same source and then compare them. To obtain sufficient resolution to measure the small diameters of quasars, the two receiving antennas must be large distances apart.

Measurements have been made with antennas 80 miles apart (SN: 3/11), but better results are achieved when the receiving stations are even farther apart. This poses a problem because the links between the two antennas make it difficult to coordinate the signals.

The Canadians have overcome this with a technique where no direct link between the two stations is required. The signals received from the quasars at the two stations are recorded on ordinary magnetic tape and synchro-