Penicillin and patents

Competition for *Lebensraum* in the invisible world of microbes is matched in pace by the competition of the great companies that produce antibiotics designed to keep the microbes in their place.

The latest episode in the dual war took place last week when both Pfizer's J. B. Roerig Division and the British-owned Beecham Pharmaceuticals, which operates a New Jersey plant, announced they were in the market with carbenicillin, a new antibiotic effective against *Pseudomonas aeruginosa,* a bacterium looming with new importance in human disease.

Why both the British and the American company are able to produce and market this drug here is a legal thicket almost as hard to penetrate as the intricate microbial relations that make *Pseudomonas* infections so newly prominent.

Long thought a harmless human parasite, *P. aeruginosa* has only recently been recognized as a predator that moves in when the body's defenses are low. Its traces are in the blue-green stains sometimes seen on surgical dressings. Of the interesting genus that includes fluorescent or light-emitting bacteria (129 other species known are all harmless to man), *P. aeruginosa* secretes both a fluorescent yellow-green pigment and a blue pigment. The pigments are the microbe's own defense against the world—they are lethal to some molds and fungi.

With *Staphlococcus aureus*, the antibiotic-resistant bacterium that yesterday plagued hospitals, beaten back by a series of new antibiotics, *P. aeruginosa* has bloomed instead. It is becoming all too common in urinary tract infections. In patients hospitalized with leukemia or with certain chronic diseases, it may invade much more deeply into body tissues, sometimes becoming an overwhelming infection.

Pseudomonas infections are difficult to diagnose, since the bacterium can seldom be cultured from the blood stream, and have been difficult to treat because antibiotics used against them before the Food and Drug Administration approval of carbenicillin are fairly toxic in the high dosages needed. Carbenicillin has "little or no toxicity even in very high dosage," according to the authoritative MEDICAL LETTER ON DRUGS AND THERAPEUTICS.

Enthusiasm is tempered by several reservations, however. Cost is one. Large amounts of carbenicillin are needed to deal with systemic *Pseudomonas* infections. Dosage may be as high as 30 grams a day. This is expensive therapy—a hospital would pay about $80 for this much carbenicillin. Treating a urinary infection would cost about $10 a day. Carbenicillin will be used chiefly by hospitals. Not absorbed orally, it is given intravenously and intramuscularly.

How long the new antibiotic will defeat *Pseudomonas* remains another question. This baffling organism has shown variation high even in the crowded microbial world where mutation is almost instantaneous. Past antibiotics effective against *Pseudomonas* strains seen in one clinic, for example, have been less effective at other clinics in the same city.

Carbenicillin is the newest chemical manipulation of the side chain that gives the penicillin molecule its therapeutic power. It is the newest step in the remarkable semisynthetic manufacturing methods launched by a British research group a decade ago.

Noting the enormous horizon of antibiotics, Beecham, a company then chiefly known as producer of the most popular British toothpaste, conferred with Sir Alexander Fleming, discoverer of penicillin, and hired a small research staff. Beecham sent its researchers to work for a while in Rome with chemist Ernest Chain, a Nobel laureate who did some of the fundamental work on penicillin.

Soon after their return from Rome, F. R. Batchelor and colleagues showed how abundantly basic research pays off. They found out how to isolate the two-ringed penicillin nucleus from the fermentation mix. This made it possible to chemically and experimentally attach any number of side chains, each of which could be tested for therapeutic action and many of which became marketable products.

The remarkable thing about all this is that when Beecham suddenly found itself discoverer and patent owner of the basic penicillin nucleus, 6-aminopenicillanic acid, it had never produced an antibiotic. Lacking both the plant and the know-how to do so, Beecham licensed the American company, Bristol-Myers, to produce the penicillin 6-APA nucleus (which by itself has no therapeutic property) as well as several of the drugs that Beecham scientists quickly discovered by trying various groups as a side chain in the molecule.

Things then moved rapidly in the American pharmaceutical industry. Soon almost everybody was capturing the 6-APA nucleus from penicillin broth and then chemically adding on various side chains thought to be therapeutic. In producing the nucleus, most companies obtained licenses to use methods on which Bristol holds the rights. One is Beecham's, which Bristol may sublicense. Another is the Sheehan patent, named for the Massachusetts Institute of Technology researcher, John Sheehan, who showed how to synthesize chemically the entire molecule of penicillin. Complete chemical synthesis is not yet a feasible production process and producers of the host of drugs that are side-chain variations still start with the penicillin nucleus as produced by the fermentation process.

One of these drugs is ampicillin, discovered and patented by Beecham, which acts against *P. aeruginosa, S. aureus* and other microorganisms that, in one of the great epics of self-defense in the natural world, came to dominate as mutant strains producing the enzyme penicillinase. Penicillinase attacks the penicillin molecule, piercing one of its carbon rings, and so brought about the widespread antibiotic resistance that has troubled medicine for several decades.

Dr. Donald C. Hobbs of the Pfizer Medical Research Laboratories at Groton, Conn., discovered that an amino group of ampicillin could be replaced by a carboxyl group, a step that sounds simple but is intricate to carry out chemically. The replacement happily produced broader power and greatly reduced the toxic potential of the parent ampicillin. The change was enough to permit Pfizer to become the happy holder of a United States patent on carbenicillin. Although Beecham holds a carbenicillin patent in Britain and many other countries, it was obliged to apply to Pfizer for license to sell this drug in the United States.

Pfizer may have had reason to license its competitor. Beecham thinks Pfizer must get to its carbenicillin by "going via our 6-APA" and "presumes that Pfizer must be operating under a Bristol patent to do this." Since pharmaceutical companies never talk to each other because of the antitrust laws, nobody can do more than "presume."

Pfizer says that the fermentative step, or nuclear isolation part of its carbenicillin production, is not under a Bristol patent, but does concede that negotiations are under way with Bristol having something to do with the Beecham-originated patent. By the intricate and precise nature of patent law, this is limited to a specific crystalline 6-APA. The whole thing is one of those fascinatingly delicate, or multi-million-dollar, matters.

Meanwhile, American physicians got a new drug that is effective against *P. aeruginosa* and other difficult things. Prominent among these are *Proteus* bacteria, a highly motile "swarming" genus abundant in nature and especially in putrefying animal matter. Common in normal feces, under circumstances as yet not understood, some *Proteus* strains produce eye and ear infections and bladder trouble. □