Case Histories of Significant Medical Advances: Cephalosporins

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Working Paper 20-133
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Abstract: Our case history describes the development of three generations of cephalosporins – antibiotics that have significantly reduced hospital infections. Specifically, we chronicle how: 1) Early (pre-cephalosporin) antibiotics were developed in the first half of the 20th century. 2) Drug companies developed first-generation cephalosporins in the 1960s using foundational discoveries made by researchers in Italy and the UK in the 1940s and 1950s. 3) Continued modifications of cephalosporin molecules resulted in second and third generation of the drugs in the 1970s and 1980s.

Note: Cephalosporins, like the others in this series of case-histories, are included in a list compiled by Victor Fuchs and Harold Sox (2001) of technologies produced (or significantly advanced) between 1975 and 2000 that internists in the United States said had had a major impact on patient care. The case histories focus on advances in the 20th century (i.e. before this millennium) in the United States, Europe, and Japan -- to the degree information was available to the researchers. Limitations of space and information severely limit coverage of developments in emerging economies.
Cephalosporins

Cephalosporins play an important, ‘behind the scenes’ role in preventing and treating hospital infections. Three generations of these antibiotics helped cut the rate of infections in patients recovering from operations in hospitals by more than half between the 1960s and 1990s. In 1986, just six years after “third-generation” cephalosporins were introduced, they accounted for 80% of the antibiotics administered in U.S. hospitals and have remained the top antibiotic given to hospitalized patients according to a 2010 survey. Some physicians call cephalosporins “wonder drugs” that, like penicillin, helped produce a “golden age” in antibiotic treatments; however, their story is not as well known.¹

This case history starts with an introductory overview of antibiotic development and its challenges. It then describes how:

- Early (pre-cephalosporin) antibiotics were developed in the first half of the 20th century.
- Drug companies developed first-generation cephalosporins in the 1960s using foundational discoveries made by researchers in Italy and the UK in the 1940s and 1950s.
- Continued modifications of cephalosporin molecules resulted in second and third generation of the drugs in the 1970s and 1980s.

Overview of Antibiotic Development and Challenges

Trillions of bacteria live in soil and water, and on plants, animals, and humans, and many can benefit humans.² However, a few bacteria can cause deadly diseases including typhoid, cholera, plague, pneumonia and tuberculosis: in 1900, before the development of effective antibiotic treatments, such diseases were the top causes of death worldwide -- and of periodic pandemics. In hospitals, where many different disease-causing germs can flourish, weakened patients recovering from operations are vulnerable to multiple bacterial infections. In addition, bacterial infections spread through sexual contact can cause chronic, debilitating diseases, such as syphilis and gonorrhea.³

Figure 1  Molecular structure of cephalosporin

Antibiotic molecules used to treat bacterial infections usually have ring and side-chain structures.⁵ (See Figure 1) Variations in the structures determine how the molecules attack bacteria and thus the range of diseases they can treat. For instance, penicillin predominantly attacks the cell walls of bacteria that do not have a protective outer membrane. Other antibiotics, notably ciprofloxacin,⁶ predominantly
attack bacteria with cell walls protected by an outer membrane. However, those that attack bacteria with protective membranes are not necessarily effective against bacteria without protective membranes. “Broad spectrum” antibiotics—such as third generation cephalosporins—can attack bacteria with or without protective membranes.7

Development of antibiotic drugs, which typically takes about a decade and can cost more than half a billion dollars, begins with molecules extracted from a living organism or synthesized from chemicals. Nearly all the antibiotics that are in use today are derived from molecules discovered in the “golden age” of antibiotics, roughly from the 1940s through the 1970s. Since the 1980s, new antibiotics have been developed mainly by modifying the side chains of previously discovered molecules.8

Modifications seek to improve potency, overcome drug resistance, reduce side effects, and make doses easier to administer to patients. Promising modifications are first tested in labs, then on animals, and eventually in human trials. The U.S. Food & Drug Administration (FDA) regulates the design of the trials and evaluates the results to decide whether and for what diseases (or “indications”) new molecules can be marketed to treat. Concern about bacteria developing antibiotic resistance is believed to make the FDA particularly cautious in approving the marketing of new antibiotics.9

The development process is both economically and technologically risky. Bacteria can acquire resistance to new antibiotics before companies have recouped their investments.10 Patents cover specific molecular structures or production processes. However, they provide limited protection: competitors can easily invent around molecules, and some countries do not recognize process patents.11

Early antibiotics (before cephalosporins)

Synthesis and Screening. German physician Paul Ehrlich collaborated with chemists and bacteriologists to synthesize the first widely used antibiotic in 1909. Ehrlich had studied dyes synthesized in the nineteenth century by German chemical companies and found that they selectively stained only some microbes. The finding led him to believe that a synthesized drug might work like a “magic bullet” that killed disease-causing germs without harming healthy cells. In 1904, he began to systematically search for a drug effective against syphilis, which until then had to be treated with mercury salts that caused severe side effects. However, he did not start with dyes. Rather he synthesized and tested variants of an arsenic-based compound that veterinarians gave to animals but was toxic to humans.12

Ehrlich’s team synthesized and screened hundreds of variants. The 606th compound they tested cured syphilis-infected rabbits, and subsequent trials suggested it could treat syphilis in humans. In 1910, Ehrlich collaborated with the German chemical company Hoechst to introduce the compound, which they first called “606,”13 as “Salvarsan.” By the 1930s, it was widely used to treat syphilis in Europe and the United States. However, Salvarsan could not effectively treat other bacterial infections. Additionally, it needed to be packaged in sealed vials with nitrogen gas.14

Pharmaceutical companies followed Ehrlich’s method of screening large numbers of synthesized compounds as they searched for new antibiotics. Notably, the German pharmaceutical company Bayer used the process to develop the first of the so-called “sulfa drugs,” known as “Prontosil.” Introduced in 1935, Prontosil, which did not need special packaging, was used for “strep” infections, pneumonia, meningitis, and uterine infections. However, sulfa drugs had limited effectiveness and patients sometimes suffered serious side effects and allergic reactions. Sulfa drugs’ reputation also suffered in 1937, when over one hundred people in the U.S. died after taking ‘Elixir Sulfanilamide’ a sulfa drug

* Bacteria that lack a protective outer membrane are known as “gram positive” bacteria. Bacteria with a protective outer membrane are known as “gram negative” bacteria.
dissolved in a then-common but highly toxic solvent.* (Sulfa drugs are still used to treat urinary tract infections today, however.)

Medicine from a Mold. Penicillin, extracted from a mold (a multicellular fungus), followed the chemically synthesized antibiotics. Healers from antiquity had noted the antibacterial effects of molds, and researchers in the late 19th century had discovered the antibacterial properties of the *penicillium* mold but could not explain why. In September 1928, Scottish physician and microbiologist Alexander Fleming, who researched, taught, and practiced at St. Mary's Hospital Medical School (London), noticed a mold killed bacteria he had cultured in a lab dish.

Fleming identified the mold as belonging to the *penicillium* genus and discovered that a “juice” it had produced, not the mold itself, had destroyed the bacteria in his petri dish. He extracted and named this “mold juice” penicillin and found it killed the bacteria that caused influenza, diphtheria, and pneumonia. He could not however extract the mold juice in large quantities or enlist chemists to further purify it. Fleming then discontinued his own research on penicillin.

About ten years later, researchers at Oxford University’s Sir William Dunn School of Pathology revived penicillin research. The Dunn School’s director, Australian pathologist and pharmacologist Howard Florey, recruited a multi-disciplinary team of about a dozen scientists including the German born Ernst Chain, Norman Heatley, and Edward Abraham. While studying antibacterial substances produced by natural microorganisms, Florey and Chain learned about Fleming’s earlier research on penicillin.

In early 1940, Chain and Abraham worked out a process to purify and concentrate penicillin and later that year Chain and Florey reported that the purified substance attacked many disease-causing bacteria in mice. In 1941, the Oxford researchers tested penicillin on a local policeman who had developed a serious wound infection from a scratch by a rose thorn. The treatment improved the policeman’s condition, but, after the supply of penicillin ran out, the wound infection spread, and he eventually died. The results, however, encouraged more research. In 1942, Florey and Abraham, determined the chemical composition of penicillin. Shortly after, Oxford chemist Dorothy Crowfoot Hodgkin used X-ray crystallography to photograph the ring and side chain structure of the molecules.†

Meanwhile, the outbreak of the Second World War had created an urgent need to treat soldiers with wound and pneumonia infections. Initially, military first aid kits contained powdered sulfa drugs, which soldiers were told to sprinkle on wounds to prevent bacterial infections. However, as mentioned, sulfa drugs had limited effectiveness. Penicillin offered the promise of greater effectiveness; however, not much penicillin could be extracted from the then-available molds and the existing extraction process introduced contaminants.

Florey first tried to persuade British pharmaceutical companies to improve the production process and make penicillin on a large scale. But the companies already had commitments to supply other drugs to the military and the bombing of their facilities had severely strained their research and production capabilities. Then, in July 1941, Florey traveled to the United States, which was half a year away from entering the war, to solicit support. A former Oxford classmate introduced Florey to researchers at the U.S. Department of Agriculture's Northern Regional Research Laboratory, who

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* The tragedy prompted the passage of the 1938 U.S. Food, Drug, and Cosmetic Act, which authorized the Food and Drug Administration to require safety testing of drugs before marketing.

† Hodgkin published her research in 1945, the same year that Chaim, Fleming, and Florey shared a Nobel prize for Medicine. Hodgkin would win a Nobel Prize in Chemistry in 1964 "for her determinations by X-ray techniques of the structures of important biochemical substances" (including penicillin and vitamin B12.)
agreed to help. Within a year, the American researchers had identified a fast-growing mold from which more penicillin molecules could be quickly extracted.  

**Scaling Up.** The high-yielding mold and military demand after the U.S. entered the War spurred rapid improvements in quantity and purity. In 1943, American drug companies produced only 29 pounds of penicillin; in 1944, they produced about 3,000 pounds; and in 1945, they produced about 14,000 pounds, exceeding military needs. Concurrently the improved filtration of contaminants changed the color of penicillin powder from brown to yellow to white. 

The War also left a regulatory mark. A War Production Board had required drug companies to test each batch of penicillin they produced. In 1945, the U.S. Congress authorized the FDA to require such testing for penicillin produced for civilian use as well. The FDA did not require testing of individual batches for other drugs. The FDA eventually stopped requiring testing for antibiotics in the 1980s.

**Soil Searching.** Penicillin’s success prompted a hunt for other antibiotics. In 1943, Rutgers researchers led by Selman Waksman (awarded a Nobel Prize in 1952) extracted streptomycin from (“good”) bacteria found in New Jersey farm soil. Other researchers also searched for antibiotics in soil and, in 1945, Lederle Laboratories researchers extracted chlortetracycline from bacteria found in an experimental agricultural plot at the University of Missouri. Streptomycin and chlortetracycline had different structures (with different center rings) than penicillin did, and they attacked a wider range of bacteria. However, bacteria quickly developed resistance to chlortetracycline, and streptomycin had serious side effects, though it continues to be used to this day.

**First-Generation Cephalosporins**

**Foundational Research.** A fungus found in sewage water in 1945, rather than soil, provided an unexpected breakthrough. Giuseppe Brotzu, a pharmacologist who taught at the University of Cagliari on the Italian island of Sardinia, had mapped outbreaks of typhoid fever in Cagliari. He inferred from the pattern of outbreaks that a mold in sewage might be attacking bacteria that caused typhoid. He then tested the sewage where outbreaks were rare and discovered a fungus, which he identified as *Cephalosporium acremonium*. Brotzu conducted lab tests on the fungus and tested it on human volunteers; the tests suggested that it might cure several diseases that penicillin could not, including cholera and bubonic plague.

Brotzu, who lacked the means to continue research, contacted a British medical officer he had met during war. The officer introduced him to Oxford scientists who had worked on penicillin, and, in 1948, Brotzu sent them samples of the sewer-dwelling Cephalosporium fungus. A team led by Edward Abraham extracted two molecules (“cephalosporin P” and “cephalosporin N”) that attacked many of the same bacteria penicillin did.

Abraham’s team then extracted a third molecule — “cephalosporin C” — that attacked an even wider range of disease-causing bacteria. It also showed evidence of the ability to attack penicillin-resistant bacteria, which had become a large problem in hospitals.

In 1957, a team at Britain’s Antibiotics Research Station found a mutant strain of the Cephalosporium fungus that yielded more cephalosporin C molecules. More plentiful molecules in turn helped Abraham and his Oxford colleagues determine cephalosporin C’s structure: two adjacent rings with a chain on each side. (As shown in Section 1, Figure 2)

**Licensing.** Before the Oxford researchers had discovered the ring-and-chain structure, Abraham had, in 1953, contacted the British National Research Development Corporation (NRDC). The NRDC was a government agency established in 1948 to promote the commercialization of British research. Famously, Chain and Florey had chosen not to patent their penicillin discoveries and had made their work freely available.
The NRDC patented and then licensed the Oxford researchers’ cephalosporin molecules, first to Glaxo Laboratories in London, England, and, shortly thereafter, to Eli Lilly and Company in Indianapolis, Indiana, in the United States. Both companies had been producing pharmaceuticals since the nineteenth century and were leading producers of penicillin: Glaxo produced approximately eighty percent of the United Kingdom’s penicillin at the time, and Lilly was one of the top seven penicillin producers in the United States (and had helped develop the mass production process for the drug).30

Drug Development. Lilly researchers modified one of the cephalosporin molecule’s side chains using techniques developed in the 1950s to modify streptomycin, chlortetracycline, and penicillin. Lilly researchers also developed a way to extract eighty times the number of molecules from the mutant Cephalosporium fungus, enabling large-scale production. In 1962, the FDA gained authority to require clinical trials to demonstrate the safety and effectiveness of new drugs before approving the drugs for marketing; Lilly passed the trials by showing that their drug cured infections in patients that other antibiotics had failed to cure. The company then marketed the drug under the brand name “Keflin” in 1964.31

The terms of the NRDC license required Lilly to share its ongoing findings with other licensees, which enabled Glaxo to introduce a more potent molecule just months after Lilly’s Keflin debuted. Meanwhile, the NRDC had continued to issue licenses to and share research with companies in Europe, the U.S., and Japan. In the next ten years, four other longtime pharmaceutical makers—one in the United Kingdom, two in the United States, and one in Japan—introduced cephalosporin drugs with slightly different molecular structures. These drugs were formulated to have fewer side effects or to be taken orally; most previous antibiotics, including penicillin, streptomycin, chlortetracycline, and the first two cephalosporins had to be injected or administered intravenously.32 (See Exhibit 1)

Sales and Marketing. Worldwide sales of these “first-generation” cephalosporin drugs reached $640 million in 1974 (about $3.3 billion in 2019 dollars). Drug companies promoted adoption through heavy marketing, especially to hospitals. Marketing efforts highlighted clinical trials showing that cephalosporins caused fewer side effects than penicillin and recommendations from medical researchers urging use of the drugs on patients with penicillin allergies.33

Sales in Japan were also helped by the government’s reimbursement rules. A 1961 law required companies to sell all drugs directly to physicians, rather than to pharmacies (or other merchants). The physicians then dispensed the drugs to patients at prices regulated by the government. Regulated prices were usually lowered on old drugs as new drugs became available, encouraging physicians to favor the new drugs. Therefore, when a longtime Japanese pharmaceutical maker, Fujisawa, introduced “cefazolin” in 1971, it quickly became a bestseller.

Second- and Third Generation cephalosporins

Improved Efficacy. The first-generation drugs had predominantly attacked bacteria without a protective outer membrane; they were also excreted before they were fully absorbed by the body. Therefore, researchers continued to search for ways to modify the side chains of cephalosporin molecules to improve effectiveness and increase absorption. They succeeded in improving effectiveness by modifying both side chains; earlier, researchers had changed one or the other. However, the “second-generation” drugs were unable to improve absorbability.34 (See Exhibit 2)

Markets and Competitors. Improved efficacy helped cephalosporin sales grow worldwide from $640 million in the early 1970s to over $1 billion in the early 1980s (or over $5.2 billion in 2019 dollars).35 Demand from hospitals was particularly strong. One reason was that second-generation drugs could be used to treat bacteria that had grown resistant to previous antibiotics. Additionally, physicians put patients undergoing surgery on intravenously administered cephalosporins to prevent infection. (However, this preventative use of cephalosporins was controversial because cephalosporin producers had sponsored some of the studies that encouraged it.)36
Lilly increased its dominance in the 1970s and by 1982 had secured a seventy-five percent share of the U.S. market. The company offered five cephalosporin drugs (targeting different infections and conditions), whereas almost all its competitors sold just one. Lilly also marketed other top-selling antibiotics it had developed such as vancomycin and erythromycin. One competitor, Smith Kline, had successfully challenged the legality of Lilly’s “bundled” discounting of its five drugs to hospitals in the mid-1970s. However, Smith Kline’s victory in the case, which went all the way to the U.S. Supreme Court, could not dislodge Lilly from its top position.37

*Third-generation Drugs.* Refined side-chain-altering techniques, like those used for second-generation cephalosporins, produced more effective, safe, and convenient treatments: patients could take smaller, less frequent doses, and better tolerate treatment. 38 Importantly, this “third-generation,” introduced in the late-1970s and 1980s, was “broad spectrum,” meaning that the drugs attacked bacteria *with or without* protective membranes (whereas second generation cephalosporins mainly targeted bacteria with protective membranes).

Broad-spectrum cephalosporins were valuable in treating infections, contracted by patients after having appendicitis, cesarean sections, cancer treatments, and spine and brain infections. The new cephalosporins could also treat bacteria resistant to penicillin and first-generation cephalosporins.39

Japanese companies led development of the third generation. Following 1967 legislation that had lowered the threshold of originality required for new patents, Japanese pharmaceutical companies invested heavily in research; they designed “super germs” to help identify the most potent antibiotic molecules in tests, developed a new antibiotic group (fluoroquinolones), and developed seven of the ten third-generation cephalosporin drugs introduced between 1978 and 1987.40 (See Exhibit 3)

After the introduction of third generation drugs, worldwide sales of cephalosporin drugs increased more than 8-fold from 1982 to 1992, reaching $8.55 billion (or about $44.6 billion in 2019 dollars). Sales in the U.S. and Japan, the two largest markets, amounted to about $3 billion each. After a brief fall in 1995, sales revenues rose even higher in 1996, to about $10 billion (or about $52.2 billion in 2019 dollars).41

Observers had hoped that the less frequent dosing, broad spectrum of activity, and greater effectiveness of third generation cephalosporins would lead to cost savings for hospitals. However, prices of some third generation cephalosporins were three times more than second-generation cephalosporins and fifteen times more than other antibiotics. Hospitals were apparently willing to pay more to treat virulent bacteria that had developed resistance to previous antibiotics. Some physicians, however, questioned “whether such excessive antimicrobial ‘firepower’ [was] really necessary,”42 and some studies suggested that third generation cephalosporins were economical treatments for some diseases but not others.43

**The Situation in 2000.**

Some drug companies were developing cephalosporins to treat specific antibiotic-resistant bacteria. Notably, Takeda, based in Japan, and Hoffmann-La Roche, based in Switzerland had targeted a virulent strain of “staph” bacteria.* Overall however antibiotic research had declined in the 1990s along with approvals of new drugs: only seventeen new antibiotics (including cephalosporins) were approved for sale in the US in the 1990s down from about thirty in the 1980s. And, in the late 1990s the

*Penicillin had been effective against staph infections when first introduced in the 1940s. However, some strains of staph bacteria had developed resistance to it in the 1960s, as well as to subsequent antibiotics. These strains had proliferated in hospitals in the ensuing decades.*

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FDA had adopted even stricter rules for antibiotics as part of a broader revision of clinical trial guidelines in the late 1990s.44

By the end of the decade, Aventis, Bristol-Myers Squibb, Eli Lilly,45 Glaxo SmithKline, Proctor and Gamble, Roche, and Wyeth were severely reducing, eliminating, or spinning off their antibacterial research whereas generic producers selling older cephalosporins whose patents had expired were expanding. Similarly, generic cephalosporins sold in high-population, low-income countries had become significant by volume (though not by revenue).46
Exhibits

Exhibit 1  First-Generation Cephalosporin Molecules

<table>
<thead>
<tr>
<th>Generation</th>
<th>Year</th>
<th>Antibiotic Molecule Name</th>
<th>Company (Origin)</th>
<th>Clinical Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>1964</td>
<td>Cephalothin</td>
<td>E.I. Lilly (USA)</td>
<td>Attacks bacteria without a protective membrane, such as &quot;staph&quot; and &quot;strep&quot; bacteria that cannot be treated with penicillin, as well as gastrointestinal, urinary tract, respiratory, blood, and skin infections (like all first generation cephalosporins), can be taken by injection</td>
</tr>
<tr>
<td>First</td>
<td>1964</td>
<td>Cephaloridine</td>
<td>Glaxo-Wellcome (UK)</td>
<td>More potent than Cephalothin</td>
</tr>
<tr>
<td>First</td>
<td>1965</td>
<td>Cephaloglycin</td>
<td>E.I. Lilly (USA)</td>
<td>More potent than Cephaloridine can be taken orally</td>
</tr>
<tr>
<td>First</td>
<td>1967</td>
<td>Cephalaxin</td>
<td>E.I. Lilly (USA)</td>
<td>More potent than Cephaloridine; can be taken orally; fewer side effects than previous cephalosporins</td>
</tr>
<tr>
<td>First</td>
<td>1970</td>
<td>Cephradin</td>
<td>Bristol Labs (UK)</td>
<td>Attacks bacteria without a protective membrane (as did previous cephalosporins), and a few types of bacteria with protective membranes</td>
</tr>
<tr>
<td>First</td>
<td>1971</td>
<td>Cepphadine</td>
<td>Squibb (USA)</td>
<td>Can be taken as a tablet or syrup</td>
</tr>
<tr>
<td>First</td>
<td>1971</td>
<td>Cefazolin</td>
<td>Fujisawa Pharmaceutical (Japan)/Smith Kline Beecham (USA)</td>
<td>Can be taken by injection or intravenously; has fewer side effects than previous cephalosporins</td>
</tr>
<tr>
<td>First</td>
<td>1974</td>
<td>Cefadroxil</td>
<td>Bristol Myers (USA)</td>
<td>Can be taken as a capsule, tablet, or liquid; has fewer side effects than previous cephalosporins</td>
</tr>
</tbody>
</table>

Sources: Levison et al (1972); Shadomy, Mayhall, and Apollo (1977); Gelijns and Halm (1991); Kumazawa and Yagisawa (2002); Dougherty and Pucci (2012); and Drugs.com.

Exhibit 2  Second-Generation Cephalosporin Molecules

<table>
<thead>
<tr>
<th>Generation</th>
<th>Year</th>
<th>Antibiotic Molecule Name</th>
<th>Company (Origin)</th>
<th>Clinical Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second</td>
<td>1973</td>
<td>Cefamandole</td>
<td>E.I. Lilly (USA)</td>
<td>Attack hard-to-treat bacteria with protective outer membranes, such as gonorrhea, some influenza, and E. coli; (like all second-generation cephalosporins); attacks some bacteria that had developed resistance to first-generation cephalosporins, taken by injection or intravenously</td>
</tr>
<tr>
<td>Second</td>
<td>1976</td>
<td>Cefalexin</td>
<td>E.I. Lilly (USA)</td>
<td>Taken orally</td>
</tr>
<tr>
<td>Second</td>
<td>1978</td>
<td>Ceforanide</td>
<td>Bristol Myers (USA)</td>
<td>More potent; taken by injection or intravenously</td>
</tr>
<tr>
<td>Second</td>
<td>1983</td>
<td>Cefuroxil</td>
<td>Bristol-Banyu (Japan)/Bristol Labs (UK)</td>
<td>Taken in tablet form; also attacks hard-to-treat bacteria in bronchial tubes, sinuses, ears, throat, tonsils, and skin</td>
</tr>
<tr>
<td>Second</td>
<td>1984</td>
<td>Cefuroxime</td>
<td>Glaxo-Wellcome (UK)</td>
<td>More potent; taken in tablet or liquid form; also attacks hard-to-treat bacteria in bronchial tubes, sinuses, ears, throat, tonsils, and skin</td>
</tr>
<tr>
<td>Second</td>
<td>1987</td>
<td>Cefuzonam</td>
<td>Lederle Japan (Japan)</td>
<td>Attacks hard-to-treat bacteria with protective outer membranes likely to cause urinary tract infections in hospitals</td>
</tr>
</tbody>
</table>

Sources: Levison et al (1972); Shadomy, Mayhall, and Apollo (1977); Gelijns and Halm (1991); Kumazawa and Yagisawa (2002); Dougherty and Pucci (2012); and Drugs.com.
### Exhibit 3  Third- and Fourth-Generation Cephalosporin Molecules

<table>
<thead>
<tr>
<th>Generation</th>
<th>Year</th>
<th>Antibiotic Molecule Name</th>
<th>Company (Origin)</th>
<th>Clinical Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Third</td>
<td>1978</td>
<td>Cefoperazone</td>
<td>Toyama (Japan)/Wyeth (UK)</td>
<td>Attack many different bacteria (those with protective outer membranes and those without); effective against hard-to-treat bacteria that automatically expel foreign molecules; builds up less in kidneys; fewer side effects: taken by injection or intravenously</td>
</tr>
<tr>
<td>Third</td>
<td>1979</td>
<td>Cefotiam</td>
<td>Taide Chemical (Japan)/Abbott (USA)</td>
<td>More potent</td>
</tr>
<tr>
<td>Third</td>
<td>1979</td>
<td>Ceffazoline</td>
<td>Fujisawa Pharmaceutical (Japan)</td>
<td>More potent as a prophylactic</td>
</tr>
<tr>
<td>Third</td>
<td>1979</td>
<td>Cefotaxime</td>
<td>Hoechst-Roussel (Germany)</td>
<td>More potent as a prophylactic</td>
</tr>
<tr>
<td>Third</td>
<td>1980</td>
<td>Ceftezil</td>
<td>Fujisawa Pharmaceutical (Japan)/Wyeth (UK)</td>
<td>Can be taken orally, in tablet or sachet form</td>
</tr>
<tr>
<td>Third</td>
<td>1981</td>
<td>Ceftriaxone</td>
<td>Glaxo-Wellcome (UK)</td>
<td>Can be used to treat central nervous system infections</td>
</tr>
<tr>
<td>Fourth</td>
<td>1983</td>
<td>Cefepime</td>
<td>Hoffmann-La Roche (Switzerland)</td>
<td>More potent</td>
</tr>
<tr>
<td>Third</td>
<td>1984</td>
<td>Cepfdoxime</td>
<td>Bristol-Myers (Japan)/Squibb (USA)</td>
<td>More rapidly attacks bacteria (those with protective outer membranes and those without), as well as hard-to-treat bacteria that automatically expel foreign molecules; effective against bacteria that have developed resistance to other cephalosporins</td>
</tr>
<tr>
<td>Third</td>
<td>1985</td>
<td>Cefditoren</td>
<td>Shionogi (Japan)/Schering (Germany)</td>
<td>Can be taken orally; effective against bacteria that have developed resistance to other cephalosporins</td>
</tr>
<tr>
<td>Third</td>
<td>1987</td>
<td>Cefdinor</td>
<td>Fujisawa Pharmaceutical (Japan)/Abbott (USA)</td>
<td>More potent; builds up less in kidneys</td>
</tr>
<tr>
<td>Fourth</td>
<td>1989</td>
<td>Cefprozole</td>
<td>Hoechst-Roussel (Germany)</td>
<td>More potent; attacks bacteria faster</td>
</tr>
</tbody>
</table>

Sources: Levison et al (1972); Shadomy, Mayhall, and Apollo (1977); Gelijns and Halm (1991); Kumazawa and Yagisawa (2002); Dougherty and Pucci (2012); and Drugs.com.
Endnotes


2 Bacteria in the gut maintain good health; others as we will see in this case history can yield molecules that can be used to fight disease.


5 “Generations” of antibiotics vary depending on the composition of the side chains. Greenwood, Antimicrobial Drugs; Thomas Dougherty and Michael J. Pucci, Antibiotic Discovery and Development; “Bacterial Infections 101.” Penicillin and cephalosporin have some molecular structures in common, making them more closely related than other antibiotics. They are sometimes referred to as belonging to the large “Beta lactams” family or class.

6 Ciprofloxacin is considered “broad spectrum” but is effective against many gram-negative bacteria and only a few gram-positive bacteria.

7 Greenwood, Antimicrobial Drugs; Thomas Dougherty and Michael J. Pucci, Antibiotic Discovery and Development; “Bacterial Infections 101”; “Third-generation antibiotics enter the fray.” Chemical Week. August 19, 1981.


10 Aminov, “A Brief History of the Antibiotic Era.”

13 They had also given the compound the name “arsphenamine.”


24 Botanist Benjamin Duggar led the Lederle team. He had retired from teaching and research at the University of Wisconsin, but had been hired as a consultant for Lederle. After Waksman gave a conference paper on streptomycin, the president of Lederle had urged Duggar to search for a similar molecule in soil bacteria. Duggar was nominated for a Nobel Prize during the same period as Waksman but did not win. Selman Waksman later faced accusations of having stolen credit for the discovery of streptomycin from his Ph.D. student, Albert Schatz. Jukes, Thomas H. “Some Historical Notes on Chlortetracycline” Reviews of Infectious Diseases. 7:5 (September-October 1985); Zaffiri, Gardner, and Toledo-Pereyra, “History of Antibiotics. From Salvarsan to Cephalosporins”; Thomas Dougherty and Michael J. Pucci, Antibiotic Discovery and Development; Greenwood, Antimicrobial Drugs; Achilladelis, “The Dynamics of Technological Innovation”; “The Nobel Prize in Physiology or Medicine 1945”; “Wit6.Pdf.” Accessed July 7, 2019. http://discovery.ucl.ac.uk/2074/1/wit6.pdf

25 Cephalosporium acremonium has now been reclassified as Acremonium chrysogenum. “Acremonium Chrysogenum - an Overview | ScienceDirect Topics.”


42 Young, “Ceftazidime,” 349.


46 Cephalosporins were popular in low income countries because their variable production costs were low and they did not require much less skill and infrastructure to dispense (unlike sophisticated operations, such as coronary artery bypass surgery and device innovations (such as magnetic resonance imaging machines).