

NAPOLEON'S BUTTONS

HOW 17 MOLECULES
CHANGED HISTORY

PENNY LE COUTEUR
JAY BURRESON

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10. WONDER DRUGS

I

T PROBABLY WOULD not have surprised William Perkin that his synthesis of mauve became the basis for the huge commercial dye enterprise. After all, he had been so sure that the manufacture of mauve would be profitable that he had persuaded his father to finance his dream—and he had been extremely successful in his lifetime. But even he likely could not have predicted that his legacy would include one of the major developments evolving from the dye industry: pharmaceuticals. This aspect of synthetic organic chemistry would far surpass the production of dyes, change the practice of medicine, and save millions of lives.

In 1856, the year when Perkin prepared the mauve molecule, the average life expectancy in Britain was around forty-five years. This number did not change markedly for the rest of the nineteenth century. By 1900 the average life expectancy in the United States had only increased to forty-six years for a male and forty-eight years for a female. A century later, in contrast, these figures have soared to seventy-two for males and seventy-nine for females.

For such a dramatic increase after so many centuries of much lower life expectancies, something amazing had to have happened. One of the major factors in longer lifespans was the introduction, in the twentieth century, of molecules of medicinal chemistry and in particular of the miracle molecules known as antibiotics. Literally thousands of different pharmaceutical compounds have been synthesized over the past century, and hundreds of them were life changing for many people. We will look at the chemistry and development of only two types of pharmaceuticals: the pain-relieving molecule aspirin, and two examples of antibiotics. Profits from aspirin helped convince chemical companies that there was a future in pharmaceuticals; the first antibiotics—sulfa drugs and penicillins—are still prescribed today.

For thousands of years medicinal herbs have been used to heal wounds, cure sickness, and relieve pain. Every human society has developed unique traditional remedies, a number of which have yielded extremely useful compounds or have been chemically modified to produce modern medicines. Quinine, which comes from the South American cinchona tree and originally used by the Indians of Peru to treat fevers, is still today an antimalarial. Foxglove containing digitalis, which is still prescribed as a contemporary heart stimulant, has long been used in western Europe to treat heart ailments. The analgesic properties of sap from the seed capsules of a poppy plant were well known from Europe to Asia and morphine extracted from this source still plays a major role in pain relief.

Historically, however, few if any effective remedies were known for treating bacterial infections. Until relatively recently even a small cut or a tiny puncture wound could, if infected, become life threatening. Fifty percent of soldiers wounded during the American Civil War died of bacterial infections. Thanks to antiseptic procedures and molecules like phenol, introduced by Joseph Lister, this percentage was smaller during the First World War. But although use of antiseptics helped prevent infection from surgery, it did little to stop an infection once it had started. The great influenza pandemic of 1918–1919 killed more than twenty

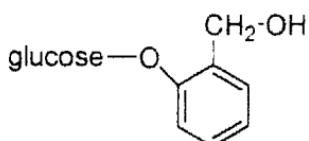
million people worldwide, a far greater toll than that of World War I. The influenza itself was viral; the actual cause of death was usually a secondary infection of bacterial pneumonia. Contracting tetanus, tuberculosis, cholera, typhoid fever, leprosy, gonorrhea, or any of a host of other illnesses was often a death sentence. In 1798 an English doctor, Edward Jenner, successfully demonstrated for the smallpox virus the process of artificially producing immunity to a disease, although the concept of acquiring immunity in this way had been known from earlier times and from other countries. Starting in the last decades of the nineteenth century, similar methods of providing immunity against bacteria were investigated as well, and gradually inoculation became available for a number of bacterial diseases. By the 1940s fear of the dreaded childhood duo of scarlet fever and diphtheria had receded in countries where vaccination programs were available.

ASPIRIN

In the early twentieth century the German and Swiss chemical industries were prospering from their investment in the manufacture of dyestuffs. But this success was more than just financial. Along with profits from dye sales came a new wealth of chemical knowledge, of experience with large-scale reactions, and of techniques for separation and purification that were vital for expansion into the new chemical business of pharmaceuticals. Bayer and Company, the German firm that got its start from aniline dyes, was one of the first to recognize the commercial possibilities in the chemical production of medicines—in particular aspirin, which has now been used by more people worldwide than any other medication.

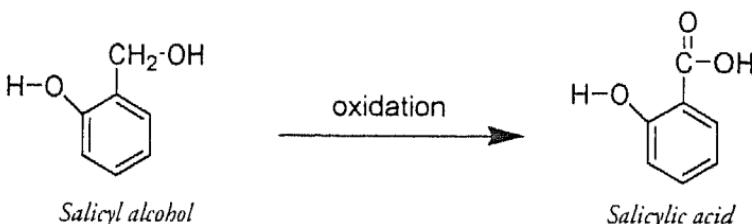
In 1893 Felix Hofmann, a chemist working for the Bayer company, decided to investigate the properties of compounds that were related to salicylic acid, a molecule obtained from salicin, a pain-relieving molecule originally isolated from the bark of trees of the willow genus

(*Salix*) in 1827. The curative properties of the willow and related plants such as poplars had been known for centuries. Hippocrates, the famed physician of ancient Greece, had used extracts from willow bark to reduce fevers and relieve pain. Although the bitter-tasting salicin molecule incorporates a glucose ring into its structure, the rest of the molecule overwhelms any sweetness from the sugar part.



The salicin molecule

Like the glucose-containing indican molecule that produces indigo, salicin breaks into two parts: glucose and salicyl alcohol, which can be oxidized to salicylic acid. Both salicyl alcohol and salicylic acid are classified as phenols because they have an OH group directly attached to the benzene ring.

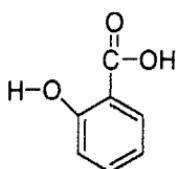


These molecules are also similar in structure to isoeugenol, eugenol, and zingerone from cloves, nutmeg, and ginger. It is probable that like these molecules, salicin acts as a natural pesticide to protect the willow tree. Salicylic acid is also produced from the flowers of meadow-sweet or *Spiraea ulmaria*, a wetlands perennial native to Europe and western Asia.

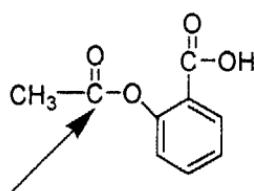
Salicylic acid, the active portion of the salicin molecule, not only reduces fever and relieves pain but also acts as an anti-inflammatory. It is much more potent than the naturally occurring salicin, but it can be

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very irritating to the lining of the stomach, reducing its medicinal value. Hofmann's interest in compounds related to salicylic acid arose out of concern for his father, whose rheumatoid arthritis was little relieved by salicin. Hoping that the anti-inflammatory properties of salicylic acid would be retained but its corrosive properties lessened, Hofmann gave his father a derivative of salicylic acid—acetyl salicylic acid, first prepared by another German chemist forty years previously. In ASA, as acetyl salicylic acid has come to be called, the acetyl group (CH_3CO) replaces the H of the phenolic OH group of salicylic acid. The phenol molecule is corrosive; perhaps Hofmann reasoned that converting the OH attached to the aromatic ring into an acetyl group might mask its irritating characteristics.



Salicylic acid



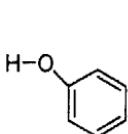
Acetyl salicylic acid. The arrow shows where the acetyl group replaces H of the phenol group.

Hofmann's experiment paid off—for his father and for the Bayer company. The acetylated form of salicylic acid turned out to be effective and well tolerated. Its potent anti-inflammatory and analgesic properties persuaded the Bayer company, in 1899, to begin marketing small packets of powdered "aspirin." The name is a combination of the *a* from *acetyl* and the *spir* from *Spiraea ulmaria*, the meadowsweet plant. The Bayer company name became synonymous with aspirin, marking Bayer's entrance into the world of medicinal chemistry.

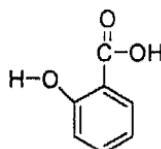
As the popularity of aspirin increased, the natural sources from which salicylic acid was produced—meadowsweet and willow—were no longer sufficient to satisfy world demand. A new synthetic method using the phenol molecule as the starting material was introduced. Aspirin sales soared; during World War I the American subsidiary of the

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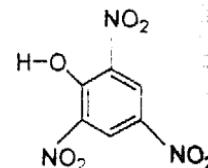
original Bayer company purchased as much phenol as possible from both national and international sources in order to guarantee an adequate supply for the manufacture of aspirin. The countries that supplied Bayer with phenol thus had reduced capacity to make picric acid (trinitrophenol), an explosive also prepared from this same starting material (see Chapter 5). What effect this may have had on the course of World War I we can only speculate, but aspirin production may have reduced reliance on picric acid for munitions and hastened the development of TNT-based explosives.



Phenol



Salicylic acid



Trinitrophenol (picric acid)

Today aspirin is the most widely used of all drugs for treating illness and injury. There are well over four hundred aspirin-containing preparations, and over forty million pounds of aspirin are produced in the United States annually. As well as relieving pain, lowering body temperature, and reducing inflammation, aspirin also has blood-thinning properties. Small doses of aspirin are being recommended as a preventive against strokes and for deep-vein thrombosis, the condition known as "economy class syndrome" in long-haul airline passengers.

THE SAGA OF SULFA

Around the time of Hofmann's experiment on his father—a drug-trial procedure that is not recommended—the German doctor Paul Ehrlich was conducting experiments of his own. Ehrlich was, by all accounts, a truly eccentric character, said to smoke twenty-five cigars a day and spend many hours in philosophical discussions in beer halls. But along

with his eccentricity came the determination and insight that gained him the 1908 Nobel Prize in medicine. Despite having no formal training in experimental chemistry or applied bacteriology Ehrlich noted that different coal tar dyes would stain some tissues and some microorganisms but not others. He reasoned that if one microorganism absorbed a dyestuff and another did not, this differentiation might allow a toxic dye to kill tissue that absorbed it without damaging nonstaining tissue. Hopefully the infecting microorganism would be eliminated while the host was unharmed. Ehrlich termed this theory the "magic bullet" approach, the magic bullet being the dye molecule targeting the tissue it stained.

Ehrlich's first success was with a dye called trypan red I, which acted very much as he had hoped against trypanosomes—a protozoic parasite—in laboratory mice. Unfortunately it was not effective against the type of trypanosome responsible for the human disease known as African sleeping sickness, which Ehrlich had hoped to cure.

Undeterred, Ehrlich continued. He had shown that his method could work, and he knew it was only a matter of finding a suitable magic bullet for the right disease. He began investigating syphilis, an affliction caused by a corkscrew-shaped bacterium known as a spirochete. Theories of how syphilis came to Europe abound; one of the most widely acknowledged was that it returned from the New World with Columbus's sailors. A form of "leprosy" reported in Europe before Columbus's time, however, was known to be highly contagious and venereally spread. Like syphilis it also sometimes responded to treatment with mercury. None of these observations fit what we know about leprosy, and it is possible that what was described was actually syphilis.

By the time Ehrlich began looking for a magic bullet against this bacterium, mercury cures had been claimed for syphilis for over four hundred years. Yet mercury could hardly be considered a magic bullet for syphilis, as it often killed its patients. Victims died of heart failure, dehydration, and suffocation during the process of being heated in an oven while breathing mercury fumes. If one survived this procedure,

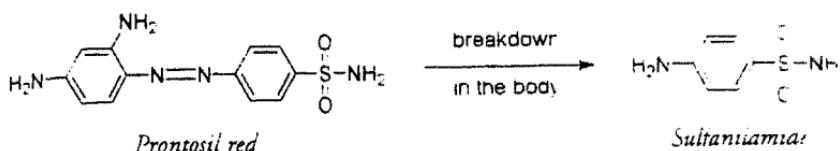
typical symptoms of mercury poisoning—loss of hair and teeth, uncontrollable drooling, anemia, depression, and kidney and liver failure—took their toll.

In 1909, after testing 605 different chemicals, Ehrlich finally found a compound that was both reasonably effective and reasonably safe. "Number 606," an arsenic-containing aromatic compound, proved active against the syphilis spirochete. Hoechst Dyeworks—the company Ehrlich collaborated with—marketed this compound in 1910, under the name salvarsan. Compared with the torture of the mercury remedy, the new treatment was a great improvement. Despite some toxic side effects and the fact that it did not always cure syphilitic patients even after a number of treatments, salvarsan greatly reduced the incidence of the disease wherever it was used. For Hoechst Dyeworks it proved extremely profitable, providing the capital to diversify into other pharmaceuticals.

After the achievement of salvarsan, chemists sought further magic bullets by testing tens of thousands of compounds for their effect on microorganisms, then making slight changes to chemical structures and testing again. There were no successes. It seemed as if the promise of what Ehrlich had termed "chemotherapy" would not live up to expectations. But then in the early 1930s Gerhard Domagk, a doctor working with the IG Farben research group, decided to use a dye called prontosil red to treat his daughter, who was desperately ill with a streptococcal infection contracted from a simple pinprick. He had been experimenting with prontosil red at the IG Farben laboratory, and though it had shown no activity against bacteria grown in laboratory cultures, it did inhibit the growth of streptococci in laboratory mice. No doubt deciding he had nothing to lose, Domagk gave his daughter an oral dose of the still-experimental dye. Her recovery was fast and complete.

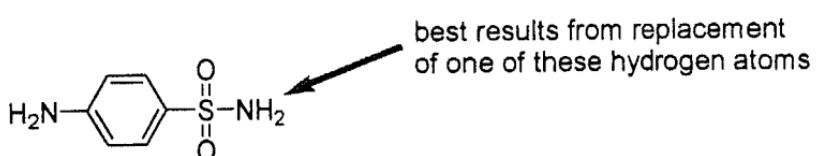
It was at first assumed that the dye action—the actual staining of the cells—was responsible for the antibacterial properties of prontosil red. But researchers soon realized that antibacterial effects had nothing to do with dye action. In the human body the prontosil red molecule

breaks down to produce sulfanilamide, and it is the sulfanilamide that has the antibiotic effect.

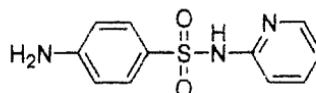


This, of course, was why prontosil red had been inactive in test tubes (*in vitro*) but not in live animals (*in vivo*). Sulfanilamide was found to be effective against many diseases other than streptococcal infections, including pneumonia, scarlet fever, and gonorrhea. Having recognized sulfanilamide as an antibacterial agent, chemists quickly started to synthesize similar compounds, hoping that slight modifications of the molecular structure would increase effectiveness and lessen any side effects. The knowledge that prontosil red was not the active molecule was extremely important. As can be seen from the structures, prontosil red is a more complicated molecule than sulfanilamide and it is more difficult to synthesize and to modify.

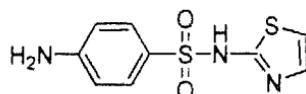
Between 1935 and 1946 more than five thousand variations of the sulfanilamide molecule were made. A number of them proved superior to sulfanilamide, whose side effects can include allergic response—rashes and fever—and kidney damage. The best results from varying the sulfanilamide structure were obtained when one of the hydrogen atoms of the SO₂NH₂ was replaced with another group.



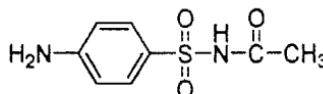
The resulting molecules are all part of the family of antibiotic drugs known collectively as *sulfanilamides* or *sulfa drugs*. A few of the many examples are



Sulfapyridine—used for pneumonia:



Sulfathiazole—used for gastrointestinal infections:



Sulfacetamide—used for urinary tract infections

Sulfa drugs were soon being described as wonder drugs and miracle cures. While such descriptives may seem unduly exaggerated nowadays, when numerous effective treatments against bacteria are available, the results obtained from these compounds in the early decades of the twentieth century appeared to be extraordinary. For example, after the introduction of sulfanilamides, the number of deaths from pneumonia dropped by twenty-five thousand a year in the United States alone.

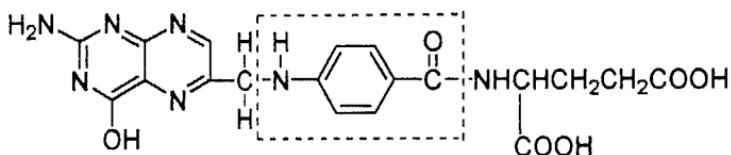
In World War I, between 1914 and 1918, death from wound infection was as likely as death from injury on the battlefields of Europe. The major problem in the trenches and in any army hospital was a form of gangrene known as gas gangrene. Caused by a very virulent species of the *Clostridium* bacteria, the same genus responsible for the deadly botulism food poisoning, gas gangrene usually developed in deep wounds, typical of injuries from bombs and artillery where tissue was pierced or crushed. In the absence of oxygen, these bacteria multiply quickly. A brown foul-smelling pus is exuded, and gases from bacterial toxins bubble to the skin's surface, causing a distinctive stench.

Before the development of antibiotics there was only one treatment

for gas gangrene—amputation of the infected limb above the site of infection, in the hope of removing all the gangrenous tissue. If amputation was not possible, death was inevitable. During World War I, thanks to antibiotics such as sulfapyridine and sulfathiazole—both effective against gangrene—thousands of injured were spared disfiguring amputations, not to mention death.

We now know that the effectiveness of these compounds against bacterial infection has to do with the size and shape of the sulfanilamide molecule preventing bacteria from making an essential nutrient, folic acid. Folic acid, one of the B vitamins, is required for human cell growth. It is widely distributed in foods, such as leafy vegetables (hence the word *folic* from *foliage*), liver, cauliflower, yeast, wheat, and beef. Our bodies do not manufacture folic acid, so it is essential that we take it in with what we eat. Some bacteria, on the other hand, do not require supplemental folic acid, as they are able to make their own.

The folic acid molecule is fairly large and looks complicated:

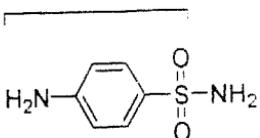


Folic acid with the middle portion from the p-aminobenzoic acid molecule outlined

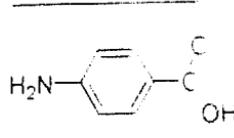
Consider just the part of its structure shown inside the outlined box in the structure above. This middle portion of the folic acid molecule is derived (in bacteria that make their own folic acid) from a smaller molecule, *p*-aminobenzoic acid. *p*-Aminobenzoic acid is thus an essential nutrient for these microorganisms.

The chemical structures of *p*-aminobenzoic acid and sulfanilamide are remarkably similar in shape and size, and it is this similarity that accounts for the antimicrobial activity of sulfanilamide. The lengths (as indicated by the square brackets) of each of these molecules measured

from the hydrogen of the NH₂ group to the doubly bonded oxygen atom are within 3 percent of each other. As well they have almost the same width.



Sulfanilamide



p-aminobenzoic acid

The bacterial enzymes involved in synthesizing folic acid appear to be unable to distinguish between the molecules of *p*-aminobenzoic acid that they need and the look-alike sulfanilamide molecules. Bacteria will thus unsuccessfully attempt to use sulfanilamide instead of *p*-aminobenzoic acid—and ultimately die because they are unable to make enough folic acid. We, relying on folic acid absorbed from our food, are not negatively affected by the action of sulfanilamide.

Technically, sulfanilamide-based sulfa drugs are not true antibiotics. Antibiotics are properly defined as "substances of microbial origin that in very small amounts have antimicrobial activity." Sulfanilamide is not derived from a living cell. It is man-made and is properly classified as an antimetabolite, a chemical that inhibits the growth of microbes. But the term *antibiotic* is now commonly used for all substances, natural or artificial, that kill bacteria.

Although sulfa drugs were not the very first synthetic antibiotic—that honor belongs to Ehrlich's syphilis-fighting molecule salvarsan—they were the first group of compounds that had widespread use in the fight against bacterial infection. Not only did they save the lives of hundreds of thousands of wounded soldiers and pneumonia victims, they were also responsible for an astounding drop in deaths of women in childbirth, because the streptococcus bacteria that cause puerperal or childbed fever also proved susceptible to sulfa drugs. More recently, however, the use of sulfa drugs has decreased worldwide, for a number

of reasons: concern over their long-term side effects, the evolution of sulfanilamide-resistant bacteria, and the development of newer and more powerful antibiotics.

PENICILLINS

The earliest true antibiotics, from the penicillin family, are still in widespread use today. In 1877, Louis Pasteur was the first to demonstrate that one microorganism could be used to kill another. Pasteur showed that the growth of a strain of anthrax in urine could be prevented by the addition of some common bacteria. Subsequently Joseph Lister, having convinced the world of medicine of the value of phenol as an antiseptic, investigated the properties of molds, supposedly curing a persistent abscess in one of his patients with a compress soaked in a *Penicillium*-mold extract.

Despite these positive results, further investigation of the curative properties of molds was sporadic until 1928, when a Scottish physician named Alexander Fleming, working at St. Mary's Hospital Medical School of London University, discovered that a mold of the *Penicillium* family had contaminated cultures of the staphylococci bacteria he was studying. He noted that a colony of the mold became transparent and disintegrated (undergoing what is called *lysis*). Unlike others before him Fleming was intrigued enough to follow through with further experimentation. He assumed that some compound produced by the mold was responsible for the antibiotic effect on the staphylococcus bacteria, and his tests confirmed this. A filtered broth, made from cultured samples of what we now know was *Penicillium notatum*, proved remarkably effective in laboratory tests against staphylococci grown in glass dishes. Even if the mold extract was diluted eight hundred times, it was still active against the bacterial cells. Moreover mice, injected with the substance that Fleming was now calling *penicillin*, showed no toxic effects. Unlike phenol, penicillin was

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nonirritating and could be applied directly to infected tissues. It also seemed to be a more powerful bacterial inhibitor than phenol. It was active against many bacteria species, including those causing meningitis, gonorrhea, and streptococcal infections like strep throat.

Although Fleming published his results in a medical journal, they aroused little interest. His penicillin broth was very dilute, and his attempts to isolate the active ingredient were not successful. We now know that penicillin is easily inactivated by many common laboratory chemicals, and by solvents and heat.

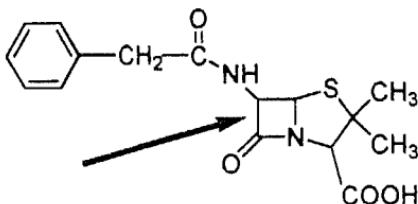
Penicillin did not undergo clinical trials for more than a decade, during which time sulfanilamides became the major weapon against bacterial infections. In 1939 the success of sulfa drugs encouraged a group of chemists, microbiologists, and physicians at Oxford University to start working on a method to produce and isolate penicillin. The first clinical trial with crude penicillin was in 1941. Sadly, the results were much like the old punch line "The treatment was a success, but the patient died." Intravenous penicillin treatment was given to one patient, a policeman suffering from both severe staphylococcal and streptococcal infections. After twenty-four hours an improvement was noted; five days later his fever was gone and his infection was clearing. But by then all of the penicillin available—about a teaspoon of the unrefined extract—had been used up. The man's infection was still virulent. It expanded unchecked, and he soon died. A second patient also died. In a third trial, however, enough penicillin had been produced to completely eliminate a streptococcal infection in a fifteen-year-old boy. After that success penicillin cured staphylococcal blood poisoning in another child, and the Oxford group knew they had a winner. Penicillin proved active against a range of bacteria, and it had no harsh side effects, such as the kidney toxicity that had been reported with sulfanilamides. Later studies indicated that some penicillins inhibit the growth of streptococci at a dilution of one to fifty million, an amazingly small concentration.

At this time the chemical structure of penicillin was not yet known,

and so it was not possible to make it synthetically. Penicillin still had to be extracted from molds, and the production of large amounts was a challenge for microbiologists and bacteriologists rather than chemists. The U.S. Department of Agriculture laboratory in Peoria, Illinois, had expertise in growing microorganisms and became the center of a massive research program. By July 1945 American pharmaceutical companies were producing 800 million units of the new antibiotic. One year later the monthly production topped 130 billion units.

It has been estimated that during World War II a thousand chemists in thirty-nine laboratories in the United States and in Britain worked on the problems associated with establishing the chemical structure of and finding a way to synthesize penicillin. Finally, in 1946, the structure was determined, although it was successfully synthesized only in 1957.

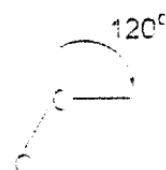
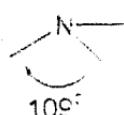
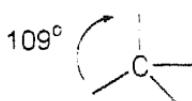
The structure of penicillin may not be as large or look as complicated a molecule as others we have discussed, but for chemists it is a most unusual molecule in that it contains a four-membered ring, known in this case as the β -lactam ring.



The structure of the penicillin G molecule. The arrow indicates the four-membered β -lactam ring.

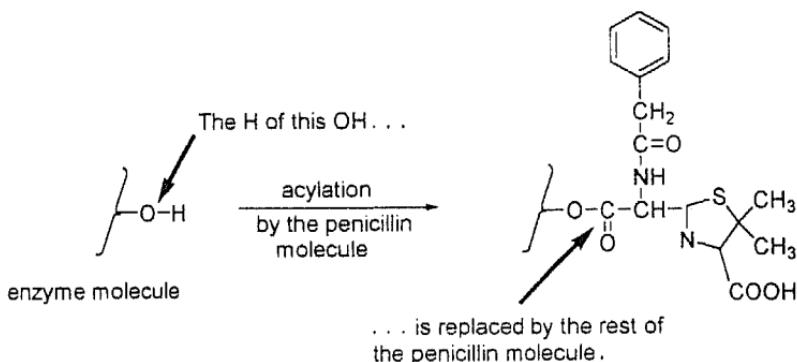
Molecules with four-membered rings do exist in nature, but they are not common. Chemists can make such compounds, but it can be quite difficult. The reason is that the angles in a four-membered ring—a square—are 90 degrees, while normally the preferred bond angles for single-bonded carbon and nitrogen atoms are near 109 degrees. For a double-bonded carbon atom, the preferred bond angle is around 120 degrees.

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The single-bonded carbon and nitrogen atom are three-dimensionally arranged in space, while the carbon double-bonded to an oxygen atom is in the same plane.

In organic compounds a four-membered ring is not flat; it buckles slightly, but even this cannot reduce what chemists call *ring strain*, an instability that results mainly from atoms being forced to have bond angles too different from the preferred bond angle. But it is precisely this instability of the four-membered ring that accounts for the antibiotic activity of penicillin molecules. Bacteria have cell walls and produce an enzyme that is essential for cell wall formation. In the presence of this enzyme, the β -lactam ring of the penicillin molecule splits open, relieving ring strain. In the process an OH group on the bacterial enzyme is *acylated* (the same type of reaction that converted salicylic acid into aspirin). In this acylation reaction penicillin attaches the ring-opened molecule to the bacterial enzyme. Note that the five-membered ring is still intact, but the four-membered ring has opened up.

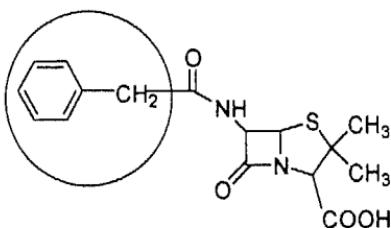


The penicillin molecule attaches to the bacterial enzyme in this acylation reaction.

This acylation deactivates the cell wall-forming enzyme. Without the ability to build cell walls, the growth of new bacteria in an organism is inhibited. Animal cells have a cell membrane rather than a cell wall and so do not have the same wall-forming enzyme as these bacteria. We are therefore not affected by the acylation reaction with the penicillin molecule.

The instability of the four-membered β -lactam ring of penicillin is also the reason that penicillins, unlike sulfa drugs, need to be stored at low temperatures. Once the ring opens—a process accelerated by heat—the molecule is no longer an effective antibiotic. Bacteria themselves seem to have discovered the secret of ring opening. Penicillin-resistant strains have developed a further enzyme that breaks open the β -lactam ring of penicillin before it has a chance to deactivate the enzyme responsible for cell wall formation.

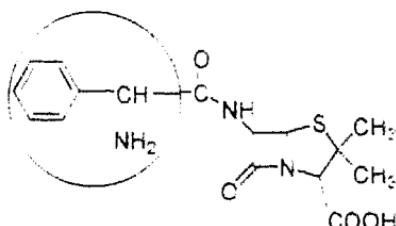
The structure of the penicillin molecule shown below is that of penicillin G, first produced from mold in 1940 and still widely used. Many other penicillin molecules have been isolated from molds, and a number have been synthesized chemically from the naturally occurring versions of this antibiotic. The structures of different penicillins vary only in the part of the molecule circled below.



Penicillin G. The variable part of the molecule is circled.

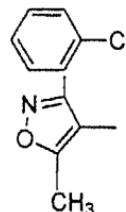
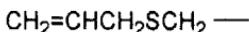
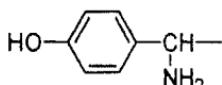
Ampicillin, a synthetic penicillin effective against bacteria that are resistant to penicillin G, is only slightly different. It has an extra NH₂ group attached.

NAPOLEON'S BUTTONS



Ampicillin

The side group in amoxicillin, today one of the most widely prescribed drugs in the United States, is very similar to ampicillin but with an extra OH. The side group can be very simple, as in penicillin O, or more complicated, as in cloxacillin.



The structure of the side groups in the circled portion of the molecule for amoxicillin (left), penicillin O (center), and cloxacillin (right)

These are only four of the ten or so different penicillins still in use today. (Many more exist that are no longer used clinically.) The structural modifications, at the same (circled) site on the molecule, can be very variable, but the four-membered β -lactam ring is always present. It is this piece of the molecular structure that may have saved your life, if you have had the occasion to need a penicillin antibiotic.

Although it is impossible to obtain accurate statistics of mortality during previous centuries, demographers have estimated average lifespans in some societies. From 3500 B.C. through to about A.D. 1750, a period of over five thousand years, life expectancy among European societies

hovered between thirty and forty years: in classical Greece, around 680 B.C., it rose as high as forty-one years; in Turkey of A.D. 1400 it was just thirty-one years. These numbers are similar to those in the underdeveloped countries of the world today. The three main reasons for these high mortality rates— inadequate food supplies, poor sanitation, and epidemic disease—are closely interrelated. Poor nutrition leads to increased susceptibility to infection; poor sanitation produces conditions conducive to disease.

In those parts of the world with efficient agriculture and a good transportation system, food supply has increased. At the same time vastly improved personal hygiene and public health measures—clean water supply, sewage treatment systems, refuse collection and vermin control, and wholesale immunization and vaccination programs—have led to fewer epidemics and a healthier population more able to resist disease. Because of these improvements, death rates in the developed world have been dropping steadily since the 1860s. But the final onslaught against those bacteria that have for generations caused untold misery and death has been by antibiotics.

From the 1930s the effect of these molecules on mortality rates from infectious diseases has been marked. After the introduction of sulfa drugs to treat pneumonia, a common complication with the measles virus, the death rate from measles declined rapidly. Pneumonia, tuberculosis, gastritis, and diphtheria, all among leading causes of death in the United States in 1900, do not make the list today. Where isolated incidents of bacterial diseases—bubonic plague, cholera, typhus, and anthrax—have occurred, antibiotics contained what might otherwise have become a widespread outbreak. Today's acts of bioterrorism have focused public concern on the possibility of a major bacterial epidemic. Our present array of antibiotics would normally be able to cope with such an attack.

Another form of bioterrorism, that waged by bacteria themselves as they adapt to our increasing use and even overuse of antibiotics, is worrying. Antibiotic-resistant strains of some common but potentially lethal

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bacteria are becoming widespread. But as biochemists learn more about the metabolic pathways of bacteria—and of humans—and how the older antibiotics worked, it should become possible to synthesize new antibiotics able to target specific bacterial reactions. Understanding chemical structures and how they interact with living cells is essential to maintaining an edge in the never-ending struggle with disease-causing bacteria.