

Ten Drugs That Have Made a Difference

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Author's note: For five years I have researched and developed a talk entitled New Drugs and Devices Which Might Change Your Practice. What I have discovered is that most new drugs and devices do not change our practice, despite what the pharmaceutical industry would like us to believe. A majority of new products are either "me, too" drugs – copies of ones already on the market – or ones which make only a marginal difference in our patients' long-term outcomes and well-being.

The burden of finding ten important drugs is compounded by trying to find drugs or devices which are known universally, rather than just in the United States or Europe.

Despite a thorough search of FDA approvals and ten years of *The Medical Letter*, I was unable to choose Ten New Drugs Which Made a Difference in Emergency Medicine. What, then, to do?

I decided instead to talk about some drugs which we have been using for years and which we probably take for granted. But these, indeed, are the drugs which have made a difference in the way we practice Emergency Medicine. They are universally known and accepted as the "big guns" in the world's armamentarium against disease and suffering.

Cocaine and Local Anesthetics

The name coca (*Erythroxylum coca*) comes from an Aymara word meaning simply "tree." The Aymara tribe lives on the plateau around Lake Titicaca in Peru. Although they primarily chewed coca leaves to obtain the benefits, some ancient cocaine users knew to use an alkaline such as crushed seashells or burnt plant ashes with the leaves in order to activate the pharmacologically active part.

Coca is used as a folk medicine for ailments as diverse as toothache and altitude sickness. Coca leaves are also an excellent source of iron and calcium, more than many of the food crops grown in the Andes. Some Peruvian scientists believe that the low incidence of osteoporosis among Andean Indians is due in part to the high level of calcium in the leaves.

European scientists first took interest in coca in 1859, when Italian neurologist Paolo Mantegazza wrote about the hygienic and medicinal virtues of the leaves. In 1860, German chemist Albert Neimann isolated cocaine, the chemical responsible for the plant's power. Viennese ophthalmologist Karl Koller found that cocaine could be used as a local anesthetic during eye surgery.

After reading of Koller's work, American Surgeon William Stewart Halsted correctly guessed that cocaine might be used to produce local anesthesia by regionally blocking individual nerves. To test this hypothesis, he his colleague Richard Hall injected each other with cocaine solutions. Halsted soon discovered that he felt wonderful under its influence. His head seemed to become

clearer, he needed little sleep, and fatigue was almost banished from his busy life. Soon he was sniffing the drug as well as injecting it. Despite years of effort to “kick the habit,” he was apparently still addicted when he died in 1922.

In the 1860's, coca derivatives were used to treat a variety of ailments. Coca tonics were popular, including a red Bordeaux wine – coca leaf creation of Corsican chemist, Angelo Mariani, called Vin Tonique Mariani. Manufactured in Paris, Vin Mariani became the most popular prescription remedy in the world, used by many celebrities. Pope Leo XIII carried a personal supply in a hip flask and awarded the wine a Vatican gold medal. In the United States, various successive adaptations – removing alcohol, adding cola (an African caffeine-containing nut) and caramel syrup – resulted in the original formula for Coca-Cola.

German physician Theodor Aschenbrandt administered cocaine to members of the Bavarian army in 1883 and found that the drug enhanced their endurance on maneuvers. A young Viennese neurologist named Sigmund Freud read Aschenbrandt's reports with interest. Later Freud wrote: "I take very small doses of it regularly and against depression and against indigestion, and with the most brilliant success." Drug giants Merck and Parke Davies both paid Freud to endorse their brands of cocaine.

The first spinal anesthetic was performed in 1898 by German physician August Bier, who was the intended subject. His graduate student placed the needle and cerebrospinal fluid poured out. It was only then that they realized that their syringe full of cocaine did not mate to the needle. This experiment preceded the universal use of the standardized needles and hubs that had been invented by German instrument maker Luer.

Bier suffered from a severe post-dural puncture headache, which he astutely attributed to loss of CSF, and thereafter advocated the use of small gauge needles. Following his recovery, Bier performed the procedure on his assistant. They were ecstatic when after the injection of cocaine the young man's legs became numb. They celebrated with wine and cigars, and demonstrated the insensibility of his legs with repeated blows and kicks. The student's recovery was complicated by a headache and very sore, bruised shins.

The cocaine derivative novocaine (procaine) was discovered in 1905 by German chemist Alfred Einhorn, who intended for it to be used for major surgery, but it wasn't suitable. Dentists immediately wanted the product, but the inventor actually tried to stop them from using it for the "mundane purpose" of drilling teeth. To the end of his days, Einhorn traveled all over the world preaching the merits of novocaine as a general anesthetic.

Curare and Paralytics

In the 16th century, a group of Spanish explorers was traveling the Amazon River when one was hit in the hand by an arrow. Within minutes he had stopped breathing and died. The culprit was curare, used widely as an arrow poison by many Amazon Indians. The name derives from wourall, urari, woorali, or woorari, all native terms meaning “poison.”

Amazonian curares are divided into two groups based upon the container the plant is stored in: pots or tubes. Pot curare in the East Amazon is predominately from the species *Strychnos guianensis*. Tube curare in the West Amazon is from *Chondrodendron tomentosum*. The curare in modern medicine is made from the latter species, therefore, its name: tubocurarine.

The complex processes used to make curare were a guarded secret, sometimes involving 30 or more ingredients. In 1800 Alexander Von Humboldt witnessed and documented curare preparation by Indians from the Orinoco River. In 1811, Sir Benjamin Brodie noted that during curare poisoning the heart continues to beat, even after breathing stops.

In 1814, an explorer named Charles Waterton injected a donkey with curare. Within ten minutes, the donkey appeared dead. Waterton cut a small hole in the animal's throat and inserted a bellows and pumped to inflate the lungs for two hours until the effects of curare had worn off. The donkey then walked away, apparently none the worse for what had happened.

In 1912 Rudolf Böhm provided Arthur Læwen, a surgeon at the Leipzig University, with raw curare. Læwen quickly learned that it was possible to paralyze the respiratory muscles and to keep animals and humans alive by artificial ventilation. He describes the curarin intoxication as a special kind of intoxication, which can be treated, with a very high degree of safety. He used artificial ventilation as a safe method to bridge the time of excretion of curarin and to wait for the restoration of the normal function of the respiratory muscles. He was also apparently the first to use curare as an adjunct to surgery in a human being.

In 1935, Dr. Herbert King described the chemical structure of d-tubocurarine. One year later King's drug was used to treat three tetanus patients. In 1938 Abram Elting Bennet suggested using curare prior to electroshock therapy.

In 1941 the pharmaceutical firm E.R. Squibb and Sons produced a special curare preparation called "intocostrin." Despite presenting at an American Medical Association meeting in 1940, the company was unable to interest anesthetists until they approached Canadian Dr. Harold Griffith, whose reputation was well established. On January 23, 1942, Griffith and his assistant Dr. Enid Johnson gave intocostrin for an appendectomy and were delighted with the muscular relaxation they were able to achieve. By 1945, intocostrin was being used in 10,000 surgeries every month.

In 1947, Swiss-born Italian pharmacologist Daniel Bovet discovered a synthetic substitute for curare called gallamine, known commercially as Flaxedil®. He received the Nobel Prize for Physiology or Medicine in 1957 for his discovery, but this compound had many undesirable vagal effects and has since been abandoned.

Succinyl-bis-choline (Anectine®) was introduced in 1951, and other, safer derivatives have followed, both depolarizing and non-depolarizing.

Digitalis

For many centuries dropsy, or cardiac edema, was a disagreeable cause of death. The name derives from the apparent "drop" of fluid from the body into the ankles and legs. Dr. Samuel Johnson died after painful suffering, his legs so bloated that his physicians tried to let the fluid out through large knife incisions.

The dried bulb of the squill is mentioned in the Ebers Papyrus, written about 1500 B.C., as dropsy therapy. Romans used squill to treat dropsy, to strengthen the heart, to induce vomiting, and to poison rats.

The Chinese use the dried skin of the common toad, called ch'an su, as treatment for toothache, gum bleeding, and dropsy. Ch'an su contains epinephrine combined with a cardiac glycoside.

Menyellydon, or "Elves' gloves" or "Little Folks' gloves" was used by Welsh physicians since at least the thirteenth century. A legend developed that the little people of the forest distributed these flowers so a fox could wear them as gloves during raids on chicken coops. Some etymologists believe the name foxglove is derived from an ancient musical instrument that consisted of bells hung from an arched support, similar to the little purple bell-shaped flowers hanging from the foxglove stalk. Even the Norwegian word for foxglove means "fox music."

In Germany, foxglove was called fingerhut, literally "finger hat" or "thimble." In 1542, the German herbalist Leonhard Fuchs described foxglove and latinized its name, coming up with *digitalis*, pertaining to a finger.

In the early 17th century, Dutch medical biologist Rembert Dodoens wrote that "for those who have water in the belly...it draws off the watery fluid, purifies the choleric fluid, and opens the obstruction."

Although it was in the London Pharmacopoeia by 1661, *digitalis* was only recommended for epilepsy and sedation. English physician William Salmon became convinced that *digitalis* was the long-sought treatment for tuberculosis, as small doses improved the breathing of patients with "lung disease." He was almost certainly treating heart failure and pulmonary edema. Salmon warned that it must be given in very small doses.

Many doctors ignored this advice, and poisoned their patients with *digitalis*. The Dutch physician Hermann Boerhaave, one of the most respected men in eighteenth-century Europe, declared that *digitalis* was a poison and cautioned against its use. Then in 1748, Dr. Salerne of Orleans stuff foxglove powder down the throats of two healthy turkeys, as if force-feeding geese to make *pâté de foie gras*. The turkeys died and autopsy showed that their intestines had been squeezed dry. Rather than conclude that *digitalis* was good for ridding the body of excess fluid, Salerne reported to the French Academy of Sciences that the compound was a powerful poison. This august body then condemned the use of *digitalis*.

Then in 1775, English physician Dr. William Withering was stunned when one of his heart patients, whom he had nothing to offer, seemed to be cured after taking an herbal remedy from a gypsy. Withering sought out the woman and, after much bargaining, learned her secret. The herbal remedy was made from many things, but the active ingredient was the purple foxglove, *Digitalis purpurea*.

Dr. Withering was a member of one of the most extraordinary groups of scientists the world has ever known, founded in 1766 by Matthew Boulton and Erasmus Darwin (grandfather of Charles Darwin). Members included steam engine inventor James Watt, pottery manufacturer Josiah Wedgwood, and Joseph Priestley, the discoverer of oxygen. They met for dinner once a month and, since they had to find their way home afterwards, arranged it for the night of the full moon. Hence, their name, the Lunar Society of Birmingham, also known as The Lunatics.

Dr. Withering also observed that when older men and women who suffered from swollen feet and ankles would receive no comfort from their physicians, they would visit a particular old woman for her special tea, which lessened the swelling. Withering tracked down the woman and studied her herbal treatment, composed of twenty or more different herbs. The active herb was again

foxglove leaf. After much experimentation he arrived at a proper dose and gave the herb to his dropsy patients. In 1785 he published his results: out of 163 dropsy patients, two-thirds improved after taking digitalis. Almost simultaneously, his old friend Darwin published similar results, borrowing much from Withering but not giving him credit. Contemporary physicians were not deceived, however, and Withering received his due credit. He and Darwin became bitter enemies.

Insulin

The word "diabetes" comes from the Greek word for "siphon," since ingested water appeared to run straight through the body and out as urine, as though through a siphon. The term "mellitus," Latin for honey or sweet, was added after doctors realized the urine was loaded with sugar.

Diabetic-like symptoms were also mentioned in the Ebers papyrus, it wasn't until the second century A.D. that Greek physician Aretaeus of Cappadocia stated, "Diabetes is a mysterious illness ... [where] the flesh and limbs melt into urine." He also reported how the disease made "life disgusting and painful; thirst unquenchable; ... and one cannot stop them either from drinking or making water." Aretaeus listed in his account a triad of symptoms—never-ending thirst, copious urination, and wasting of the body.

In 1674 the Englishman Thomas Willis published "The Diabetes or Pissing Evil." Willis observed that diabetic urine "differed both from the drink taken in, and...from any humor that is wont to be begot in our Body...wonderfully sweet as if it were imbued with Honey or Sugar."

Matthew Dobson, a physician practicing at the Liverpool Public Infirmary, reported in 1776 about studies he had conducted on a thirty- three-year-old former soldier, Peter Dickonson, who had been well until his diabetes began. Dobson used a "gentle heat" to evaporate two quarts of Dickonson's urine, leaving behind a granulated cake which smelled and tasted like sweet brown sugar. Dobson deduced that this explained the thinness of victims of diabetes "...from so large a proportion of the alimentary matter being drawn off by the kidneys, before it is perfectly assimilated, and applied to the purposes of nutrition."

What followed were attempts to manipulate diet, including John Rollo's prescription of an "animal diet" in 1797 that included "plain blood-puddings" and "fat and rancid old meats." Each diet attempted to feed diabetics foods that their bodies could assimilate.

All of these diets were ultimately of minimal benefit in staving off death. Patients under ten years of age lived no more than three years after they received the diagnosis. Many diabetic patients spent these terminal years living in a semi-starved state that ended in coma, infection, or starvation.

The prognosis for people with diabetes was forever rewritten in the summer of 1921 and the year that followed with the discovery and initial development of insulin by Frederick G. Banting, Charles H. Best, James B. Collip, John J. R. Macleod, and other researchers in Toronto.

Experiments done in the 1880s showed that when a dog's pancreas was removed by surgery the animal developed the symptoms of diabetes: it would grow insatiably thirsty, begin excreting large amounts of sugar in its urine, and then become listless, go into a coma, and die. Banting thought that pancreas must secrete something in addition to its digestive enzymes in order to

prevent this process, and was convinced that the crucial substance would be found in the islets of Langerhans.

Banting's job was surgery, Best was the chemist. Banting would remove the pancreas from some dogs to make them diabetic, and tied off the pancreatic ducts in others to isolate the islet cells. On July 30, 1921, Banting removed the shriveled pancreas from a dog whose ducts had been tied. He and Best prepared an extract from it by chopping the pancreas into small pieces, grinding it in a chilled mortar with salt water, and filtering the mixture through cheesecloth. A blood sample from the diabetic dog showed its blood sugar level to be 0.2. Banting and Best injected some of their extract into the dog. An hour later its blood sugar level had dropped to 0.12. After another injection it registered 0.11. They tested their extract, which they named "isletin," on more dogs.

Banting and Best found ways of obtaining the extract more easily and in larger quantities from the pancreases of fetal calves obtained from a local slaughterhouse. Macleod made suggestions for further studies, and hired James Bertram Collip, a Ph.D. biochemist, to help purify the active component of the extract. That fall Banting and Best wrote their first paper describing the experiments with dogs, titled "The Internal Secretion of the Pancreas." It was accepted for publication in the February 1922 issue of the Journal Of Laboratory And Clinical Medicine.

By the time the paper was published, Banting and Best had treated a human being with the extract, which they now called insulin, based on the Latin word for island. The first patient to receive insulin was 14-year-old Leonard Thompson, whose weight had shriveled to 65 pounds, and was so weak that he had been admitted to Toronto General Hospital. His doctors expected him to live for only a few more weeks. Before administering insulin to the boy, Banting and Best injected each other with their extract. There seemed to be no side effects, except a sore arm. In January 1922 they went ahead and injected the boy, and his condition began to improve. He regained his energy and put on weight. Thompson lived another 11 years, dying in 1935 from pneumonia contracted after a motorcycle accident.

Elizabeth Hughes, daughter of U.S. Secretary of State Charles Evans Hughes, weighed 45 pounds and could barely walk when she first saw Banting in Toronto on August 16, 1922. "Patient extremely emaciated...skin dry and scaly, hair brittle and thin...shoulders drooped, muscles extremely wasted," wrote Banting of that first exam. Within weeks, Elizabeth was writing to her mother back in Washington, "I declare you'd think it was a fairy tale...I look entirely different, everybody says. She graduated from Barnard College in 1929. In 1930 she married William T. Gossett, and had three children. Elizabeth Hughes Gossett died of pneumonia on April 21, 1981 at the age of seventy-three. She had lived for fifty-eight years on insulin. Twenty-six pound Ted Ryder, age five, received his first injection of insulin in Toronto in July 1922. He lived until 1993.

The 1923 Nobel Prize in physiology and medicine for that year was awarded to Banting and Macleod for the discovery of insulin. Banting was furious. In his opinion, Macleod had done little more than provide laboratory space, whereas Best had shared the work of research. Best was in Boston the day the news arrived, giving an address to medical students at Harvard. Banting immediately sent Best a telegram stating that he would share both the credit for the discovery and the Nobel Prize cash award with Best. Macleod, who considered the work a collaboration, divided his portion of the prize with Collip.

Aspirin

- 1500 BC (?) – Egyptians record a collection of recipes for medicines, which includes a recipe using an infusion of dried myrtle leaves – which contain salicylic acid – to relieve back pain.
- 200 BC – Hippocrates prescribes leaves and bark from willow tree – which, like the myrtle tree, contains salicylic acid – to relieve fever and pain, including labor pains.
- 100 AD – Greek surgeon Dioscorides mentions the use of willow leaves to relieve pain.
- 200 – Pliny the Elder describes the use of willow leaves in his writings, as does Galen.
- Middle Ages – Europeans stop using willow bark remedies, as the willow bark supply was earmarked for making wicker. Use of willow for medicinal purposes is banned in some places.
- 1500 – Native people of North America make salicylate pain remedies from birch bark.
- 1763 – Edward Stone, an English clergyman, reports to the Royal Society of London his successful experiments involving the use of willow bark to reduce fever in fifty of his patients. Meanwhile, on the European mainland, quinine is used to treat pain.
- 1828 – Johann Büchner of Munich isolates pure salicin from willow bark. Salicin is the compound in willow bark that relieves pain. The name salicin was derived from *salix*, which is the Latin word for willow tree.
- 1835 – Karl Lowig makes salicylic acid from meadowsweet flowers.
- 1838 – Raffaele Piria converts salicin into salicylic acid. This is the first time salicylic acid is obtained from willow bark in the laboratory.
- 1853 – Charles Frederic Gerhardt first synthesizes acetylsalicylic acid; he fails to understand its molecular structure and its potential importance to humanity.
- 1859 – H. von Glim describes the preparation of ASA, but he, too, fails to grasp its molecular structure.
- 1859 – Herman Kolbe discovers how to synthesize salicylic acid from coal tar. The method he uses is still used and is called the "Kolbe synthesis."
- 1869 – Karl-Johann Kraut repeats the previous two scientists' experiments and gives the first accurate information about the molecular structure of ASA, the ester of salicylic acid (SA).
- 1874 – Salicylic acid is first made industrially in Dresden, Germany, using Kolbe's method. It is sold as a painkiller but severely irritates the stomach.
- 1897 – On August 10, 1897, Felix Hoffmann, chemist in the Bayer chemical factory in Germany, reportedly prepares the first pure sample of acetylsalicylic acid (ASA). His laboratory journal notes the test he performed to assess the purity of his product. The account of his discovery first appears in 1934 as a footnote in a history of chemical engineering written by Albrecht Schmidt, a chemist who had recently retired from the IG Farbenindustrie organization into which F Bayer & Company had been incorporated in 1925. Until recently, it was generally accepted that Felix Hoffmann developed aspirin to help his rheumatic father. In 1949 Hoffman's former colleague Arthur Eichengrün claimed that the work had been done under his direction. Eichengrün, a German Jew, was prevented by the Nazis from challenging Hoffmann's claim; he also spent 14 months of World War II in Theresienstadt, a Czech concentration camp.
- 1899 – The first publication of clinical trial results appears and shows the promising healing effects of ASA. Bayer refers to acetylsalicylic as "Aspirin" for the first time. The German name of Acetylirte Spirsaure, or "acetylated spiraeic acid" (Latin *Spiraea*, or Greek *speiraia*, a plant), was considered too difficult to remember. The company distributes Aspirin (as a powder) to physicians to give to their patients in this same year. Over time, lacking enforcement by the trademark owner to maintain the proprietary nature of this

mark, the term “aspirin” comes into public usage as a generic description of the chemical composition originally sold under the mark. As a result, Bayer & Company is no longer able to assert exclusive ownership of the term and prevent others from using it.

- 1900 – Bayer introduces the first water-soluble tablet form of aspirin. This process cuts production costs in half.
 - 1903 – Bayer attempts to corner the large potential aspirin market in the United States and avoid the country's high import duties, so it establishes a large aspirin plant in Rensselaer, New York. By holding both the U.S. patent on aspirin and its trade name, Bayer was well-positioned to capture the minds and pocketbooks of a large portion of the American citizenry. But during World War I its U.S. assets were seized by the government and sold at auction. The highest bidder, Sterling Drug Company, bought not only Bayer's assets, but also its rights to its name and to the famous trademark of BAYER crossed vertically with BAYER at the Y.
 - 1915 – Aspirin first becomes available without a prescription.
 - 1920 – Bayer's patent on aspirin expires.
 - 1948 – Dr. Lawrence Craven discovers that men to whom he prescribed aspirin suffered no heart attacks. He recommends "an aspirin a day" to both patients and colleagues alike to decrease risk of heart attack.
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Penicillin

Early attempts at antimicrobial therapy involved using nonpathogenic bacteria to fight disease-producing germs. In 1877, Louis Pasteur showed that anthrax could be rendered harmless in animals by injecting them with soil bacteria. In 1887, Rudolf Emmerich showed that cholera could be prevented in animals by infecting them with the streptococcus bacterium before injecting the cholera bacillus.

In 1888, German scientist de Freudenreich isolated a product from a bacterium that had antibacterial properties, the blue pigment released in culture by *Bacillus pyocyaneus*. His experiments showed that pyocyanase could kill a multitude of disease-causing bacteria, but the substance was toxic and unstable, and could not be developed into an effective drug.

In the early 1920s, British scientist Alexander Fleming reported that a product in human tears, which he called lysozyme, could lyse bacterial cells. Further experiments showed it was effective primarily against non-pathogenic bacteria.

In 1928, Fleming discovered another antibacterial agent. He returned from a weekend vacation and was looking at a set of culture dishes which he had streaked with *Staphylococcus aureus*. Some mold had inadvertently grown on one of the plates, and no bacteria would grow near this mold. Fleming followed up this observation experimentally placing mold on more plates and noticing the same phenomenon – bacteria would not grow near the mold. He named this substance penicillin after the *Penicillium* mold that had produced it.

Fleming had rediscovered a phenomenon first described in 1896 by the French medical student Ernest Duchesne. In 1897 in Lyon he defended his doctoral thesis, “Contribution à l'étude de la concurrence vitale chez les micro-organismes: antagonisme entre les moisissures et les microbes” (Contribution to the study of vital competition in micro-organisms: antagonism between moulds and microbes) in which he considered the therapeutic possibilities resulting from the antimicrobial activity of moulds. He pursued his research after joining the Army's Health Department, where he noted that barracks stablehands purposely stored saddles in dark and humid

places in order for a kind of fungus to form on the leather. According to the stablehands these fungi were excellent for healing wounds on the backs of the horses. The Army doctor then experimented with sick guinea pigs by injecting half with a fungus concentrate; the injected animals were all better within hours, but every untreated guinea pig died.

While Fleming had made the initial discovery, he was unable to carry his research significantly further. He was discouraged by many experts who were convinced that once bacteria had infected a human being there was no way to treat it safely. Fleming was also unable to purify significant quantities of penicillin and could not conduct any clinical trials. His last published work on penicillin was in 1931.

In 1939 Howard Florey, Ernst Chain, and Norman Heatley picked up the project. They obtained the *Penicillium* fungus from Fleming and were able to overcome the technical difficulties that had plagued him. Small amounts of the drug, even in its crude form, were injected into animals and humans near death from bacterial infections; most were miraculously.

By now, England was at war and lacked capabilities to mass produce the drug. The British worked together with the United States to make penicillin a reality, and initially it was used almost exclusively to treat soldiers injured during the war. That would change, though, with one fateful disaster.

On November 28, 1942, a disastrous fire at Boston's Coconut Grove nightclub killed nearly 500 celebrants – mostly members of the military – and caused severe burns in hundreds of others. It was common for severe burn victims to die of bacterial infections, so pharmaceutical giant Merck sent a large supply of this “priceless” drug to the Massachusetts General Hospital. Many burn victims survived who would have otherwise died, and the success of penicillin made national headlines. By 1946, the drug had become widespread for clinical use.

Fleming, Chain, and Florey won the Nobel Prize for Medicine or Physiology in 1945. Fleming was interviewed by *The New York Times* that year, and warned of the possible misuse of penicillin, which was sold in the United States without a prescription until the mid 1950s. He had experimentally derived penicillin-resistant strains by varying the dosage and conditions upon which he added the antibiotic to bacterial cultures. By 1946, hospitals were reporting that 14% of the strains of *Staphylococcus aureus* isolated from sick patients were penicillin resistant. By the end of the decade, resistance had risen to 59%.

NRTIs, NNRTIs, HAART, and Protease Inhibitors

In the early 1980s, before the discovery that AIDS was caused by a new immunodeficiency virus, most patients with AIDS died within 2 years. Early in the epidemic, therapy was restricted to the treatment and control of the numerous unusual and overwhelming opportunistic infections, which were frequently the cause of death in AIDS patients.

The first big breakthrough was in 1983, when the HIV-1 virus was isolated. The first therapy targeting this human retrovirus was in 1987 when zidovudine, a nucleoside analog that inhibits HIV-1 reverse transcriptase, was approved by the FDA. HIV-1 must be integrated into the host DNA to be able to use the host cells' genetic machinery to produce new virus. HIV-1 single-stranded viral RNA is first converted to double-stranded DNA by reverse transcriptase. The

nucleoside reverse transcriptase inhibitors (NRTIs) interfere with HIV-1 replication by competitively inhibiting this enzyme, thus leading to chain termination of HIV-1 proviral DNA.

Despite zidovudine and didanosine (released in 1991) scientists began to recognize that monotherapy was brief and limited in activity. By 1993, AIDS was the number one killer of young adults in the USA.

With a greater understanding of the virus came new targets for drugs; including viral protease, the enzyme responsible for the maturation of viral particles to infectious virions ready to infect new host cells. Core proteins of HIV-1 are produced as part of long polypeptides that are cut into smaller pieces by protease to create functional, mature proteins. Protease inhibitors bind to the active site of the enzyme where protein cleavage occurs and new viral particles cannot mature and become infectious.

In 1995, the clinical efficacy of a protease inhibitor in combination with two NRTIs was determined. The subsequent approvals of more potent protease inhibitors, such as indinavir, ritonavir and nelfinavir, rendered feasible the prolonged survival of patients with AIDS and HIV-1 infection. Subsequent studies have proven the efficacy of triple combination therapy, or highly active antiretroviral therapy (HAART). Sufficient antiviral potency can be sustained to drive plasma viral load below detection limits. Sustained suppression of HIV-1 titers minimizes viral replication, which deters the development of resistance to the new agents and allows for immune reconstitution. The duration of this suppression now exceeds 4 years.

Other triple combination therapies became possible with the introduction of non-nucleoside reverse transcriptase inhibitors (NNRTIs), which, when combined with two NRTIs, are very effective in suppressing HIV-1 replication.

Initial excitement about triple combination therapy has been tempered by the recognition of sometimes fatal metabolic complications (lactic acidosis, diabetes mellitus, lipodystrophy, pancreatitis). Some patients encounter difficulty in staying on complicated regimens requiring high pill burdens, multiple daily administrations, and interactions with food. These problems have been overcome in part by combining low-dose ritonavir with other protease inhibitors in combined pill formulations, allowing fewer pills to be taken less frequently.

A recent editorial by Farmer in the *New England Journal of Medicine* stated, "Excellence without equity looms as a chief human-rights dilemma of health care in the twenty-first century". The annual direct expenditures for the care of HIV-1 in the US exceed \$20,000 per patient.

Quinine

Cinchona is a genus of tropical evergreen trees and shrubs, with rather large laurel-like leaves, and white or pink fragrant flowers arranged in clusters. It belongs to the family *Rubiaceae*, which also includes other members like coffee and gardenia. The most important and useful species are *Cinchona officinalis*, *C. calisaya* and *C. pubescens* (also known as *C. succirubra*).

Cinchona apparently originated on the slopes of the Andes in South America. By the early sixteenth century, natives were treating various maladies using their "Indian fever bark." Soon it was known as "Jesuit fever bark," since this religious group had a monopoly on its production. Its name *cinchona* apparently came from the Countess of Chinchon, wife of the Spanish Viceroy

of Peru, who contracted malaria in 1638. She was cured with administration of "quinquina" bark, and the tree was named Cinchona in her honor.

Word spread about her miraculous cure, and demand for the remedy soon out-stripped supply. The bark was so valuable that at one point, the cost of powdered was often determined by its weight in gold. This prompted uncontrolled harvesting of the bark, leading to severe depletion of the plant in South America.

In 1820, Parisians Pierre Peletier and Joseph Coventou isolated a bitter gum from the bark that was soluble in both alcohol and acid. Eventually 36 alkaloids were described in cinchona bark, of which four possess antimalarial properties. Quinine is most effective.

During the Second Seminole War in Florida (1835 – 1842), 75% of the deaths were from disease, usually malaria. Surgeon General Lawson approved large-scale trials of quinine in amounts far greater than previously considered to be safe. The survival rate increased, and the treatment of malaria throughout the United States changed, saving many lives.

By 1865, the cinchona was endangered from over-harvesting, but Englishman Charles Ledger smuggled some seedlings out of South America. The British had commissioned their own smugglers, so declined to purchase Ledger's seedlings. But the Dutch were eager to develop a supply for their colonies and bought some seeds. Within ten years cinchona trees were growing on the Island of Java (Indonesia), where by 1930, more than 95% of the world's quinine supply was grown.

On August 20th, 1897, Sir Ronald Ross, while working as a military physician in India, demonstrated malarial oocysts in the gut tissue of female Anopheles mosquito, thus first describing the vector for malaria. August 20th is still observed as "Mosquito Day" in India. Ross was awarded the Nobel Prize in 1902. Interestingly, Ross never wanted to be a physician; he hoped to be a writer, but his father forced him to join medicine.

When Japan captured Java during World War II, America and her allies lost their supply of quinine. The German pharmaceutical giant Bayer had developed synthetic antimalarial 4-amino quinolines in 1934, first Resochin, then Sontochin. When Americans liberated Tunis from the Germans in 1943, they acquired some Sontochin and sent it to the Rockefeller Institute in New York for analysis. It was found to be identical with material synthesized at the Winthrop laboratories three years earlier. This *faux pas* was quickly covered up by giving the compound a new development number and declaring the biological data secret.

Further trials on Sontochin, now SN-6911, confirmed its considerable effectiveness, and also generated several ideas that resulted in the synthesis of a new chemical, SN-7618. But Winthrop Laboratories had also patented this compound years before. It was, in fact, a different salt of the same base as Bayer's Resochin. After much comparison with other related compounds it was recognized formally in February 1946 under the name chloroquine. Winthrop had synthesized and first tested it in animals about 12 years earlier, at the same time as the Germans, but had rejected, or ignored it, twice.

Ivermectin and Azithromycin to Prevent Blindness

Trachoma responsible for 15 % of the world's blindness. Presently there are about 6 million people with irreversible blindness and an estimated 146 million cases of active disease in need of treatment, if blindness is to be prevented.

The agent is *Chlamydia trachomatis*, an atypical microorganism which spreads through contact with eye discharge from the infected person on towels, handkerchiefs, fingers, etc., and through transmission by eye-seeking flies. Infection provokes an inflammatory reaction in the eye with formation of follicles in the conjunctiva. After years of repeated infections, the eyelids may be scarred so severely that intropion develops (the eyelid turns inwards) and the eyelashes rub on the eyeball, leading to scarring and blindness.

Azithromycin, a macrolide antibiotic with a long half-life developed and produced by Pfizer International, Inc., has been tested in a number of countries. The initial results are amazing: one dose of azithromycin per year could eliminate blinding from trachoma.

Onchocerciasis is the world's second leading infectious cause of blindness. It is most closely associated with Africa, where it constitutes a serious obstacle to socio-economic development. Onchocerciasis is often called "river blindness" because the blackfly vector flourishes in the fertile riverside areas.

Of 120 million people world-wide who are at risk of onchocerciasis, 96% are in Africa. A total of 18 million people are already infected with the disease and have dermal microfilariae; more than 6.5 million suffer from severe itching or dermatitis and 270 000 are blind.

Onchocerciasis is caused by *Onchocerca volvulus*, a parasitic worm that lives for up to 14 years in the human body. Each adult female worm produces millions of microfilariae that migrate through the body and cause many symptoms: serious visual impairment, including blindness; rashes, lesions, intense itching and skin depigmentation; lymphadenitis leading to elephantiasis; and general debilitation. Microfilariae from one person are carried to another by the blackfly, (*Simulium damnosum*).

The Onchocerciasis Control Programme (OCP) was launched in 1974 and currently has 11 participating countries, covering 1.23 million sq. km and a population of about 30 million people. Estimated total cost is US\$550 million, or less than US\$1 per year for each protected person. In 1987 ivermectin's manufacturer, Merck & Co., Inc., pledged to provide at no cost all the drug necessary for as long as necessary to overcome onchocerciasis as a public health problem.

Although OCP's principal method for controlling onchocerciasis has been to break the cycle of transmission by eliminating the black fly, ivermectin was distributed where needed in the operations area through a community directed approach. Ivermectin kills the larval worms that cause blindness and other onchocercal manifestations and acts to decrease transmission as well. Some 1.5 million people who were once infected with onchocerciasis no longer have any trace of the disease. Eleven million children born in the operational area since the program's inception are now free of risk of contracting the disease.

Elixir Sulfanilamide

Sulfanilamide was a drug commonly used to treat streptococcal infections, available in tablet and powder, but not liquid, forms. In 1937, the S.E. Massengill company decided to develop a liquid form of Sulfanilamide for the pediatric market. Massengill's chief chemist and pharmacist, Harold Cole Watkins, found that diethylene glycol was a good medium for the elixir Sulfanilamide, giving it a nice appearance and a pleasant taste. What Watkins did not realize was that diethylene glycol is a deadly poison, chemically very similar to ethylene glycol, the toxin found in antifreeze and other chemicals. Existing laws did not require studies proving a drug's safety, and 240 gallons of Elixir Sulfanilamide went on the market.

Many children who took this drug, commonly used for sore throats, lapsed into severe illness, including renal failure, severe abdominal pain, vomiting, convulsions, and coma. Eventually 107 people died.

The American Medical Association started getting complaints from physicians a few weeks after the drug went on the market and quickly identified diethylene glycol as the offending ingredient. Warnings were issued not to use the drug. Once the FDA was notified of the problem, it insisted that letters be sent to distributors warning of the lethal nature of the product. They then sent 239 investigators to track down the remaining unused portions of the medicine. Eventually they recovered 234 gallons and 1 pint of the 240 gallons. The remaining amount had been consumed.

Massengill denied any responsibility for the tragic outcome of its quest for liquid Sulfanilamide, but Harold Watkins committed suicide. Massengill was fined, charged on a technicality in the incident, as their product did not violate any existing law. (Massengill called its product an "elixir," which is incorrect. Elixirs are dissolved in an alcohol medium. Since Sulfanilamide was in a diethylene glycol base, it could not be called an elixir, allowing the government to step in and level charges of fraud and misrepresentation). Soon after, the 1906 Food and Drug Act was replaced by the Federal Food, Drug, and Cosmetic Act of 1938.

Legislation had been enforced by the Bureau of Chemistry until 1927, when the Food, Drug, and Insecticide Administration was created. In 1931 it was renamed the Food and Drug Administration. In 1940, the FDA was transferred from the U.S. Department of Agriculture to the Federal Security Agency, which later became the Department of Health, Education, and Welfare, and then the Department of Health and Human Services.

In 1938, this law introduced the following improvements to the existing legislation:

- ◆ cosmetics and therapeutic devices were regulated for the first time
- ◆ fraud no longer needed to be proved to prevent false claims for drugs
- ◆ scientific proof of safety for new drugs was required before they could be marketed
- ◆ addition of poisonous substances to food was outlawed in most cases, and tightly regulated in others
- ◆ authority was created for factory inspections
- ◆ food standards were required to be created
- ◆ federal court injunctions against violations were made legal.

This law, after many revisions, is still in effect today.
