

INTRODUCTION

The modern era of the pharmaceutical industry—of isolation and purification of compounds, chemical synthesis, and computer-aided drug design—is considered to have begun in the 19th century, thousands of years after intuition and trial and error led humans to believe that plants, animals, and minerals contained medicinal properties. The unification of research in the 20th century in fields such as chemistry and physiology increased the understanding of basic drug-discovery processes. Identifying new drug targets, attaining regulatory approval from government agencies, and refining techniques in drug discovery and development are among the challenges that face the pharmaceutical industry today. The continual evolution and advancement of the pharmaceutical industry is fundamental in the control and elimination of disease around the world.

HISTORY

THE ORIGIN OF MEDICINES

MEDICINES OF ANCIENT CIVILIZATIONS

The oldest records of medicinal preparations made from plants, animals, or minerals are those of the early Chinese, Hindu, and Mediterranean civilizations. An herbal compendium, said to have been written in the 28th century BC by the legendary emperor Shennong, described the antifever capabilities of a substance known as *chang shan* (from the plant species *Dichroa febrifuga*), which has since been shown to contain antimalarial alkaloids (alkaline organic chemicals containing nitrogen). Workers at the school of alchemy that flourished in Alexandria, Egypt, in the 2nd century BC prepared several relatively purified inorganic chemicals, including lead carbonate, arsenic, and mercury. According to *De materia medica*, written by the Greek physician Pedanius Dioscorides in the 1st century AD, verdigris (basic cupric acetate) and cupric sulfate were prescribed as medicinal agents. While attempts were made to use many of the mineral preparations as drugs, most proved to be too toxic to be used in this manner.

Many plant-derived medications employed by the ancients are still in use today. Egyptians treated constipation with senna pods and castor oil and indigestion with peppermint and caraway. Various plants containing digitalis-like compounds (cardiac stimulants) were employed to treat a number of ailments. Ancient Chinese physicians employed ma huang, a plant containing ephedrine,

for a variety of purposes. Today ephedrine is used in many pharmaceutical preparations intended for the treatment of cold and allergy symptoms. The Greek physician Galen (c.130–c. 200 AD) included opium and squill among the drugs in his apothecary shop (pharmacy). Today derivatives of opium alkaloids are widely employed for pain relief, and, while squill was used for a time as a cardiac stimulant, it is better known as a rat poison. Although many of the medicinal preparations used by Galen are obsolete, he made many important conceptual contributions to modern medicine. For example, he was among the first practitioners to insist on purity for drugs. He also recognized the importance of using the right variety and age of botanical specimens to be used in making drugs.

PHARMACEUTICAL SCIENCE IN THE 16TH AND 17TH CENTURIES

Pharmaceutical science improved markedly in the 16th and 17th centuries. In 1546 the first pharmacopoeia, or collected list of drugs and medicinal chemicals with directions for making pharmaceutical preparations, appeared in Nürnberg, Ger. Previous to this time, medical preparations had varied in concentration and even in constituents. Other pharmacopoeias followed in Basel (1561), Augsburg (1564), and London (1618). The *London Pharmacopoeia* became mandatory for the whole of England and thus became the first example of a national pharmacopoeia. Another important advance was initiated by Paracelsus, a 16th-century Swiss physician-chemist. He admonished his contemporaries not to use chemistry as it had widely been employed prior to his time in the speculative science of alchemy and the making of gold. Instead, Paracelsus advocated the use of chemistry to study the preparation of medicines.

In London the Society of Apothecaries (pharmacists) was founded in 1617. This marked the emergence of pharmacy as a distinct and separate entity. The separation of apothecaries from grocers was authorized by King James I, who also mandated that only a member of the society could keep an apothecary's shop and make or sell pharmaceutical preparations. In 1841 the Pharmaceutical Society of Great Britain was founded. This society oversaw the education and training of pharmacists to assure a scientific basis for the profession. Today professional societies around the world play a prominent role in supervising the education and practice of their members.

In 1783 the English physician and botanist William Withering published his famous monograph on the use of digitalis (an extract from the flowering purple foxglove, *Digitalis purpurea*). His book, *An Account of the Foxglove and Some of Its Medicinal Uses: With Practical Remarks on Dropsy and Other Diseases*, described in detail the use of digitalis preparations and included suggestions as to how their toxicity might be reduced. Plants containing digitalis-like compounds had been employed by ancient Egyptians thousands of years earlier, but their use had been erratic.

Withering believed that the primary action of digitalis was on the kidney, thereby preventing dropsy (edema). Later, when it was discovered that water was transported in the circulation with blood, it was found that the primary action of digitalis was to improve cardiac performance, with the reduction in edema resulting from improved cardiovascular function. Nevertheless, the observations in Withering's monograph led to a more rational and scientifically based use of digitalis and eventually other drugs.

ISOLATION AND SYNTHESIS OF COMPOUNDS

In the 1800s many important compounds were isolated from plants for the first time. About 1804 the active ingredient, morphine, was isolated from opium. In 1820 quinine (malaria treatment) was isolated from cinchona bark and colchicine (gout treatment) from autumn crocus. In 1833 atropine (variety of uses) was purified from *Atropa belladonna*, and in 1860 cocaine (local anesthetic) was isolated from coca leaves. Isolation and purification of these medicinal compounds was of tremendous importance for several reasons. First, accurate doses of the drugs could be administered, something that had not been possible previously because the plants contained unknown and variable amounts of the active drug. Second, toxic effects due to impurities in the plant products could be eliminated if only the pure active ingredients were used. Finally, knowledge of the chemical structure of pure drugs enabled laboratory synthesis of many structurally related compounds and the development of valuable drugs.

Pain relief has been an important goal of medicine development for millennia. Prior to the mid-19th century, surgeons took great pride in the speed with which they could complete a surgical procedure. Faster surgery meant that the patient would undergo the excruciating pain for shorter periods of time. In 1842 ether was first employed as an anesthetic during surgery, and chloroform followed soon after in 1847. These agents revolutionized the practice of surgery. After their introduction, careful attention could be paid to prevention of tissue damage, and longer and more-complex surgical procedures could be carried out more safely. Although both ether and chloroform were employed in anesthesia for more than a century, their current use is severely limited by their side effects; ether is very flammable and explosive and chloroform may cause severe liver toxicity in some patients. However, because pharmaceutical chemists knew the chemical structures of these two anesthetics, they were able to synthesize newer anesthetics, which have many chemical similarities with ether and chloroform but do not burn or cause liver toxicity.

THE DEVELOPMENT OF ANTI-INFECTIVE AGENTS DISCOVERY OF ANTISEPTICS AND VACCINES

Prior to the development of anesthesia, many patients succumbed to the pain and stress of surgery. Many other patients had their wounds become infected and died as a result of their infection. In 1865 the British surgeon and medical scientist Joseph Lister initiated the era of antiseptic surgery in England. While many of the innovations of the antiseptic era are procedural (use of gloves and other sterile procedures), Lister also introduced the use of phenol as an anti-infective agent.

In the prevention of infectious diseases, an even more important innovation took place near the beginning of the 19th century with the introduction of smallpox vaccine. In the late 1790s the English surgeon Edward Jenner observed that milkmaids who had been infected with the relatively benign cowpox virus were protected against the much more deadly smallpox. After this observation he developed an immunization procedure based on the use of crude material from the cowpox lesions. This success was followed in 1885 by the development of rabies vaccine by the French chemist and microbiologist Louis Pasteur. Widespread vaccination programs have dramatically reduced the incidence of many infectious diseases that once were common. Indeed, vaccination programs have eliminated smallpox infections. The virus no longer exists in the wild, and, unless it is reintroduced from caches of smallpox virus held in laboratories in the United States and Russia, smallpox will no longer occur in humans. A similar effort is under way with widespread polio vaccinations; however, it remains unknown whether the vaccines will eliminate polio as a human disease.

IMPROVEMENT IN DRUG ADMINISTRATION

While it may seem obvious today, it was not always clearly understood that medications must be delivered to the diseased tissue in order to be effective. Indeed, at times apothecaries made pills that were designed to be swallowed, pass through the gastrointestinal tract, be retrieved from the stool, and used again. While most drugs are effective and safe when taken orally, some are not reliably absorbed into the body from the gastrointestinal tract and must be delivered by other routes. In the middle of the 17th century, Richard Lower and Christopher Wren, working at the University of Oxford, demonstrated that drugs could be injected into the bloodstream of dogs using a hollow quill. In 1853 the French surgeon Charles Gabriel Pravaz invented the hollow hypodermic needle, which was first used in the treatment of disease in the same year by Scottish physician Alexander Wood. The hollow hypodermic needle had a tremendous influence on drug administration. Because drugs could be injected directly into the bloodstream, rapid and dependable drug action became more readily producible. Development of the hollow hypodermic needle also led to an understanding that drugs could be administered by multiple routes and was of great significance for the development of the modern science of pharmaceuticals, or dosage form development.

DRUG DEVELOPMENT IN THE 19TH AND 20TH CENTURIES

NEW CLASSES OF PHARMACEUTICALS

In the latter part of the 19th century a number of important new classes of pharmaceuticals were developed. In 1869 chloral hydrate became the first synthetic sedative-hypnotic (sleep-producing) drug. In 1879 it was discovered that organic nitrates such as nitroglycerin could relax blood vessels, eventually leading to the use of these organic nitrates in the treatment of heart problems. In 1875 several salts of salicylic acid were developed for their antipyretic (fever-reducing) action. Salicylate-like preparations in the form of willow bark extracts (which contain salicin) had been in use for at least 100 years prior to the identification and synthesis of the purified compounds. In 1879 the artificial sweetener saccharin was introduced. In 1886 acetanilide, the first analgesic-antipyretic drug (relieving pain and fever), was introduced, but later, in 1887, it was replaced by the less toxic phenacetin. In 1899 aspirin (acetylsalicylic acid) became the most effective and popular anti-inflammatory, analgesic-antipyretic drug for at least the next 60 years. Cocaine, derived from the coca leaf, was the only known local anesthetic until about 1900, when the synthetic compound benzocaine was introduced. Benzocaine was the first of many local anesthetics with similar chemical structures and led to the synthesis and introduction of a variety of compounds with more efficacy and less toxicity.

TRANSITIONS IN DRUG DISCOVERY

In the late 19th and early 20th centuries, a number of social, cultural, and technical changes of importance to pharmaceutical discovery, development, and manufacturing were taking place. One of the most important changes occurred when universities began to encourage their faculties to form a more coherent understanding of existing information. Some chemists developed new and improved ways to separate chemicals from minerals, plants, and animals, while others developed ways to synthesize novel compounds. Biologists did research to improve understanding of the processes fundamental to life in species of microbes, plants, and animals. Developments in science were happening at a greatly accelerated rate, and the way in which pharmacists and physicians were educated changed. Prior to this transformation the primary means of educating physicians and pharmacists had been through apprenticeships. While apprenticeship teaching remained important to the education process (in the form of clerkships, internships, and residencies), pharmacy and medical schools began to create science departments and hire faculty to teach students the new information in basic biology and chemistry. New faculty was expected to carry out research or scholarship of their own. With the rapid advances in chemical separations and synthesis, single pharmacists did not have the skills and resources to make the newer, chemically pure drugs. Instead, large chemical and

pharmaceutical companies began to appear and employed university-trained scientists equipped with knowledge of the latest technologies and information in their fields.

As the 20th century progressed, the benefits of medical, chemical, and biological research began to be appreciated by the general public and by politicians, prompting governments to develop mechanisms to provide support for university research. In the United States, for instance, the National Institutes of Health, the National Science Foundation, the Department of Agriculture, and many other agencies undertook their own research or supported research and discovery at universities that could then be used for pharmaceutical development. Nonprofit organizations were also developed to support research, including the Australian Heart Foundation, the American Heart Association, the Heart and Stroke Foundation of Canada, and H.E.A.R.T UK. The symbiotic relationship between large public institutions carrying out fundamental research and private companies making use of the new knowledge to develop and produce new pharmaceutical products has contributed greatly to the advancement of medicine.

ESTABLISHING THE FIGHT AGAINST INFECTIOUS DISEASE

EARLY EFFORTS IN THE DEVELOPMENT OF ANTI-INFECTIVE DRUGS

For much of history, infectious diseases were the leading cause of death in most of the world. The widespread use of vaccines and implementation of public health measures, such as building reliable sewer systems and chlorinating water to assure safe supplies for drinking, were of great benefit in decreasing the impact of infectious diseases in the industrialized world. However, even with these measures, pharmaceutical treatments for infectious diseases were needed. The first of these was arsphenamine, which was developed in 1910 by the German medical scientist Paul Ehrlich for the treatment of syphilis. Arsphenamine was the 606th chemical studied by Ehrlich in his quest for an antisyphilitic drug. Its efficacy was first demonstrated in mice with syphilis and then in humans. Arsphenamine was marketed with the trade name of Salvarsan and was used to treat syphilis until the 1940s, when it was replaced by penicillin. Ehrlich referred to his invention as chemotherapy, which is the use of a specific chemical to combat a specific infectious organism. Arsphenamine was important not only because it was the first synthetic compound to kill a specific invading microorganism but also because of the approach Ehrlich used to find it. In essence, he synthesized a large number of compounds and screened each one to find a chemical that would be effective. Screening for efficacy became one of the most important means used by the pharmaceutical industry to develop new drugs.

The next great advance in the development of drugs for treatment of infections came in the 1930s, when it was shown that certain azo dyes, which contained sulfonamide groups, were effective

in treating streptococcal infections in mice. One of the dyes, known as Prontosil, was later found to be metabolized in the patient to sulfanilamide, which was the active antibacterial molecule. In 1933 Prontosil was given to the first patient, an infant with a systemic staphylococcal infection. The infant underwent a dramatic cure. In subsequent years many derivatives of sulfonamides, or sulfa drugs, were synthesized and tested for antibacterial and other activities.

DISCOVERY OF PENICILLIN



The first description of penicillin was published in 1929 by the Scottish bacteriologist Alexander Fleming. Fleming had been studying staphylococcal bacteria in the laboratory at St. Mary's Hospital in London. He noticed that a mold had contaminated one of his cultures, causing the bacteria in its vicinity to undergo lysis (membrane rupture) and die. Since the mold was from the genus *Penicillium*, Fleming named the active antibacterial substance penicillin. At first the significance of Fleming's discovery was not widely recognized. It was more than 10 years later before British biochemist Ernst Boris Chain and Australian pathologist Howard Florey, working at the University of Oxford, showed that a crude penicillin preparation produced a dramatic curative effect when administered to mice with streptococcal infections.

The production of large quantities of penicillin was difficult with the facilities available to the investigators. However, by 1941 they had enough penicillin to carry out a clinical trial in several patients with severe staphylococcal and streptococcal infections. The effects of penicillin were remarkable, although there was not enough drug available to save the lives of all the patients in the trial.

In an effort to develop large quantities of penicillin, the collaboration of scientists at the United States Department of Agriculture's Northern Regional Research Laboratories in Peoria, Ill., was enlisted. The laboratories in Peoria had large fermentation vats that could be used in an attempt to grow an abundance of the mold. In England the first penicillin had been produced by growing the *Penicillium notatum* mold in small containers. However, *P. notatum* would not grow well in the large fermentation vats available in Peoria, so scientists from the laboratories searched for another strain of *Penicillium*. Eventually a strain of *Penicillium chrysogenum* that had been isolated from an overripe cantaloupe was found to grow very well in the deep culture vats. After the process of growing the penicillin-producing organisms was developed, pharmaceutical firms were recruited to further develop and market the drug for clinical use. The use of penicillin very quickly revolutionized the treatment of serious bacterial infections. The discovery, development, and marketing of penicillin provides an excellent example of the beneficial collaborative interaction of not-for-profit researchers and the pharmaceutical industry.

DISCOVERY AND DEVELOPMENT OF HORMONES AND VITAMINS

ISOLATION OF INSULIN

The vast majority of hormones were identified, had their biological activity defined, and were synthesized in the first half of the 20th century. Illnesses relating to their excess or deficiency were also beginning to be understood at that time. Hormones, produced in specific organs, released into the circulation, and carried to other organs, significantly affect metabolism and homeostasis. Some examples of hormones are insulin (from the pancreas), epinephrine (or adrenaline; from the adrenal medulla), thyroxine (from the thyroid gland), cortisol (from the adrenal cortex), estrogen (from the ovaries), and testosterone (from the testes). As a result of discovering these hormones and their mechanisms of action in the body, it became possible to treat illnesses of deficiency or excess effectively. The discovery and use of insulin to treat diabetes is an example of these developments.

In 1869 Paul Langerhans, a medical student in Germany, was studying the histology of the pancreas. He noted that this organ has two distinct types of cells—acinar cells, now known to secrete digestive enzymes, and islet cells (now called islets of Langerhans). The function of islet cells was suggested in 1889 when German physiologist and pathologist Oskar Minkowski and German physician Joseph von Mering showed that removing the pancreas from a dog caused the animal to exhibit a disorder quite similar to human diabetes mellitus (elevated blood glucose and metabolic changes). After this discovery, a number of scientists in various parts of the world attempted to extract the active substance from the pancreas so that it could be used to treat diabetes. We now know that

these attempts were largely unsuccessful because the digestive enzymes present in the acinar cells metabolized the insulin from the islet cells when the pancreas was disrupted.

One of the first successful attempts to isolate the active substance was reported in 1921 by Romanian physiologist Nicolas C. Paulescu, who discovered a substance called pancrein in pancreatic extracts from dogs. Paulescu found that diabetic dogs given an injection of pancrein experienced a temporary decrease in blood glucose levels. Although he did not purify pancrein, it is thought that the substance was insulin. That same year, working independently, Frederick Banting, a young Canadian surgeon in Toronto, persuaded a physiology professor to allow him use of a laboratory to search for the active substance from the pancreas. Banting guessed correctly that the islet cells secreted insulin, which was destroyed by enzymes from the acinar cells. By this time Banting had enlisted the support of Charles H. Best, a fourth-year medical student. Together they tied off the pancreatic ducts through which acinar cells release the digestive enzymes. This insult caused the acinar cells to die. Subsequently, the remainder of the pancreas was homogenized and extracted with ethyl alcohol and acid. The extract thus obtained decreased blood glucose levels in dogs with a form of diabetes. Banting and Best worked with Canadian chemist James B. Collip and Scottish physiologist J.J.R. Macleod to obtain purified insulin, and shortly thereafter, in 1922, a 14-year-old boy with severe diabetes was the first human to be treated successfully with the pancreatic extracts.

After this success other scientists became involved in the quest to develop large quantities of purified insulin extracts. Eventually, extracts from pig and cow pancreases created a sufficient and reliable supply of insulin. For the next 50 years most of the insulin used to treat diabetes was extracted from porcine and bovine sources. There are only slight differences in chemical structure between bovine, porcine, and human insulin, and their hormonal activities are essentially equivalent. Today, as a result of recombinant DNA technology, most of the insulin used in therapy is synthesized by pharmaceutical companies and is identical to human insulin.

IDENTIFICATION OF VITAMINS

Vitamins are organic compounds that are necessary for body metabolism and, generally, must be provided from the diet. For centuries many diseases of dietary deficiency had been recognized, although not well defined. Most of the vitamin deficiency disorders were biochemically and physiologically defined in the late 19th and early 20th centuries. The discovery of thiamin (vitamin B₁) exemplifies how vitamin deficiencies and their treatment were discovered.

Thiamin deficiency produces beriberi, a word from the Sinhalese meaning “extreme weakness.” The symptoms include spasms and rigidity of the legs, possible paralysis of a limb, personality disturbances, and depression. This disease became widespread in Asia in the 19th century because steam-powered rice mills produced polished rice, which lacked the vitamin-rich husk. A dietary deficiency was first suggested as the cause of beriberi in 1880 when a new diet was instituted for the Japanese navy. When fish, meat, barley, and vegetables were added to the sailor’s diet of polished rice, the incidence of beriberi in the navy was significantly reduced. In 1897 the Dutch physician Christiaan Eijkman was working in Java when he showed that fowl fed a diet of polished rice developed symptoms similar to beriberi. He was also able to demonstrate that unpolished rice in the diet prevented and cured the symptoms in fowl and humans. By 1912 a highly concentrated extract of the active ingredient was prepared by the Polish biochemist Casimir Funk, who recognized that it belonged to a new class of essential foods called vitamins. Thiamin was isolated in 1926 and its chemical structure determined in 1936. The chemical structures of the other vitamins were determined prior to 1940.

EMERGENCE OF MODERN DISEASES AND TREATMENT

The rapid decline in the number of deaths from infections due to the development of vaccines and antibiotics led to the unveiling of a new list of deadly diseases in the industrialized world during the second half of the 20th century. Included in this list are cardiovascular disease, cancer, and stroke. While these remain the three leading causes of death today, a great deal of progress in decreasing mortality and disability caused by these diseases has been made since the 1940s. As with treatment of any complex disease, there are many events of importance in the development of effective therapy. For decreasing death and disability from cardiovascular diseases and stroke, one of the most important developments was the discovery of effective treatments for hypertension (high blood pressure)—i.e., the discovery of thiazide diuretics. For decreasing death and disability from cancer, one very important step was the development of cancer chemotherapy.