1 Evolution of Drug Discovery

1.1 Antiquity

Adam and Eve lived in paradise and did not know disease nor suffering; when they were expelled they discovered misery and disease.

It is not surprising that throughout history man has searched for remedies to fight against disease. Historically speaking, man has explored nature to satisfy two major needs – food and herbs for alleviating pain and suffering. Ancient civilizations had comprehensive treatises where herbs or mixtures of them represented the “corpus therapeuticum” to alleviate and treat disease. One of these compendia was the Ebers Papyrus. Egyptian culture already used a range of herbs from medicinal plants that were described in the Ebers Papyrus that was dated about 1550 BC. The papyrus was purchased in Thebes in 1872 by German Egyptologist Dr. George Ebers who had recognized its content and extraordinary value. It incorporates about 800 prescriptions written as hieroglyphics for over 700 remedies. It is preserved at the University of Leipzig (Figure 1.1). B. Ebbell produced a good translation in 1937 [1]. Most of the Egyptian names of drugs and ingredients, at least a third, have been identified with drugs and active principles that appear in current formularies and recipe books. In addition to recipes for purgatives, it also mentions some alkaloid plants as well as essentials oils, turpentine, cedar wood, soothing balms for skin problems, and many other prescriptions. Fragrant resins of *Boswellia* trees growing on the southern coast of Arabia such as frankincense (also known as olibanum) and myrrh were prized by Egyptian embalmers. Later, they were cited in the Bible, and have been used along with other balsams and gums throughout the centuries as deodorants and antiseptic drugs.

Another compendium is the Indian Ayurveda (“science and knowledge of life”) dating back to 900 years BC. Ayurveda has been used in India for thousands of years. Among their components are likely hallucinogenic plants, cannabis, datura metel, and others such as serpaphanda, later classified as *Rauwolfia serpentine*, which has been used for thousands of years as a remedy against hypertension.
and insanity. In the 1950s, CIBA scientifics isolated reserpine (amongst other alkaloids) from the roots of *Rauwolfia*, and demonstrated its efficacy as an antihypertensive and tranquilizer. The antileprosy activity of chaulmoogra oil was also known in ancient India. It has been reported that much of the folk medicine practiced by various North American Indian nations can be traced back to the Ayurvedic system of medicine. It is believed that the Asian Indians migrated to America via Russia across the Bering Strait to Alaska and then spread out to the south. There are similarities in the medicinal plants used by American Indians and the East Indian Ayurvedic medicines for the treatment of disease. The Chinese have consumed (and consume) considerable quantities of herbal remedies, many of which have been in use for centuries. The first written book on *materia medica*, *Shen Nong Ben Cao Jing* (*Shen Nong’s Canon on Materia Medica*), appeared around the first centuries before and after Jesus Christ, and described the characteristics, processing, and prescription of about 250 drugs from plant origin, 60 from animal origin, and another 50 related to minerals. This book is the earliest Chinese pharmacopoeia and has been extensively documented over the centuries.

Chinese medicine reached its summit during the Ming dynasty (1368–1644) when Li Shih Chen (1518–1593) wrote his *Pen ts’ao kang mu* (*The Great Herbal*), the best know of the Chinese herbals, with 520 volumes and nearly 11,000 prescriptions. The most-valued Chinese drug in the West is the main active principle of Ma Huang or *Ephedra sinensis* – isolated and identified as the alkaloid ephedrine by the Chinese-American pharmacologist K. K. Chen in 1930 (Section 5.2.3.2) [2].

**Figure 1.1** (Left) Fragment of the Ebers Papyrus (Universitätsbibliothek Leipzig, Papyrus Ebers, Tf. 20, Kol. 69). (Right) *Aconitum* in the Dioscorides.
1.1.1

Greek and Roman Pharmacy

Greek medicine was greatly influenced by Egyptian medicine. The mythological Asklepios (Latinized as Aesculapius) was the god of healing. Asklepios’s daughters were Hygea, goddess of hygiene, and Panacea, creator of infallible remedies. Temples were dedicated to Asklepios, the most famous being Epidaur. When illnesses were brought to these temples, the treatment was diet (dieta is a Greek word), fasting, sleep, and hygiene. Most of these temples became schools for the training of physicians—the school on the island of Cos being one of them. This school was the oldest and most famous medical school of classic Greece, and under the leadership of Hippocrates, the “Father of Medicine,” had a great influence in later medical schools. In this school the illness was completely examined and studied. All medical knowledge was employed to overcome the disease, which is not equal for everybody. The gods do not breed the diseases. The Hippocratic Oath was a compendium of medical and pharmaceutical ethics. The writings or medical treatises of this school, known as the Hippocratic Corpus, were collected at the great library of Alexandria around 280 BC. The philosopher Aristotle (384–322 BC), one of greatest savants of all times, was head of the Academy of Athens that had been founded by Plato in 387 BC. Aristotle was succeeded by his friend and former disciple, the botanist Teophastrus (about 370 to 287 BC), who wrote the book Historia Plantarum in which he classified and described over 500 plants, including those sent by the soldiers of Alexander the Great from territories conquered in the east (India). Teophastrus classified plants into trees, shrubs, subshrubs, and herbs—a very simple classification, but the most rational up to Linnaeus. Homer (ninth or eighth century BC), in the Odyssey, uses the word ‘pharmakon’ to refer to a drug, and the derived words “pharmacy” and “pharmacology” deal with the sciences of drugs or medicines.

In Rome, the knowledge of medicinal plants reached an early peak with Dioscorides (first century AD) and Galen or Galenus (second century AD). Pedanio or Pedacio Dioscorides (born in Sicilia, first century BC) was a physician/military surgeon who voyaged throughout the Roman Empire incorporated into Emperor Nero’s legions. During their voyages he collected plants and minerals that he classified according to their medicinal properties. His work De Materia Medica was written in Greek between 60 and 78 AD, and is divided into five books. Dioscorides gives a careful description of over 900 drugs from plant, animal, and mineral origin. Most of this material, known already by the Egyptians and Greeks, was later scientifically identified. Dioscorides gives comprehensive details of the drugs deriving from the three realms (animal, plants, and minerals), the preparations obtained from them, and even recommendations for special diseases. He also describes some rudimentary chemical procedures such as distillation, sublimation, mercury extraction from cinnabar, and others.

Dioscorides may be considered as the first compendium of pharmacy and De Materia Medica was among the first books to be printed; several printed Latin
Figure 1.2 Cover of Dioscorides (1554) (University of Santiago de Compostela Library).
editions were produced, such as those in Basel (1520) or Lugduni (Lyon, 1554) (Figure 1.2). Dioscorides was the indisputable reference book on drugs until the nineteenth century.

Claudius Galen or Galenus (135–201 AD) was born in Pergamun (Asia Minor), studied in Smirna and Alexandria, and traveled to Rome. As a physician, he performed a great deal of work in Rome, where he wrote about 400 works covering all aspects of medicine. His work Opera Omnia was one of the greatest, where he mentions numerous drugs and the methods of their use. Galen’s medicine was addressed to cure an imaginary disease, a humoral imbalance, instead of searching for the origin of the disease and then the remedy. For Galen, the body is an instrument of the soul. Galen thought that the origin of disease was an imbalance between the four humors of ancient Greece (heat, cold, moisture, and dryness). This imbalance could be corrected not only by adding herbal extracts of similar properties, but also other extracts with opposite properties ("contraria contraris oponenda").

Claudius Galen was a pharmacist and his approach to therapy involved also the polypharmacy. He prescribed medicines in simple or complex mixtures called "galenicals" specifically devised for each therapy. Galen prepared the theriac (the Greek word theriake = antidotes in Latin), a complex mixture of more than 30 ingredients, with the greatest care. (The Theriac Magna of Nero’s physician Andromachus had more than 70 components.) Galen argued that, for each disease, the body would be able to select the appropriate ingredient. The Aristotelian philosophical background of his "doctrinal" thinking was accepted, recognized, and fostered by the Church, and through the Middle Age reached the Renaissance, causing considerable difficulties to the progress of medical science.

In the fourth century, after the decline and fall of the Roman Empire, the cultural center transferred to the east, to the Byzantine Empire, and then to the Arab world. In the west, Europe entered a period of obscurity where the use of plants and remedies came under the domination of witchcraft and sorcery.

The ancient science was completely neglected and, in part, was saved by scholars that flourished in isolated places of the old Empire. Isidoro de Sevilla (560–630) wrote a compendium, Ethymologiae, which holds most of the Greco-Roman knowledge. Also, in Rome, Cassiodorus (490–583) and Boethius (480–524) recovered in their works some of the ancient wisdom and transmitted it to later centuries. Other contributions to the recovery of Greco-Latin texts were: Islam, Salerno’s School, and the monastic abbeys.

1) Very soon, translations to other languages were made, generally very well illustrated: Flemish (1540), Italian (1542), German (1546), and Spanish (1555). A French translation was made by Martin Mathée (Lyon, 1533). A Spanish translation was made by Andrés Laguna (1499–1560), Emperor Charles V physician’s, who also added numerous illustrations. The first edition was published in Antwerp (1555). A copy, luxuriously bound, was given (as a gift) to Prince Phillip (later King Phillip II) which is preserved at the Spanish National Library (Madrid). An English translation was made between 1652 and 1655 by the botanist John Goodyer and preserved for centuries in Magdalen College (Oxford).
1.1.2 Arabian Period

The invasion of the Mediterranean countries by Islam gave rise to the exchange of knowledge between the east (China, India, Persia) and west, allowing the flourishing of all sciences, specially medicine and pharmacology.

Between the seventh and thirteenth centuries the Arabic world enjoyed great splendor. The Greco-Latin texts (including the Hebrew Bible) were translated to Arabic. In the ninth century, Baghdad was the center of Muslim culture. Arabs conquered the Iberian Peninsula about 710–720. The great Arabian/Spanish culture reached its summit in the ninth to twelfth centuries, Cordoba being their capital. Arabian pharmacology is fundamentally related to the Greeks and Dioscorides serves as a model. Great scientific figures of the Arabian Caliphate were Razés, Avicena, Abulcasis, Inb-al Baytar, and others.

The physician Razés, born in Persia, was Director of Baghdad’s Hospital. He wrote about 200 books, 50 of which were devoted to collecting medical knowledge from Hindi, Syrian, Persian, Greek, and Latin. One part of his work was translated into Latin by Gerardo de Cremona at the Toledo School of Translators (second half of the twelfth century). Razés was known by his differentiation of small pox and measles, and also by the introduction of the mercurial ointment.

Avicenna (Ibn Sina) was another famous Arabic scientist. Avicena was a follower of Galen, whose ideas he developed. He wrote the *Canon Medicinae* compendium of both Greek and Arabic medicines, where he describes the use and efficacy of about 750 drugs arranged alphabetically. The *Canon Medicinae*, one of greatest encyclopedic medical texts ever written, was translated to Latin by Gerardo de Cremona at the Toledo School of Translators and is preserved in the El Escorial Monastery Library. The influence of the thinking of Avicenna (980–1037) ensured the perpetuation of Galen’s medical “doctrinal” so disastrous to the progress of the medical sciences. Another Arabic scientist of this period was Abulcasis (Abu al-Qasim al-Zahrawi, 936–1013) born in Medina-Zahara near Córdoba, who wrote the medical encyclopedia *al-Tasrif*. One part is devoted to surgery; it was translated to Latin by the Toledo School of Translators and became a text in the European Medical Schools in the High Middle Age. Another part is devoted to the therapy and practice of pharmacy where rudimentary physicochemical procedures such as distillation or sublimation and pharmaceutical formulations are described. The 28th volume *Liber Servitoris de praeparatione medicinarum simplicium* describes about 1500 drugs of which about 400 are Arabic contributions to Pharmacy. It was printed in Venice in 1471 as *Liber Servitoris*.

In the Arabian apothekes, plants and drugs were shown, outside, at the door, and in many cases formulations were elaborated publicly. The apothekes had books with protocols for the elaboration of galenical remedies. Most of these protocols, called “akrabâdin” (*grabadin* in Latin) would become the embryo of the future pharmacopoeias.

As a conclusion, it must be noticed that the Iberian Peninsula has been the place where the exchanges between two great cultures took place – the Christian world
and the Arab civilization. Throughout the Iberian Peninsula, especially during the Córdoba Caliphate Arabic alchemist science passed to the West.

Also, we must not forget the role of Benedictine abbeys in the preservation of Greco-Latin texts (Figure 1.3).

Box 1.1: The Salerno School – Arabian Medicine in Europe

At the end of the sixth century, Benedictine monks set up a hospital in Salerno, and gradually this hospital became a famous scholastic center for medical learning in Europe during the eleventh and twelfth centuries. The great splendor of this school was reached in the ninth century with the arrival (from Tunisia) of Constantinus Africanus who translated to Latin a vast number of Arabic texts. Most of his translation work took place at the nearby Benedictine monastery of Monte Casino where he came to reside. The main work made in this School was the Antidotarium, which was translated into European languages as well as into Arabic. It was one of the first drug formularies to be printed in Venice in 1471 after Gutenberg’s development of the printing press. Constantinus introduced mercurial ointment in the treatment of skin diseases – a formulation that centuries later came to be used on syphilitic venereal lesions. Following the arrival of Constantinus, the Salerno School became greater than others because he did not stop at accepting Arab writings, but also created his own science critically fusing the Greco-Latin and Arabian cultures.
1.1.3

Discovery of America

The discovery of America by the Spanish meant the incorporation of new drugs into the armamentarium of those times. The first American universities to be founded were Mexico (1551) and Lima (1551). Previously, in 1536, the Colegio Mayor of Tlatelolco was founded (near Mexico, today inside of this city) “for the education of noble Indians.” A student of the College christened Martin de la Cruz, an Indian doctor and expert in medicinal plants, transmitted his knowledge to a native Professor named Juan Badiano, who translated it directly from Nahua to Latin and simultaneously drew images of hundreds of plants. Under the title of *Libellus de Medicinabolus Indorum Herbis*, the *Codex Badianus* remained ignored for centuries at the Cardinal Barberini Library in the Vatican (Rome). In 1929, it was rediscovered by researchers from Johns Hopkins University (Baltimore), translated into English (by Dr. Emily M. Emmart), and published as the *Badianus Manuscript* [3].

The voyages of discovery were opening new ways and new routes to the study and knowledge of New World plants. The first reports were not supplied by specialists but by monks such as Fray Bernardino de Sahagún, politicians such as the Viceroy Fernández de Oviedo, and military men such as Cieza de Leon. Fernández de Oviedo y Valdés, Viceroy of Mexico, sent a report of medicinal plants from Mexico to King Charles V of Spain. This report was later published in Toledo in 1622 as *Historia Medicinal de las Indias Occidentales*. The physician Nicolas Monardes, without traveling to the New World, published in Seville a detailed book with a long title: *Medicinal de las cosas que se traen de nuestras Indias Occidentales* (A book on the things brought from our West Indies that are used in medicine). This book appeared in several editions (1565, 1569, and 1574), and was translated into Latin, French, and English.

The monk Fray Bernardino de Sahagún was one of the first professors of Tlatelolco’s College who traveled all over the territory of Nueva España (New Spain) (today, the national territory of Mexico and the southwestern part of the United States). The *Historia de las Cosas de la Nueva España* is a monumental work where all aspects of pre-Columbian civilizations, including medicinal plants, are detailed. The information system of this ancient scholar of the University of Salamanca is outstanding. For years Sahagún collected thousands of anthropological, ethnological, and ecological data and news regarding the native Indians and their life conditions, distributed in more than 100 races and cultures of New Spain’s territory. *La Crónica del Peru* by Pedro Cieza de Leon, published in Seville in 1533, is worth mentioning because of its scientific completeness and historic rigor. It is not limited only to Peru but comprises also southwestern territories. Each chapter is a masterpiece of narrative where the costumes and

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2) In 1964, under the direction of Professor Efren del Pozo, a Spanish edition of the *Codex Badianus* entitled *Codice de Medicina Azteca de la Cruz Badiano* was published by the Instituto Mexicano de Seguridad Social. This manuscript must be considered as the first American Pharmacopoeia or, at least, the first treatise of pharmacognosy of the American continent based on indigenous knowledge.
lifestyles of the Incas and other native Indians are thoroughly and meticulously detailed.

Unlike his father Charles V, King of Spain Philip II recognized the importance that the discovery of the New World would have and sent a Commission to Mexico heralded by his doctor Francisco Hernández. This royal commission worked between 1571 and 1577, and may be considered the first scientific expedition of the modern era. The monumental work of Hernández is devoted to the study and description of more than 4000 medicinal plants of New Spain’s territory. The work was brought to Spain and preserved at the El Escorial Monastery Library. Hernández died without seeing his work published. There, Nardo Antonio Recchi (or Reccho) made a summary of the work, which was published in Rome as Rerum Medicarum Novae Hispaniae Thesaurus (Figure 1.4). The extract elaborated by Reccho only describes 412 plants. Hernández’s original work was partially lost after a fire in the El Escorial Library in 1671; the volumes not affected by the fire were published later (1790) as Historia Plantarum Novae Hispaniae (2900 plants).

1.1.4 The Renaissance

With the Renaissance, absolute true thoughts were in doubt, and figures such as Copernicus and Vesalio began to appear with essential questions for scientific thought. The Swiss physician, Philippus Teophastrus Bombastus von Hohenheim (1493–1541), who later called himself Paracelsus, was the son of a doctor and spent his youth in Einsiedeln (Switzerland). He studied arts and medicine, and traveled all over Europe where he practiced medicine as an itinerant doctor. Paracelsus introduced metal salts in medicine, particularly those of mercury for the treatment of syphilis and antimony in cure-all elixirs. He introduced distilled oils as remedies. With Paracelsus, opium became widely known throughout Europe. He incorporated it in his formulations and increased its range of applications, although without therapeutic bases. Paracelsus developed the concept of dose dependency for drug action and toxicity (‘’sola dosis facit venenum’’). Paracelsus was a controversial figure with a very advanced vision for his time. His “iatrochemistry” – therapeutics with elements – was the predecessor of current chemical therapeutics.

Valerius Cordus (1514–1544) was a German botanist who came to be Docent (an academic appointment) in Wittenberg, where, for some years, he gave lectures on Dioscorides. He was extremely interested in botany, and made long excursions by foot in Germany studying plants, animals, and minerals. In 1542, he went to Italy to continue his studies in botany, but his botanical activities in the malarial region cost him his life when he was only 29 years old. He wrote a Dispensatorium Pharmacophorum, but died before the book was printed. In 1546, the book was finally published by the senate of the city of Nürnberg. In 1760, an English physician, Thomas Sydenham (1624–1689), introduced the
Figure 1.4 Francisco Hernández’s work. Cover of Rerum Medicarum Novae Hispaniae Thesaurus (Historic Complutense University of Madrid Library).
1.1 Antiquity

formulation known as “laudanum” (i.e., tincture of opium) in Europe, which incorporates opium together with other ingredients, such as cinnamon, clover, and saffron, in Spanish wine. This formulation, “Sydenham’s Laudanum,” with variable dosages, was used widely by European doctors until the mid-nineteenth century.

1.1.5

Nineteenth Century

Most of the drugs used before 1800 were prepared with water- or water/alcohol-based plant extracts as tinctures, decoctions, infusions, and so on. Some of them were highly efficacious (or toxic). However, none of them could fit a chemical definition of what today represents scientifically a drug. Their exact chemical identity was unknown (Table 1.1). It was necessary to wait for the breakthroughs of chemical and biological sciences, which were opening the way toward the isolation, chemical characterization, analytical determination, and dosage of the active principles of these plant extracts.

In the nineteenth century, with the development of organic chemistry and chemical analysis the door toward the isolation and characterization of numerous active plant principles was opened. The great discovery that launched the first generation of drugs was the isolation of morphine from opium in 1806 by Sertürner, a student in practice in a pharmacy of Paderborn (Westfalia, Germany). Sertürner, 20 years old, was the first investigator to use chemical methods to isolate an active plant principle, morphine, and to make pharmacological studies in animals, in this case dogs. Examining opium during his apprenticeship, he was able to isolate an organic compound, meconic acid (Greek mekon = poppy), which was not active when tested in dogs, but the alkanization of mother liquors with ammonia caused the precipitation of a substance, a weak base, that he crystallized from alcohol. (The crystals were probably a mixture of morphine and narcotine.) Since it induced sleep in dogs, Sertürner supposed it to be the specific narcotic element of opium (“der eigentliche belaubende Grundstoff”). He named the

<table>
<thead>
<tr>
<th>Ancient Greece</th>
<th>America (1500 AD)</th>
<th>China (BC)</th>
<th>Europe (1700s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opium (<strong>Papaver somniferum</strong>)</td>
<td>Cinchona bark (Cinchona spp.)</td>
<td>Ma Huang (Ephedra spp.)</td>
<td>Ergot (<strong>Claviceps purpurea</strong>)</td>
</tr>
<tr>
<td>Belladona (<strong>Atropa belladona</strong>)</td>
<td>Coca leaves</td>
<td>–</td>
<td>Foxglove (<strong>Digitalis spp.)</strong></td>
</tr>
</tbody>
</table>

*We could add hemlock (**Conium maculatum**) and mandrake (**Mandragora officinalis**) from ancient Greece as well as curare (**Strychnos spp.**) and ipecacuanha from America.*
Evolution of Drug Discovery

substance morphine, after Morpheus, the Greek God of dreams. By this time, the experimental method of Sertürner was applied successfully to different drugs; between 1820 and 1850 numerous compounds and active principles were isolated and evaluated for medicinal application, and many more were to follow.

In Paris, in 1817, Pierre Joseph Pelletier, Professor at L’Ecole Supérieure de Pharmacie, and Francois Magendie, Professor of Physiology at L’École Supérieure de Medicine, isolated emetine from ipecacuanha root (ipecacuanha, Portuguese word) – a drug that occurred mainly in Brazil (Matto Grosso) and Peru. This drug was used by natives in the treatment of amoebic dysentery (Figure 1.5). In the search for other plant basic (alkaline) compounds, French pharmacists Dr. Pierre Joseph Pelletier and his associate Joseph Bienaimé Caventou isolated a convulsant poison from the seeds of the small Indian tree Strychnos nux vomica, strychnine, which became a tool in Magendie’s study of reflex activity in the spinal cord. In 1820, Pelletier and Caventou isolated quinine as a sulfate from cinchona bark (Section 4.1.4.1). (Previously, the Portuguese Bernardo Gomes had obtained crystals of cinchona by extracting the powdered bark with diluted alkali and neutralizing it with alkali). In 1826, in their pharmacies in Paris, Pelletier, and Caventou produced 1800 kg of pure crystalline, quinine sulfate by processing 150 ton of imported cinchona bark. Historically, this was the first commercial natural product to be produced and the process might be considered as the embryo of that would become, in the not too distant future, a factory – the first pharmaceutical industry. Very soon, factories in other European countries were established. The first one was established by Emmanuelle Merck (1794–1855) in Darmstadt (Germany). Merck transformed his family’s seventeenth century apothecary into the manufacturing apothecary E. Merck, which produced alkaloids and other medicinal chemical products not only in bulk, but also as pharmaceutical presentations such as pills, powders, syrups, and so on. In 1848, his son isolated papaverine from mother liquors of the crystallization of morphine.

With the isolation of pure alkaloids and other plant principles as well as the preparation of synthetic pure organic chemicals it was possible to study and to examine systematically their effects by using accurately measured quantities. This process of quantitative experimentation led to the establishment of pharmacology as a science, as an independent scientific discipline. The beginning of pharmacology as a science can be traced back to France early in the nineteenth century with the works of Francois Magendie (1783–1855) and his disciple Claude Bernard (1813–1878). Both were convinced of the importance of using experimental methods and,

3) Sertürner was not an academic and published his work in the journal Pharmacie für Aerzte und Apotheker (1806) – a journal read in Germany mainly by apothecaries, and its importance was not recognized until 10 years later. It was rediscovered by the French chemist Gay-Lussac, who immediately translated it into French and republished it in the prestigious Annales de Chimie – the journal founded by the great Lavoisier. Gay-Lussac wrote an editorial in this issue to accompany the translation of Sertürner’s paper stating the significance of the discovery of a salt-forming organic plant alkali analogous to the common organic acids, and encouraged French professors and researchers to work on the isolation of the active principles of plants.
influenced by the development of organic chemistry, extended their work to studying the physiological effects of certain alkaloids. Their teachings gave a strong impetus to the young discipline. Magendie, physician at the Paris hospitals, first at the Salpêtrière, and then at the Hôtel-Dieu, was also, from 1831, Professor of Medicine at the College of France. Magendie was the first physiologist to use alkaloids for the treatment of diseases. He wrote a *Formulaire* which was used extensively by doctors in those times (Figure 1.6, left).

However, the great impetus of the new science proceeds from Rudolph Buchheim and Oswald Schmiedeberg, and is a consequence of the scientific thinking and experimental methodologies that were replacing the speculative medicine of the Romanticism. Rudolph Buchheim was a physiologist who, in 1826, was offered the first Chair of Pharmacology ever established at the University of Dorpat in Estonia when he was only 27 years old [4]. Although Dorpat (now Tartu) belonged to Imperial Russia, the professors and the language of instruction were German. In Dorpat, Buchheim displayed great activity. He founded the experimental pharmacology discipline, organized the first laboratory of this discipline, and translated into German Jonathan Pereira’s book *Elements of Materia Medica and Therapeutics*. In 1856, he published a textbook of pharmacology (*Lerhbuch der Arzneimittelkunde*). Some years later, in 1869, he and Oskar Liebreich discovered the hypnotic properties of chloral hydrate, which had been previously prepared by chlorination of the absolute alcohol by Justus von Liebig. Schmiedeberg may be considered the father of pharmacology. He became Buchheim’s successor at Dorpat and stayed there until 1872 when he moved to Strasbourg to create his magnificent Institute of Pharmacology. At that time, Strasbourg, the former French
city, capital of Alsace, belonged to Germany (after the Franco-Prussian war Alsace and Lorraine were returned to Germany as Reichsland von Elsass-Lothringen). The University of Strasbourg became one of the stars of the world’s German universities. In Strasbourg, in 1883, Schmiedeberg published the first edition of the *Grundriss der Pharmakologie* (Textbook of Pharmacology), a textbook that soon became a classic (Figure 1.6, right) and, together with the medical clinician Bernhard Naunyn, founded the journal *Archiv für experimentelle Pathologie und Pharmakologie* (currently *Naunyn-Schmiedeberg’s Archives of Pharmacology*) as well as the famous Institute of Pharmacology. Schmiedeberg had a great influence on the development of pharmacology as a science. In fact, he may be considered the most prominent pharmacologist of his time. Numerous disciples from about 20 different countries were trained in his Institute; many of them became professors of pharmacology in their own countries.

In the mid-nineteenth century, pharmacy began to undergo numerous transformations as a consequence of the introduction of new pharmaceutical forms such as gelatin capsules (Mothes, 1883) or tablets (Brockedon, 1843). In 1853, Charles Pravaz invented the hypodermic syringe, which has since undergone numerous modifications. In the last third of the nineteenth century, once the conditions of preparation of solutions for injection had been adequately studied, elaborated, and perfectly established, injections, were introduced as a new pharmaceutical form.

The chronology of isolation (or discovery) of some medicinal alkaloids is summarized schematically in Figure 1.7.
1.2 Great Periods of Drug Discovery

Broadly speaking, the history of innovation and discovery of drugs can be divided into two great periods (Figure 1.8). During the first period, which begins at the beginning of the nineteenth century and ends toward 1930, the scientific method is aimed at isolating and purifying natural products, obtaining new compounds by chemical synthesis, and studying their physiological properties. During this period, two generations of drugs were introduced: between 1820 and 1880, alkaloids and
some inorganic and organic products were introduced, and second-generation drugs such as vaccines, serums, analgesics, antipyretics, hypnotics, or antiprotozoa can also be included. It is in this period when the birth of pharmaceutical (medicinal) chemistry could be defined, when Dr. Paul Ehrlich demonstrated that infectious disease can be treated (and cured) with drugs and postulated the receptor concept – one of the masterpieces of scientific thought on drug research. The discovery of prontosil in 1932–1935 can be considered the inflexion point of the second period.
The second period, the Golden Age of drug discovery, begins in 1935–1940, at the dawn of World War II. It starts around 1930 with the introduction of vitamins, hormones, sulfonamides, antibiotics, and their derivatives. This generation of drugs revolutionized the structure and practice of the pharmaceutical industry. It was followed by two more generations. In the fourth generation (1960–1980) we can include, among others, semisynthetic antibiotics, central nervous system agents (psychopharmacological agents), autonomous nervous systems agents ($\beta$-blockers), and cardiovascular agents (diuretics, antihypertensive agents). Finally, in the fifth generation, where we are now, we would include enzyme inhibitors (angiotensin-converting enzyme inhibitors, cyclooxygenase inhibitors, enzyme inhibitors against virus and cancer), biotechnologically derived drugs, and so on.4)

1.3 Vaccines

The best and cheapest way to prevent an infectious disease is by getting immunized against it. Rudimentary vaccination has been an old concept in ancient civilizations. It appears that in China and India the practice of variolation, where small quantities of material from disease pustules were used to immunize people against smallpox, was practiced before 1000 BC.5) Thanks to vaccines, people managed to stop the epidemics that have been a constant for mankind. The epidemics, together with their disasters and miseries, have marked the evolution of our society. Currently, about a dozen vaccines are used to prevent diseases that had once caused thousands of deaths (e.g., cholera, typhus, smallpox, diphtheria, tetanus, poliomyelitis, measles, and so on). Vaccines are suspensions of killed or weakened (attenuated) microorganisms whose ability to produce disease has been eliminated or highly reduced, but which trigger the generation of antibodies able to neutralize not only the vaccine antigens, but also those produced by microorganisms responsible for the disease. The immunization is active when the vaccine contains killed or attenuated microorganisms that are administered as a suspension – the body produces its own antibodies. The immunization is passive when the administered antibodies

4) A comprehensive review of drug discovery with the names of researchers, dates, and indications of times of isolation, in tabular format, is given by Professor Alfred Burger in the 4th edition of *Burger’s Medicinal Chemistry*, edited by Professor M. E. Wolf and written by 82 experts (Part I, Wiley Interscience, New York, 1980, Chapter 1: Introduction: history and economics of medicinal chemistry.) This revision has over 1300 references and was probably the material used by Professor Burger to produce the basic book *A Guide to the Chemical Basis of Drug Design* (Wiley Interscience, New York, 1983). In only 300 pages, Professor Burger paved the path for the chemistry of drug discovery. As Dr. Miguel A. Ondetti reports in comments about this book [7], “this herculean task is so awesome that only Professor Burger could succeed at it.” It has been documented that the first smallpox vaccination procedure was prevalent in China in the sixteenth century and traces it origin possibly as early as 1000. The method of prophylaxis predates Jenner’s discovery of cowpox lymph in 1798 by about 300 years. There are plausible arguments about how the Turks could have learned about the procedure from the Chinese via the Silk Road and passed it on to England [2].
are preformed in factories, such as in animals (as in the past, horse serum) or human donors instead of microorganisms. A donor who has had a specific disease donates blood and an immunoglobulin is isolated from the blood plasma. This is then administered by injection.

The words vaccine and vaccination come from the word “cow” (Latin vacca) and they were introduced by the English physician E. Jenner (1749–1823) who discovered the smallpox vaccine. Jenner’s famous experiment is well known. Farmers were aware of the fact that smallpox could be transmitted from cows to people who milked them, but when there was a smallpox epidemic these people remained immune or rarely fell ill. By skin scarification, Jenner inoculated an 8-year-old boy with the exudates from the smallpox pustule of a woman who milked cows and who had been infected with smallpox from these animals (“cowpox”). After a few weeks, he inoculated him with the exudates again, but this time from the pustule of human smallpox, and the child did not fall ill.

By the end of the nineteenth century, smallpox alone would kill 400,000 people a year in the Old World.
Later, in 1870, Louis Pasteur discovered that a severe form of a disease could manifest itself in a mild form if the microbe that produces it is attenuated and this mild form could be used as an immunization agent, such as a vaccine to prevent the disease. This vaccine contains cellular and surface antigens ("epitopes") of microorganisms, which stimulate the production of antibodies in the body, neutralizing those antigens. Pasteur applied this principle to the preparation of various vaccines: anthrax, rabies, cholera. This went a long way to saving thousands of lives (Figure 1.9) [5].

**Figure 1.9** Landmarks of vaccine introduction in the last century. In 1881, sheep, cows, and one goat were immunized against anthrax by Louis Pasteur, Emile Roux, and Charles Chamberland. The Spanish bacteriologist Jaime Ferrán (1852–1929), who had worked under Pasteur, prepared a vaccine against cholera with attenuated viruses. As this vaccine caused a strong reaction; it was abandoned and replaced by Haßkine's vaccine prepared with viruses killed by heat. The Hindi bacteriologist Waldemar Haßkine (1860–1930) was another of Pasteur's disciples.

*Working with pure cultures of the *Diphtheria bacillus* in Pasteur's Laboratory, in 1888, Emile Roux (1853–1933) and Alexander Yersin (1863–1943) isolated the toxin that causes diphtheria (a soluble product in a culture of diphtheria bacilli). In 1891, Emil von Behring (Nobel Laureate for Medicine, 1901) in Berlin, in Koch’s Laboratory, established that the disease could be prevented in animals by immunization with crude diphtheria toxin (isolated from cultures and injected in less than lethal doses). Blood serum taken from such animals could be used to treat infection in unprotected animals. In 1894, by injecting horses with attenuated toxins, Emile Roux obtained horse diphtheria serum antitoxin. The Pasteur Institute (established by public subscription in Paris in 1888) and the Lister Institute (established in London in 1891) were among the first to manufacture the diphtheria antitoxin. In Germany, it was produced by Meister, Lucius, and Brunning at their Hoechst factory. In the United States, by the New York State Board of Health (1894) followed by the US Marine Hospital Service, in Washington. In Spain, in 1894, by the Instituto Llorente. Dr. Llorente had worked with Roux at the Pasteur Institute in Paris.

**Live Bacillus Calmette–Guérin (BCG) is an attenuated culture of the Calmette and Guérin strain of *Mycobacterium tuberculosis* bovis. BCG induces a granulomatous reaction at the site of administration. Currently, it is indicated for the *in situ* treatment of urinary bladder carcinoma.

***Toxoids are inactivated vaccines used to initiate active immunity. They have lost their toxicity but still retain the ability to stimulate the production of antitoxin (antibody). Usually, the inactivation is produced by treatment with formaldehyde solutions (e.g., formalin). The currently used diphtheria toxoid was introduced by the French bacteriologist Gaston Ramon in 1923. It is produced by formaldehyde treatment of *Corynebacterium* filtrates (formalin 0.3%, 3 weeks at 37°C) and subsequent treatment with aluminum phosphate or hydroxide, where it remains adsorbed. Gaston Ramon also developed the antitetanus vaccine, in 1924, consisting of tetanus toxin treated with formaldehyde on heat, which he called "anatoxin" (i.e., toxoid). He also proposed that the efficacy of this anatoxin could be enhanced by using "adjuvants" of immunity, such as aluminum hydroxide, thus creating the first adjuvant vaccine.

****Polio (infantile paralysis). Inactivated polio vaccine (IPV) or Salk vaccine was introduced in 1954. This is a trivalent vaccine (strains 1–3) grown in monkey kidney culture. Trivalent oral polio vaccine (TOPV) or Sabin vaccine was introduced in 1960. This is a live attenuated whole virus vaccine grown in monkey kidney tissue.
Bluevac®. Inactivated monovalent and bivalent vaccines against blue tongue viral disease. Blue tongue is a non-contagious viral disease that can infect most ruminants, sheep being especially susceptible to infection. A virus of the Orbivirus genus causes the disease. It is transmitted by an insect of the genus Culicoides, meaning this disease is closely related to the seasonal presence of the insect. The disease causes heavy losses to farmers and communities as a whole. Blue tongue disease is present on almost all continents and is currently on the rise in northern Europe. (Courtesy of CZ Veterinaria, Porriño, Pontevedra, Spain.)

In the field of veterinary vaccines (Figure 1.10), at the end of the nineteenth century, foot and mouth disease vaccines were among the first veterinary vaccines to be developed. Thanks to the research of Vallée (France), Waldman (Germany), Frenkel (Holland), and Caspick (Great Britain), foot and mouth vaccines began to be produced on an industrial scale from 1950. Between 1950 and 1990, millions of animals were vaccinated in Europe and many other countries worldwide. The reader is referred to the excellent revision of the current status of veterinary vaccines by Dr. N. T. Meusen and other authors [6].

Biotechnology opens up new avenues in vaccine development. The hepatitis B vaccine was the first vaccine to be routinely produced by recombinant DNA technology, in 1986. Basically, the vaccine against hepatitis B virus is prepared by isolation the gene encoding the viral surface protein, hepatitis B surface antigen (HBsAg), and inserting it into an expression vector such as yeast (Saccharomyces cerevisiae). The vaccine (viral surface protein) is then produced on a large scale from the new cell cultures (Section 7.3.5). This recombinant vaccine was approved in 1986 and has no association with human blood or blood products. Previously, in 1981, a vaccine obtained from human donors, carefully selected, had been approved. Given the relevance of hepatitis B, and its major social and economic pathological connotations, it is undoubtedly one of the most outstanding medicines in the last quarter of the twentieth century.

6) Aiptous fever, Fièvre aphteuse, Fiebre aftosa. Another name is glosopeda (from the Greek glossa = tongue and Latin pes, pedis = foot).
1.3.1

Conjugate Vaccines

The inability of children to generate antibodies against the polysaccharide capsule that coats *Haemophilus influenzae* (type b) and *Neisseria meningitidis* made it difficult to produce an effective vaccine against bacterial meningitis. These difficulties were overcome with the technology of conjugate vaccines consisting of an antigen of glucidic nature chemically bound (conjugated) to a support protein, usually non-toxic variants of diphtheria or tetanus toxins. The success of conjugate vaccines for *H. influenzae* (type b) and *Neisseria meningitidis* has allowed extending this technology to the development of a vaccine against *Streptococcus pneumoniae* – a vaccine that covers 80% of the strains of this organism responsible for pneumococcal diseases in European children under 2 years of age.

Currently, several pharmaceutical companies are engaged in the research and development of vaccines against many types of viruses and bacteria. By means of recombinant DNA technology, vaccines against human papillomavirus that causes cervical cancer have been developed and marketed as *Gardasil®* by Sanofi Pasteur MSD (approved in 2006) and *Cervarix®* by GlaxoSmithKline (approved in 2007).

New strategies are to follow.

Immunization of an individual against pathogenic viruses may be achieved using new strategies consisting of the use of viral vectors designed to give to the immune system the proteins of pathogenic viruses. This system triggers an immune response equivalent to that produced in a normal infection by a virulent agent, but no pathogenesis is associated with the pathogenic agent. The experimental use of oral vaccination against rabies of wild animals showed that vaccines with the recombinant virus vaccinia may have considerable potential for vaccination against other viral infections.

In 1992, a new approach was introduced in the field of vaccination. This relates to vaccines consisting of DNA instead of proteins. In this case, the DNA is a plasmid containing a viral gene that encodes for the synthesis of an immunogenic viral protein and can be expressed inside the cell. Research and development in this field is novel, and its future is still uncertain. Most of the studies have been carried out in animals and there is still a long way to go before their application in humans.

References

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of 1552, Johns Hopkins University Press, Baltimore.


Further Reading
