

APPENDIX 1

HISTORY OF DRUG DISCOVERY AND DEVELOPMENT

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A1.1 EARLY HISTORY OF MEDICINE

Drug discovery and development has a long history and dates back to the early days of human civilization. In those ancient times, drugs were not just used for physical remedies but were also associated with religious and spiritual healing. Sages or religious leaders were often the administrators of drugs. The early drugs or folk medicines were derived mainly from plant products and supplemented by animal materials and minerals. These drugs were most probably discovered through a combination of trial and error experimentation and observation of human and animal reactions as a result of ingesting such products.

Although these folk medicines probably originated independently in different civilizations, there are a number of similarities, for example, in the use

of the same herbs for treating similar diseases. This is likely to be a contribution by ancient traders, who in their travels might have assisted the spread of medical knowledge.

Folk medicines were the only available treatments until recent times. Drug discovery and development started to follow scientific techniques in the late 1800s. From then on, more and more drugs were discovered, tested, and synthesized in large-scale manufacturing plants, as opposed to the extraction of drug products from natural sources in relatively small batch quantities. After World War I, the modern pharmaceutical industry came into being, and drug discovery and development following scientific principles was firmly established.

Although pharmaceutical drugs are now widely used worldwide, many ethnic cultures have retained their own folk medicines. In certain instances, these folk medicines exist side by side and are complemented by pharmaceutical drugs.

The following are some snapshot examples of how drugs were discovered from the early human civilizations.

A1.1.1 Chinese Medicine

Traditional Chinese medicine (TCM) is believed to have originated in the times of the legendary emperor Sheng Nong in 3500 BC. The dynasty system and meticulous recording have helped to preserve the TCM scripts of old China. Some important medical writings are *Shang Han Lun* (Discussion of Fevers), *Huang Di Nei Jing* (The Internal Book of Emperor Huang), and *Sheng Nong Ben Cao Jing* (The Pharmacopoeia of Sheng Nong—a legendary emperor). Exhibit A1.1 relates a legend about the discovery of a herb for treating injuries.

The Chinese pharmacopoeia is extensive. Some of the active ingredients from Chinese herbs have been used in Western drugs; for example, reserpine

Exhibit A1.1 A Legend about San Qi

Chinese legend describes the story of the emperor Sheng Nong, who one day tried to kill a snake by beating it. The snake returned a few days later, apparently none the worse after the beating. He beat it again and left it mortally injured. Again, the snake returned several days later. This time, after the beating, he observed that the snake crawled back into the bush and ate a plant material. This plant is now called San Qi (*Panax notoginseng*) and is used for treating external injuries. It is an ingredient for the well-known TCM herbal formula known as Yunnan Bai Yao.

Source: Reid D. *Chinese Herbal Medicine*, Shambhala Publications, Boston, 1996.

from *Rauwouofia* for antihypertensive and emotional and mental control, and the alkaloid ephedrine from *Mahuang* for the treatment of asthma.

A1.1.2 Egyptian Medicine

Ancient papyrus provided written records of early Egyptian medical knowledge. The Ebers papyrus (from around 3000 BC) provided 877 prescriptions and recipes for internal medicine, eye and skin problems, and gynecology. Another record, from the Kahun papyrus of around 1800 BC, detailed treatments for gynecological problems. Medications were based mainly on herbal products such as myrrh, frankincense, castor oil, fennel, sienna, thyme, linseed, aloe, and garlic.

A1.1.3 Indian Medicine

The Indian folk medicine, called Ayurvedic medicine, can be traced back 3000–5000 years and was practiced by the Brahmin sages of ancient times. The treatments were set out in sacred writings called Vedas. The material medica are extensive and most are based on herbal formulations. Some of the herbs have appeared in Western medicines, such as cardamom and cinnamon. Susruta, a physician in the fourth century AD, described the use of henbane as antivenom for snakebites.

A1.1.4 Greek Medicine

Some of the Greek medical ideas were derived from the Egyptians, Babylonians, and even the Chinese and Indians. Castor oil was prescribed as a laxative; linseed or flaxseed was used as a soothing emollient, laxative, and antitussive. Other treatments include fennel plant for relief of intestinal colic and gas, and asafetida gum resin as an antispasmodic. The greatest Greek contribution to the medical field is perhaps to dispel the notion that diseases are due to supernatural causes or spells. The Greeks established that diseases result from natural causes. Hippocrates, the father of medicine, at about 400 BC is credited with laying down the ethics for physicians. Exhibit A1.2 describes the mythology of Asclepius, the Greek God of Medicine.

A1.1.5 Roman Medicine

As great administrators, the Romans instituted hospitals, although these were used mainly to cater to the needs of the military. Through this work, organized medical care was made available. The Romans also extended the pharmacy practice of the Greeks. Dioscorides and Galen were two noted physicians in Roman days. Dioscorides's *Materia Medica* contains descriptions of treatments based on 80% plant, 10% animal, and 10% mineral products.

Exhibit A1.2 Asclepius: Greek God of Medicine

In Greek mythology, Asclepius, the god of medicine, studied medicine under Chiron. He excelled over Chiron, and his medical skills were reputed to be able to bring back the dead. This incurred the wrath of Pluto, the god of the underworld, and the envy of other gods. They complained to Zeus, who also thought that he alone should have the power of life and death. Zeus slew Asclepius with a thunderbolt. However, Asclepius's daughters, Panacea and Hygeia, survived and carried on to tend to the sick.

Source: Leadbetter R. *Asclepius*. <http://www.pantheon.org/articles/a/asclepius.html> [accessed May 31, 2001].

A1.2 DRUG DISCOVERY AND DEVELOPMENT IN THE MIDDLE AGES

The Middle Ages, from around AD 400 to 1500, witnessed the decline of the Roman influence. This was also the time when plagues scourged many parts of Europe. Diseases such as bubonic plague, leprosy, smallpox, tuberculosis, and scabies were rampant. Many millions of people succumbed to these diseases.

A1.2.1 The Early Church

There are some references to herbs in the Bible. However, the Church's main contribution to medicines is the preservation and transcription of Greek medical manuscripts and treatises. This enabled the knowledge developed in the ancient times to be continued and later used in the Renaissance period.

A1.2.2 Arabian Medicine

Through trade with many regions, the Arabians learned and extended medical knowledge. Their major contribution is perhaps the knowledge of medical preparations and distillation methods, although the techniques were probably derived from the practices of alchemists. Avicenna, around AD 900–1000, recorded a vast encyclopedia of medical description and treatment. Another noted physician was Rhazes, who accurately described measles and smallpox.

A1.3 FOUNDATION OF CURRENT DRUG DISCOVERY AND DEVELOPMENT

The Renaissance period laid the foundation for scientific thoughts in medicinal preparations and medical treatments. There were many advances made in

Exhibit A1.3 Edward Jenner's Smallpox Vaccine

In the late 1700s, Jenner heard that people who worked with cattle and had caught the cowpox disease (a mild disease related to smallpox) were immune and never caught smallpox. In 1796, he proceeded to inoculate a boy using the fluid from the blister of a woman with cowpox. The boy developed cowpox. Two months later, Jenner inoculated the boy with fluids from the blister of a smallpox sufferer. The boy became immune and did not get smallpox.

Through his work, Jenner invented vaccination and saved many lives. However, in today's regulatory control, Jenner's method would not have been approved.

Source: BBC. *Medicine Through Time, Edward Jenner (1749–1823)*. <http://www.bbc.co.uk/education/medicine/nonint/indust/dt/indtbi2.shtml> [accessed May 25, 2002].

anatomy, physiology, surgery, and medical treatments, including public health care, hygiene, and sanitation.

A1.3.1 Smallpox

In 1796, Edward Jenner successfully experimented with smallpox inoculations (Exhibit A1.3). This paved the way for the use of vaccination against some infectious diseases.

A1.3.2 Digitalis

In the late 1700s, William Withering introduced digitalis, an extract from the plant foxglove, for treatment of cardiac problems.

A1.3.3 Scurvy

John Hunter (1768) noted that scurvy was caused by the lack of vitamin C. He prescribed the consumption of lemon juice to treat scurvy.

A1.3.4 Rabies

Louis Pasteur (1864) discovered that microorganisms cause diseases, and he devised vaccination against rabies. This was achieved through the use of attenuated rabies virus.

A1.4 BEGINNINGS OF MODERN PHARMACEUTICAL INDUSTRY

Despite the advances made in the 1800s, there were only a few drugs available for treating diseases at the beginning of the 1900s:

- *Digitalis*: Extracted from a plant called foxglove, digitalis stimulates the cardiac muscles and was used to treat cardiac conditions.
- *Quinine*: Derived from the bark of the Cinchona tree, quinine was used to treat malaria.
- *Ipecacuanha*: Extracted from the bark or root of the Cephaelis plant, ipecacuanha was used to treat dysentery.
- *Aspirin*: Extracted from the bark of willow tree, aspirin was used for the treatment of fever.
- *Mercury*: This was used to treat syphilis.

More systematic research was being performed to discover new drugs from the early 1900s.

Paul Ehrlich used an arsenic compound, arsphenamine, to treat syphilis. Gerhard Domagha found that the red dye Prontosil was active against streptococcal bacteria. Later, French scientists isolated the active compound to be sulfanilamide, and this gave rise to a new range of sulfa drugs against hosts of bacteria.

A1.4.1 Penicillin

In 1928, Alexander Fleming discovered that *Penicillium* mold was active against staphylococcus bacteria. Ernst Chain rediscovered this fact some 10 years later, when he collaborated with Howard Florey. By 1944, large-scale production of penicillin was available through the work of Howard Florey and Ernst Chain. This work foreshadowed the commencement of biotechnology, where microorganisms were used to produce drug products. A description of the discovery and large-scale manufacturing of penicillin is given in Exhibit A1.4.

A1.5 EVOLUTION OF DRUG PRODUCTS

In the early days, until the late 1800s, most drugs were based on herbs or extraction of ingredients from botanical sources.

The synthetic drugs using chemical methods were heralded at the beginning of the 1900s, and the pharmaceutical industry was founded. Many drugs were researched and manufactured, but mostly they were used for therapeutic purposes rather than completely curing the diseases.

From the early 1930s, drug discovery concentrated on screening natural products and isolating the active ingredients for treating diseases. The active ingredients are normally the synthetic version of the natural products. These synthetic versions, called new chemical entities (NCEs), have to go through many iterations and tests to ensure they are safe, potent, and effective.

Exhibit A1.4 The Development of Penicillin

In the 1930s, Howard Florey and Ernst Chain worked with a team of scientists at Oxford University in Britain. Ernst Chain discovered an earlier paper by Alexander Fleming on the antibacterial properties of penicillin.

The Florey–Chain team’s investigation showed that penicillin interferes with the cell wall of bacteria. Bacteria cells ruptured instead of continuing to grow. In 1938, their animal test, on eight mice given lethal doses of infectious bacteria, showed stunning results. The four mice with penicillin survived, whereas four controls with no medication died. Their first human patient who suffered from infection showed early improvement with penicillin, but died subsequently when the stock of penicillin was exhausted.

The team worked on the technology for large-scale production of penicillin. Commercial quantities were available before the end of World War II and saved millions of lives, especially soldiers wounded in the war.

Source: Torok S. *Howard Florey—The Story: Maker of the Miracle Mould*. <http://www.abc.net.au/science/slab/florey/story.htm> [accessed June 2, 2002].

In the late 1970s, development of recombinant DNA products utilizing knowledge of cellular and molecular biology commenced. The biotechnology industry became a reality.

The pharmaceutical industry, together with the advances in gene therapy and understanding of mechanisms of causes of diseases, and the research results from the Human Genome Project have opened up a plethora of opportunities and made possible the development and use of drugs specifically targeting the sites where diseases are caused.

A1.6 FURTHER READING

Smith CG, O’Donnell JT, eds. *The Process of New Drug Discovery and Development*, 2nd ed., Informa Healthcare, 2006.

The Next Pharmaceutical Century: Ten Decades of Drug Discovery, 2007. <http://pubs.acs.org/journals/pharmcent/Ch10.html> [accessed September 29, 2007].