Chapter 1

Introduction

1.1 Medicinal Chemistry Folklore

Medicinal chemistry is the science that deals with the discovery and design of new therapeutic chemicals and their development into useful medicines. Medicines are substances used to treat diseases. Drugs are molecules used as medicines or as components in medicines to diagnose, cure, mitigate, treat, or prevent disease. Medicinal chemistry may involve isolation of compounds from Nature or the synthesis of new molecules, investigations of the relationships between the structure of natural and/or synthetic compounds and their biological activities, elucidations of their interactions with receptors of various kinds, including enzymes and DNA, the determination of their absorption, transport, and distribution properties, and studies of the metabolic transformations of these chemicals into other chemicals and their excretion. More recently, genomics, the investigations of an organism’s genome (all of the organism’s genes) to identify important target genes and gene products (that is, proteins expressed by the genes), and proteomics, the investigations of new proteins in the organism’s proteome (all of the proteins expressed by the genome) to determine their structure and/or function often by comparison with known proteins, have become increasingly important approaches to identify new drug targets.

Medicinal chemistry, in its crudest sense, has been practiced for several thousand years. Man has searched for cures for illnesses by chewing herbs, berries, roots, and barks. Some of these early clinical trials were quite successful; however, not until the last 100–150 years has knowledge of the active constituents of these natural sources been known. The earliest written records of the Chinese, Indian, South American, and Mediterranean cultures described the therapeutic effects of various plant concoctions. A Chinese health science anthology called Nei Ching is thought to have been written by the Yellow Emperor in the 13th century B.C., although some believe that it was backdated by the 3rd-century compilers. The Assyrians described on 660 clay tablets 1000 medicinal plants used from 1900–400 B.C.

Two of the earliest medicines were described about 5100 years ago by the Chinese Emperor Shen Nung in his book of herbs called Pen Ts’ao. One of these is Ch’ang Shan, the root
Dichroa febrifuga, which was prescribed for fevers. This plant contains alkaloids that are used even today in the treatment of malaria. Another plant called Ma Huang (now known as Ephedra sinica) contains ephedrine, a drug that raises the blood pressure and relieves bronchial spasms; this herb was used as a heart stimulant, a diaphoretic agent (perspiration producer), and for treatment of asthma, hay fever, and nasal and chest congestion. It is also used today (unadvisably) by some body builders and endurance athletes because it promotes thermogenesis (the burning of fat) by release of fatty acids from stored fat cells, leading to quicker conversion of the fat into energy. Ephedra also tends to increase the contractile strength of muscle fibers, which allows body builders to work harder with heavier weights.

Theophrastus in the 3rd-century B.C. mentioned opium poppy juice as an analgesic agent, and in the 10th-century A.D. Rhazes (Persia) introduced opium pills for coughs, mental disorders, aches, and pains. The opium poppy, Papaver somniferum, contains morphine, a potent analgesic agent and codeine, which is prescribed today as a cough suppressant. The East Asians and the Greeks used henbane, which contains scopolamine (truth serum) as a sleep inducer. Inca mail runners and silver miners in the high Andean mountains chewed coca leaves (cocaine) as a stimulant and euphoric. The antihypertensive drug reserpine was extracted by ancient Hindus from the snakelike root of the Rauwolfia serpentina plant and was used to treat hypertension, insomnia, and insanity. Alexander of Tralles in the 6th-century A.D. recommended the autumn crocus (Colchicum autumnale) for relief of pain of the joints, and it was used by Avrienna (11th-century Persia) and by Baron Anton von Störck (1763) for the treatment of gout. Benjamin Franklin heard about this medicine and brought it to America. The active principle in this plant is the alkaloid colchicine, which is used today to treat gout.

In 1633 a monk named Calancha, who accompanied the Spanish Conquistadors to Central and South America, introduced one of the greatest herbal medicines to Europe on his return. The South American Indians would extract the cinchona bark and use it for chills and fevers; the Europeans used it for the same and for malaria. In 1820 the active constituent was isolated and later determined to be quinine, an antimalarial drug.

Modern therapeutics is considered to have begun with an extract of the foxglove plant, which was cited by Welsh physicians in 1250, named by Fuchsius in 1542, and introduced for the treatment of dropsy (now called congestive heart failure) in 1785 by Withering. The active constituents are secondary glycosides from Digitalis purpurea (the foxglove plant) and Digitalis lanata, namely, digitoxin and digoxin, respectively, both important drugs for the treatment of congestive heart failure. Today, digitalis, which refers to all of the cardiac glycosides, is still manufactured by extraction of foxglove and related plants.

1.2 Discovery of New Drugs

Nature is still an excellent source of new drugs or, more commonly, of precursors to drugs. Of the 20 leading drugs in 1999, 9 of them were derived from natural products. Almost 40% of the 520 new drugs approved for the drug market between 1983 and 1994 were natural products or derived from natural products. Greater than 60% of the anticancer and anti-infective agents that are on the market or in clinical trials are of natural product origin or derived from natural products. This may be a result of the inherent nature of these secondary metabolites to act in defense of their producing organisms; for instance, a fungal natural product might be produced against bacteria or other fungi or against cell replication of foreign organisms.

Typically, when a natural product is found to be active, it is chemically modified to improve its properties. As a result of advances made in synthesis and separation methods and in
biochemical techniques since the late 1940s, the early random approach to drug discovery (Figure 1.1) was supplanted by a more rational approach, namely, one that involves the element of design. A discussion of how drugs are discovered and chemically modified to improve or change their medicinal properties is presented in Chapter 2. As we will see, the random approach still is important!

1.3 General References

The following references are excellent sources of material for this entire book.

**Journals**

*Annual Reports in Medicinal Chemistry*; *Academic Press, San Diego*

*Current Opinion in Investigational Drugs*

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1.4 References


