CHAPTER

Introduction and historical background

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CHAPTER OUTLINE

1.1 INTRODUCTION

The word "toxicology" is derived from the Greek word "toxicon," which means "poison," and logos, which means to study. Thus, toxicology literally means the study of poisons. It can thus be defined as the "study of poisons that include their physical and chemical properties, detection and identification, biological effects, treatment, and prevention of disease conditions produced by them." It also includes the study of special effects of toxicant developmental toxicity, teratogenicity, carcinogenicity, mutagenesis, immunotoxicity, neurotoxicity, and endocrine disruption.

1.2 HISTORICAL BACKGROUND

1.2.1 ANTIQUITY

The knowledge of poisons is as old as human civilization. Early poisons were almost exclusively plant and animal toxins and some minerals. They were used mainly for hunting. Some were used as "ordeal poisons," such as physostigmine from *Physostigma venenosum* (Calabar bean) and amygdalin from peach pits. Arrow and dart poisons were very popular for hunting animals (and sometimes fellow humans!). Common arrow poisons included strophanthin, aconitine, and extracts from hellebores (a cardiotoxic plant) and történelmi venoms. Since ancient times, people have learned how to protect themselves from the harmful

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effects of plants and animals. They also knew how to use poisons to destroy their enemies. The earliest records are available in the form of ancient books on mythology and legendry, archeological literature, and history books. The Ebers Papyrus (1550 BC) is perhaps the earliest medical record that contains a number of disease conditions and prescriptions; it was previously used in Egyptian medicine. Many of these contain recognized poisons such as aconite, an arrow poison of ancient times, and opium (both as a poison and antidote).

Hippocrates (460–375 BC) is regarded as the "Father of Rational Medicine." The Hippocrates School was formed by a group of physicians to provide an ethical basis for the practice of therapeutics by those who have knowledge of lead, mercury, copper, antimony, and others as poisons and who have some knowledge of their properties. They advocated hot oil as an antidote to poisoning and induced vomiting to prevent absorption of the poisons. Hemlock, which contains the alkaloid coniine, was one of the poisons used during that time. Socrates (470–390 BC) was sentenced to death by hemlock. Theophrastus (371–287 BC), the most dedicated pupil of Aristotle, provided an early treatise on plant poisons. Experimental toxicology perhaps began with Nicander (204–135 BC). Homicidal poisoning has also had a hoary past. One of the earliest laws against the murderous use of poisons was the *Lex Cornelia* passed in Rome in 81 BC.

During AD 40–80, Pedanius Dioscorides, a Greek army physician, classified poisons according to their origin (animal, vegetable, or mineral). His classification of natural substances as being toxic or therapeutic is still valid today. Dioscorides is famous for writing a five-volume book, *De Materia Medica*, that is a precursor to all modern pharmacopeias and is one of the most influential herbal books in history.

1.2.2 MIDDLE AGES

After the fall of the Roman empire, there was a lull in the development of toxicology until 1198, when a famous Swiss Philosopher, Maimonides (Moses ben Maimon) (1135–1204), published his classic work *Treatise on Poisons and Their Antidotes* in 1198, which describes the treatment of poisonings from insects, snakes, and dogs. During the early Renaissance, the Italians, with characteristic pragmatism, brought the art of poisoning to its zenith. The poisoner became an integral part of the political scene. The records of the city councils of Florence, particularly those of the infamous Council of Ten of Venice, contain ample testimony about the political use of poisons. Victims were named, prices were set, and contracts were recorded; when the deed was accomplished, payment was made. An infamous figure of the time was a lady named Toffana, who peddled specially prepared arsenic-containing cosmetics (*Agua Toffana*).

Unfortunately, during this period, poisoning as a method of homicide became increasingly popular in several parts of Europe, particularly Italy and France, where schools actually existed for teaching the art of poisoning. Among the notorious poisoners, Madame Guilia Toffana killed more than 600 people with white arsenic solution called aqua Toffana that was freely sold as a cosmetic in Italy. Toward the end of the 16th century, the wave was spread

from Italy to France, where poisons were commonly used by all classes of society to get rid of enemies or persons considered undesirable. Criminal poisoning continued in many parts of the world during the 18th and 19th centuries.

1.2.3 AGE OF ENLIGHTENMENT

A significant figure in the history of science and medicine in the late Middle Ages was the renaissance man Philippus Aureolus Theophrastus Bombastus von Hohenheim-Paracelsus (1493–1541), who referred to himself as Paracelsus because of his belief that his work was beyond the work of Celsus, a first-century Roman physician who was perhaps the first to promote a focus on toxicon, a toxic agent, as a chemical entity. He recognized the dose–response concept and, in one of his writings, stated: "All substances are poisons, there is none which is not a poison. The right dose differentiates a poison and a remedy." Paracelsus advanced many views that were revolutionary for his time and that are now accepted as fundamental concepts for the field of toxicology. In contrast to previous emphasis on mixtures, he focused on toxicon as a specific primary chemical entity that was toxic. Paracelsus advanced four fundamental concepts:

1. Experimentation is required for examining responses to chemicals.
2. A distinction should be made between the therapeutic and toxic properties of chemicals.
3. The therapeutic and toxic properties are closely related and distinguished by dose.
4. It is possible to ascertain a degree of specificity for chemicals and their therapeutic or toxic effects.

Modern toxicology is a relatively young science based on scientific work performed by numerous dedicated workers. It is the outcome of rational thinking, experimentation, the relationship between dose and therapeutics (as compared with toxic), and the responses to chemicals. Advances made in all allied disciplines contributed to the better understanding of effects of a number of toxicants in humans and animals. Modern toxicology began with Friedrich Serturner (1783–1841), a German pharmacist who isolated the specific narcotic substance from opium and named it morphine after Morpheus, the Roman God of sleep. Subsequently, Mattie Josesph Benaventura Orfila (MJB; 1787–1853), a Spanish physician who is considered the "Father of Toxicology," established toxicology as a discipline distinct from others and defined toxicology as the study of poisons. He advocated the practice of autopsy followed by chemical analysis of viscera to prove that poisoning had taken place. His treatise *Traite des Poisons* published in 1814 laid the foundation for forensic toxicology. In 1829, one of his students, Robert Christison (1797–1882), published a simplified English version titled *A Treatise on Poisons*. The first published work (published in 1848) on clinical toxicology was *A Practical Treatise on Poisons*, written by O. Costill.

Francois Magendie (1783–1855), a pioneer French physiologist and toxicologist, studied the mechanism of action of emetine, morphine, quinine, strychnine,

and other alkaloids, for which he is also called the "Father of Experimental Pharmacology" Magendie passed on his interest to his famous student Claude Bernard (1813–78), who continued to study arrow poisons and used these toxicants to learn more about the mechanism of body functions.

Louis Lewin (1854–1929) was a German scientist who accepted the task of classifying drugs and plants in accordance with their psychological effects. He also published many articles and books dealing with toxicology of methyl alcohol, ethyl alcohol, chloroform, opium, and some other chemicals. His important publications are *Toxicologist's View of World History* and *A Textbook of Toxicology*. Development occurred rapidly in the 20th century with the development of dimercaprol (BAL) as an antidote for arsenic and the discovery of insecticidal properties of DDT by Paul Hermann Muller in 1939. He was awarded a Nobel Prize in 1948 "for his discovery of the high efficiency of DDT as a contact poison against several arthropods."

Gerhard Schrader (1903–90) was a German chemist who accidentally developed the toxic nerve agents serin, tabun, soman, and cyclosarin while attempting to develop new insecticides. Schrader and his team therefore introduced a new class of synthetic insecticides, the organophosphorus insecticides (OP), and defined the structural requirements for insecticidal activity of anticholinesterase (anti-ChE) compounds. He is called the "Father of Nerve Agents."

1.3 MODERN TOXICOLOGY

Toxicology has evolved rapidly during the 1900s. The exponential growth of the discipline can be traced to the World War II era, with its marked increase in the production of drugs, pesticides, synthetic fibers, and industrial chemicals. It also marked the beginning of understanding in-depth the nature and mechanism of the effects of poisons and the invention of their specific antidotes. Along with other sciences, toxicology contributes to the development of safer chemicals to be used as drugs, food additives, pesticides, industrial chemicals, and several other chemicals required for use in everyday life.

Because of the need for an affluent society to protect itself from injurious effects resulting from the introduction of new chemicals, physical agents, and various industrial and consumer products, there has been an expansion of the various facets of toxicology. Therefore, application of the discipline of toxicology to safety evaluation and risk assessment is of utmost importance in today's modern world.

1.3.1 AFTER WORLD WAR II

The mid 1950s witnessed the strengthening of the US Food and Drug Administration's commitment to toxicology under the guidance of Arnold Lehman. Lehman, Fitzhugh, and their co-workers formalized the experimental program for the appraisal of food, drug, and cosmetic safety in 1955, and it was

updated by the US FDA in 1982. The Delaney clause (1958) of these amendments stated broadly that any chemical found to be carcinogenic in laboratory animals or humans could not be added to the US food supply. Regardless of one's view of Delaney, it has served as an excellent starting point for understanding the complexity of the biological phenomenon of carcinogenicity and the development of risk assessment models.

The end of the 1960s witnessed the discovery of TCDD as a contaminant in the herbicide Agent Orange (the original discovery of TCDD toxicity, the "Chick Edema Factor," was reported in 1957). The expansion of legislation, journals, and new societies involved with toxicology was exponential during the 1970s and 1980s and shows no signs of slowing down. Currently, in the United States, there are dozens of professional, governmental, and other scientific organizations with thousands of members and more than 120 journals dedicated to toxicology and related disciplines. As an example of this diversification, one now finds toxicology graduate programs in medical schools, schools of public health, and schools of pharmacy, as well as programs in environmental science and engineering and undergraduate programs in toxicology at several institutions. Surprisingly, courses in toxicology are now being offered in several liberal arts undergraduate schools as part of their biology and chemistry curricula. Some important developments in the field of toxicology are summarized in Table 1.1.

Table 1.1 Some Important Developments in the Field of Toxicology

F. Magendie, 1809: study of "arrowpoisons," mechanism of action of emetine and strychnine
Marsh, 1836: development of method for arsenic analysis
Reinsh, 1841: combined method for separation and analysis of As and Hg
Fresenius, 1845 and von Babo, 1847: development of screening method for general poisons
Stas-Otto, 1851: detection and identification of phosphorus
C. Bernard, 1850: carbon monoxide combination with hemoglobin, study of mechanism of action of strychnine, site of action of curare
Friedrich Gaedcke, 1855: first isolated cocaine from leaves of Erthroxylon coca
Oswald Schmiedeberg, 1869: isolated muscarine from Amanita muscaria
R. Bohm, approximately 1890: active anthelmintics from fern, action of croton oil catharsis, poisonous mushrooms
C. Voegtlin, 1923: mechanism of action of As and other metals in the SH groups
K.K. Chen, 1934: demonstrated antagonistic effect of sodium nitrite and sodium thiosulphate in cyanide poisoning
P. Müller, 1944–46: introduction and study of DDT (dichlorodiphenyltrichloroethane) and related insecticide compounds
R.A. Peters, L.A. Stocken, and R.H.S. Thompson, 1945: development of British anti-Lewisite (BAL) as a relatively specific antidote for arsenic
Judah Hirsch Quastel, 1946: developed 2,4-D, the first widely used systemic herbicide
G. Schrader, 1952: introduction and study of organophosphorus compounds
Rachel Carson, 1962: started crusade against the use of DDT and published the great book, *Silent Spring*