CASARETT AND DOULL'S TOXICOLOGY

The Basic Science of Poisons

THIRD EDITION

EDITORS

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Preface to the First Edition

THIS VOLUME has been designed primarily as a textbook for, or adjunct to, courses in toxicology. However, it should also be of interest to those not directly involved in toxicologic education. For example, the research scientist in toxicology will find sections containing current reports on the status of circumscribed areas of special interest. Those concerned with community health, agriculture, food technology, pharmacy, veterinary medicine, and related disciplines will discover the contents to be most useful as a source of concepts and modes of thought that are applicable to other types of investigative and applied sciences. For those further removed from the field of toxicology or for those who have not entered a specific field of endeavor, this book attempts to present a selectively representative view of the many facets of the subject.

Toxicology: The Basic Science of Poisons has been organized to facilitate its use by these different types of users. The first section (Unit I) describes the elements of method and approach that identify toxicology. It includes those principles most frequently invoked in a full understanding of toxicologic events, such as dose-response, and is primarily mechanistically oriented. Mechanisms are also stressed in the subsequent sections of the book, particularly when these are well identified and extend across classic forms of chemicals and systems. However, the major focus in the second section (Unit II) is on the systemic site of action of toxins. The intent therein is to provide answers to two questions: What kinds of injury are produced in specific organs or systems by toxic agents? What are the agents that produce these effects?

A more conventional approach to toxicology has been utilized in the third section (Unit III), in which the toxic agents are grouped by chemical or use characteristics. In the final section (Unit IV) an attempt has been made to illustrate the ramifications of toxicology into all areas of the health sciences and even beyond. This unit is intended to provide perspective for the nontoxicologist in the application of the results of toxicologic studies and a better understanding of the activities of those engaged in the various aspects of the discipline of toxicology.

It will be obvious to the reader that the contents of this book represent a compromise between the basic, fundamental, mechanistic approach to toxicology and the desire to give a view of the broad horizons presented by the subject. While it is certain that the editors' selectivity might have been more severe, it is equally certain that it could have been less so, and we hope that the balance struck will prove to be appropriate for both toxicologic training and the scientific interest of our colleagues.

L.J.C.
J.D.

Although the philosophy and design of this book evolved over a long period of friendship and mutual respect between the editors, the effort needed to convert ideas into reality was undertaken primarily by Louis J. Casarett. Thus, his death at a time when completion of the manuscript was in sight was particularly tragic. With the help and encouragement of his wife, Margaret G. Casarett, and the other contributors, we have finished Lou's task. This volume is a fitting embodiment of Louis J. Casarett's dedication to toxicology and to toxicologic education.

J.D.

Preface to the Third Edition

THE GOALS of the editors for the third edition of this textbook have remained those of the earlier editions. This volume is designed to serve primarily as a textbook for, or adjunct to, courses in toxicology. Because the two previous editions have also been widely used in courses in environmental health and related areas, we have attempted to maintain those characteristics that make it useful to scientists from other disciplines. This third edition will again provide those in other professions, as well as toxicologists, with information on the many facets of toxicology and on the principles, concepts, and modes of thought that are the foundation of the discipline. Research toxicologists who have used the previous editions of this book as a reference source will find updated material in areas of their special or peripheral interests.

The overall framework of the third edition is similar to that of the second edition, with major sections covering "General Principles of Toxicology" (Unit I), "Systemic Toxicology" (Unit II), "Toxic Agents" (Unit III), "Environmental Toxicology" (Unit IV), and "Applications of Toxicology" (Unit V). In accord with a policy adopted for the second edition, we have changed the authorship of one-third of the chapters in this edition to broaden input and provide new coverage of the many aspects of toxicology. New chapters have been added on toxic responses of the immune system, the cardiovascular system, and the skin, and many other chapters have been extensively updated.

The editors are grateful to our colleagues in academia, industry, and government who have made useful suggestions for improving this third edition both as a textbook and as a reference source. We are especially grateful to the contributors, whose combined expertise has made possible a volume of this breadth. We appreciate the efforts of those who revised chapters and those who prepared new ones to limit their chapters to lengths that would keep the third edition from becoming unwieldy in size and prohibitive in cost.

C.D.K.
M.O.A.
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UNIT V
Applications of Toxicology

UNIT I

GENERAL PRINCIPLES OF TOXICOLOGY

Chapter 1

ORIGIN AND SCOPE OF TOXICOLOGY

John Doull and *Margaret C. Bruce*

INTRODUCTION

In selecting a subtitle for this textbook of toxicology, the authors have utilized the traditional definition that defines toxicology as the basic science of poisons. To use this definition, we need to define a poison. If we define a poison as any agent that is capable of producing injury or death when ingested or absorbed, then, as pointed out by Paracelsus over 400 years ago (see first page of this text), "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy." Since all chemicals can produce injury or death under some exposure conditions, it is evident that there is no such thing as a "safe" chemical in the sense that it will be free of injurious effects under all conditions of exposure. However, it is also true that there is no chemical that cannot be used safely by limiting the dose or exposure. By defining toxicology as the study of the adverse effects of chemical agents on biologic systems, we avoid the use of the term "poison" and all of the legal and historic problems associated with attempts to provide a precise and quantifiable definition of a poison.

Toxicologists, then, are individuals who study the adverse effects of chemical agents on living organisms. With this broad definition, most biomedical scientists and many others can be considered to be toxicologists. Pharmacologists, for example, usually study the adverse effects as well as the beneficial effects of drugs, and emergency room physicians treating acute poisoning or epidemiologists investigating the effects of chronic exposure to chemicals are engaged in toxicology. What distinguishes the toxicologist is a primary focus on the adverse effects of chemical agents in his research and activity as well as in his training and experience. The important role of experience in becoming a toxicologist is illustrated by Dr. A. J. Lehman's oftenquoted remark that, "Anyone can become a toxicologist in two easy lessons, each of which takes ten years."

The contributions and activity of toxicologists are diverse and widespread. In the biomedical area, toxicologists are concerned with exposure to chemical agents as a cause of both acute and chronic illness. They are involved in the recognition, identification, and quantitation of hazards resulting from occupational exposure to chemicals and the public health aspects of chemicals in air, water, food, drugs, and other parts of the environment. Toxicologists also participate in the development of standards and regulations designed to protect human health and the environment from the adverse effects of chemicals. Conversely, they also contribute to the development of new agents that are selectively toxic for microorganisms (antibiotics) and insects, weeds, fungi, and other unwanted organisms (pesticides). They explore the mechanisms by which chemicals produce adverse effects in biologic systems and develop antidotes and treatment regimes for treating such injury. Toxicologists carry out some or all of these activities as members of academic, industrial, and governmental organizations. In doing so, they share common methodologies for obtaining data on the toxicity of materials and the responsibility for using this information to make reasonable predictions regarding the hazards of the material to man and to his environment. These two different but complementary activities characterize the discipline of toxicology.

Toxicology, like medicine, is both a science and an art. Having defined toxicology as the study of the adverse effects of chemicals on biologic systems, the science of toxicology can be defined as the observational or data-gathering phase and the art of toxicology as the predictive phase of the discipline. In most cases, these two phases are linked since the "facts" generated by the science of toxicology are used to develop the prediction or "hypothesis" for the adverse effects of chemical agents in situations where there is little or no information. For example, the observation that exposure to chloroform can produce hepatomas in B6C3F1 mice is a docu-

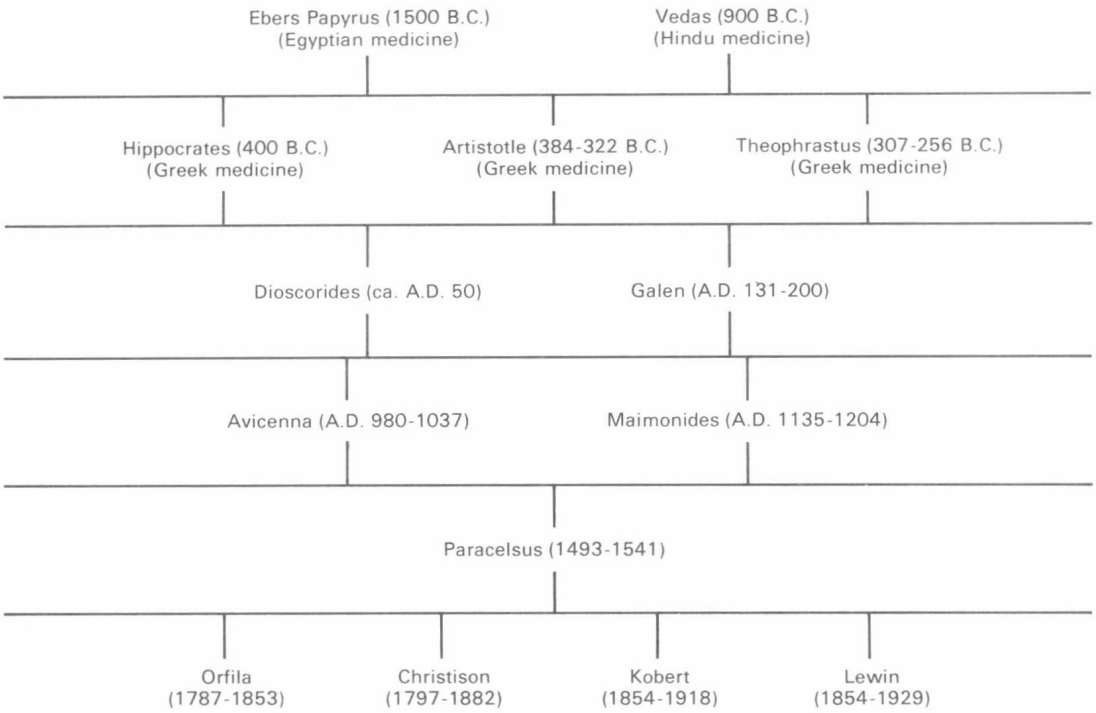

Figure 1–1. Major reference points in the evolution of toxicology as a science.

mented fact, whereas the conclusion that it will also do so in man is a prediction or hypothesis.

It is useful to distinguish the facts generated by the science of toxicology from the predictions generated by the art of toxicology as a means of testing the validity of each. When we fail to distinguish between the science and the art of toxicology, we tend to confuse our facts with our predictions and to argue that they have equal validity, which they clearly do not. In toxicology, as in other biologic sciences, theories have a higher level of certainty than hypotheses, which in turn are more certain than speculations, opinions, conjectures, and guesses.

Some insight into the development of the scope of toxicology and the roles, points of view, and activities of the toxicologist can be obtained by an examination of the historic evolution of the discipline.

HISTORY OF TOXICOLOGY

Antiquity

Toxicology, in a variety of specialized and primitive forms, has been a relevant part of the history of man (Figure 1–1). Earliest man was well aware of the toxic effects of animal venoms and poisonous plants. His knowledge was used for hunting, for waging more effective warfare, and, probably, to remove undesirables from the small groups of primitive society. The Ebers papyrus, perhaps our earliest medical record (circa 1500 B.C.), contains information extending back many centuries. Of the more than 800 recipes given, many contain recognized poisons. For example, one finds hemlock, which later became the state poison of the Greeks; aconite, an arrow poison of the ancient Chinese; opium, used as both poison and antidote; and such metals as lead, copper, and antimony. There is also an indication that plants containing substances akin to digitalis and belladonna alkaloids were known. Hippocrates, while introducing rational medicine about 400 B.C., added a number of poisons. He further wrote instructions that might be considered primitive principles of toxicology, in the form of attempts to control absorption of the toxic materials in therapy and overdosage.

In the mythology and literature of classic Greece, one finds many references to poisons and their use, and it was during this period that the first professional treatment of the subject began to appear. For example, Theophrastus (370–286 B.C.), a student of Aristotle, included numerous references to poisonous plants in *De Historia Plantarum*. Dioscorides, a Greek physician in the court of Emperor Nero, made the first attempt at a classification of poisons, which was accompanied by descriptions and drawings. The separation into plant, animal, and mineral poisons he used not only remained a standard for 16 centuries, but is still a convenient classifi-

cation today (see Gunther, 1934). Dioscorides also dabbled in therapy, recognizing the use of emetics in poisoning and the use of caustic agents or cupping glasses in snakebite.

Poisoning with plant and animal toxins was quite common. Perhaps the best-known recipient of a poison used as a state method of execution was Socrates (470–399 B.C.), although he was in distinguished company. Expeditious suicide on a voluntary basis also made use of toxicologic knowledge. Demosthenes (385–322 B.C.), who took poison hidden in his pen, was only one of many examples. The mode of suicide calling for one to fall on his sword, although manly and noble, carried little appeal and less significance for ladies of the day. Cleopatra's (69–30 B.C.) knowledge of natural, primitive toxicology permitted her the more genteel method of falling on her asp instead.

The Romans too made considerable use, often political, of poisons. Much legend and myth have grown out of the skill of poisoners and the occupational hazards of political life. One such legend tells of the King Mithridates VI of Pontus whose numerous experiments on unfortunate criminals led to his eventual claim that he had discovered "an antidote for every venomous reptile and every poisonous substance" (Guthrie, 1946). He himself was so fearful of poisons that he regularly ingested a mixture of 36 ingredients (Galen reports 54) as protection against assassination. On the occasion of his imminent capture by enemies, his attempts to kill himself with poison failed because of his successful concoction and he was forced to use his own sword held by a servant. From this tale comes the term "mithridatic" referring to an antidotal or protective mixture. Another term from the Greek, "theriac," also has become a synonym for "antidote" although the word derives from a poetic treatise by Nicander of Colophon (204–135 B.C.) entitled "Theriaca," which dealt with poisonous animals. Another poem, "Alexipharmaca," was about antidotes.

This search for antidotal measures or chemicals remained a preoccupation for centuries. In addition to the terms given above, others were applied such as Alexiteria and Bezoardica, the latter referring to concretions found in the goat bladder. The practice of medicine was based largely on an "antidoting" of disease, and descriptions of therapeutic agents also were so classified. For example, an early respectable forerunner of the modern pharmacopoeia was the *Antidotarium of Nicholaus*. It was not until the seventeenth century that a commission appointed by the Pope to Matthiolus opened the horizons to a search for *Antidota specifica*.

In Rome, poisoning seemed to take on epidemic characteristics, which are described by Livy as being especially distressing to the public in the fourth century B.C. It was during this period that a conspiracy of women to remove those from whose death they might profit was uncovered, and similar large-scale poisoning continued from time to time until 82 B.C., when Sulla issued the *Lex Cornelia*. This appears to be the first law against poisoning, and it later became a regulatory statute directed at careless dispensers of drugs.

The history of poisons and their use is the basis of entertaining retrospective diagnosis, as described by Meek in his essay *The Gentle Art of Poisoning* (1928) and in a book by Thompson entitled *Poisons and Poisoners* (1931). Although most poisons used during the period were of vegetable origin, the sulfide of arsenic and arsenous acid were known to be used. It has been postulated that arsenic was the poison with which Agrippina killed Claudius to make Nero the emperor of Rome. This postulate is supported by the later use of the same material by Nero in poisoning Britannicus, Claudius's natural son. The deed was performed under the direction of Locusta, a professional poisoner attached to the family.

The mixture of fact and legend surrounding that murder illustrates the practices of the times. A first attempt to poison Britannicus failed, but the illness reported contained evidence of all the symptoms of arsenic poisoning. The failure led to suspicion and the hiring of a taster. The second, and successful, attempt involved a more devious scheme. The arsenic was placed in cold water and Britannicus was served excessively hot soup. The taster had demonstrated the safety of the soup, but it was not retested after the water had been added to cool the soup.

Here superstition and legend embellish the story. Nero claimed that Britannicus had died of epilepsy and ordered immediate burial to prevent others from seeing the blackening of the body believed to occur after poisoning. As the legend continues, the corpse was painted with cosmetics to hide the deed, but, in a raging storm, the cosmetics washed off, revealing Nero's perfidy.

Middle Ages

Prior to the Renaissance and extending well into that period, the Italians, with characteristic pragmatism, brought the art of poisoning to its zenith. The poisoner became an integral part of the scene, if not as a social being, at least as a political tool and as custodian of a common social expedient. The records of the city councils of Florence, and particularly the infamous Council of Ten of Venice, contain ample testimony of the political use of poisons. Victims

were named, prices set, contracts recorded, and when the deed was accomplished, payment made. The notation *"factum"* often appeared after the entry in the archives, indicating successful accomplishment of its transaction.

In less organized but more colorful ways, the citizens of Italy in the Middle Ages also practiced the art of poisoning. A famous figure of the time was a lady named Toffana, who peddled specially prepared arsenic-containing cosmetics *(Agua Toffana)*. Accompanying the product were appropriate instructions for use. Toffana was succeeded by an imitator with organizational genius, a certain Hieronyma Spara, who provided a new fillip by directing her activity toward specific marital and monetary objectives. A local club was formed of young, wealthy, married women, which soon became a club of eligible young, wealthy widows, reminiscent of the matronly conspiracy many centuries earlier.

Among the prominent families engaged in poisoning, the Borgias are the most notorious. Although there is no doubt that they were among the leading entrepreneurs in the field, they probably received more credit than their due. Many deaths that were attributed to poisoning are now recognized as having occurred from infectious diseases such as malaria, which was sufficiently bad as to make Rome virtually uninhabitable during the summer months. It appears true, however, that Alexander VI, his son Cesare, and Lucretia were quite active. Aside from personal reasons, the deft applications of poisons to men of stature in the Church swelled the holdings of the Papacy, which was the prime heir.

A paragon of the distaff set of the period was Catherine de Medici. Catherine, although not so thoroughly fabled as her Borgia relatives and ancestors, was, in tune with her time, a practitioner of the art of applied toxicology. She also represented a formidable export from Italy to France. As appeared to be all too common in this period, the prime targets of the ladies were their husbands. However, unlike others of an earlier period, the circle represented by Catherine (and epitomized by the notorious Marchioness de Brinvillers) depended on direct evidence to arrive at the most effective compounds for their purposes. Under guise of delivering provender to the sick and the poor, Catherine tested toxic concoctions, carefully noting the rapidity of the toxic response (onset of action), the effectiveness of the compound (potency), the degree of response of the parts of the body (specificity, site of action), and the complaints of the victim (clinical signs and symptoms). Clearly, Catherine must be given credit as perhaps the earliest untrained experimental toxicologist.

Culmination of the practice in France is represented by the commercialization of the service by a Catherine Deshayes, who earned the title *La Voisine*. Her business was dissolved by her execution. Her trial was one of the most famous of those held by the Chambre Ardente, a special judicial commission established by Louis XIV to try such cases without regard to age, sex, or national origin. La Voisine was convicted of many poisonings, including over 2000 infants among the victims.

During the Middle Ages and on into the Renaissance, poisoning seems to have been accepted as one of the normal hazards of living. It had some elements of sport, with a code, unwritten rules of honor, and a fatalistic attitude on the part of the selected victim. Devices and methods of poisoning proliferated at an alarming rate. The Chambre Ardente created in France was but a mild deterrent, and it remained for the rise of scientific methods in modern times to make the practice more risky for poisoners.

Another individual whose contributions to toxicology have survived through the years was Moses ben Maimon, or Maimonides (A.D. 1135–1204). In addition to being a competent and well-respected physician, Maimonides was also a prolific writer. Of particular significance was his volume entitled *Poisons and Their Antidotes* (1198), a first-aid guide to the treatment of accidental or intentional poisonings and insect, snake, or mad dog bites. Maimonides recommended that suction be applied to insect stings or animal bites as a means of extracting the poison and advised application of a tight bandage above a wound located on a limb. He also noted that the absorption of toxins from the stomach could be delayed by ingestion of oily substances such as milk, butter, or cream. A cautious and critical observer, Maimonides rejected numerous popular remedies of the day after finding them to be ineffective (e.g., the use of unleavened bread in the treatment of scorpion stings) and mentioned his doubts concerning the efficacy of others.

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). Between the time of Aristotle and the age of Paracelsus there was little substantial change in the biomedical sciences. In the sixteenth century the revolt against the authority of the Church was accompanied by a parallel attack on the godlike authority exercised by the followers of Hippocrates and Galen. Paracelsus, personally and professionally, embodied the