Fifth Edition

CASARETT & DOULL'S TOXICOLOGY

THE BASIC SCIENCE OF POISONS

毒理学袖珍手册

Curtis D. Klaassen

John B. Watkins III

COMPANION HANDBOOK

世界图书出版公司

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PREFACE

This *Companion Handbook* to the 5th edition of *Casarett and Doull's Toxicology: The Basic Science of Poisons* was prepared to meet the needs of students and practitioners of toxicology for a concise and portable textbook and reference. The Handbook was intended to be used in conjunction with the original text, as well as to stand alone as a text for undergraduate and graduate courses in toxicology. Important basic science concepts from anatomy, physiology, and biochemistry have been included to facilitate the understanding of the principles and mechanisms of toxicant action on specific organs systems. The location of the detailed discussions in the full textbook is presented at the end of each chapter in the Handbook.

We would like to thank the original chapter authors for their efforts in distilling the vast information of their subjects into a format that was readily condensable. We also invite our readers to send us their suggestions of ways to improve this Handbook to make it more useful.

We especially appreciate Ruth A. Sanders, who has worked tirelessly and provided invaluable assistance on this project. Without the love and support of our families, this book would not be possible. We also appreciate the staff at McGraw-Hill, especially James Morgan and Lester Sheinis, for their advice, encouragement, expertise, and patience.

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UNIT 1 GENERAL PRINCIPLES OF TOXICOLOGY

1 | History and Scope of Toxicology

Modern toxicology goes beyond the study of the adverse effects of exogenous agents to the study of molecular biology, using toxicants as tools. Historically, toxicology formed the basis of therapeutics and experimental medicine, but it continues to develop and expand by assimilating knowledge and techniques from most branches of biology, chemistry, mathematics, and physics. A recent addition to the field of toxicology is the application of the discipline to safety evaluation and risk assessment.

In all branches of toxicology, scientists explore the mechanisms by which chemicals produce adverse effects in biological systems.

- Mechanisms of action and exposure to chemical agents as a cause of acute and chronic illness
- Physiological phenomena
- Occupational exposure to chemicals
- Public health aspects of chemicals in the environment, foods, and drugs
- Discovery and development of new drugs and pesticides
- Development of standards and regulations
- Effects of chemicals in flora and fauna
- Mechanisms by which toxicants modulate cell growth and differentiation and cells respond to toxicants at the level of the gene
- Development of antidotes and treatment regimens to alleviate poisonings and xenobiotic injury.

An insight into modern toxicology and the roles, points of view, and activities of toxicologists can be obtained from an examination of the discipline's historical evolution.

ANTIQUITY

Toxicology dates back to the earliest humans, who used animal venoms and plant extracts for hunting, warfare, and assassination. It is safe to assume that prehistoric humans categorized some plants and animals as harmful and others as safe. The Ebers papyrus (circa 1500 B.C.) contains information pertaining to many recognized poisons, including hemlock (the state poison of the Greeks), aconite (a Chinese arrow poison), opium (used as both a poison and an antidote), and metals such as lead, copper, and antimony. There is also an indication that plants containing substances similar to digitalis and belladonna alkaloids were known. Hippocrates (circa 400 B.C.) added a number of poisons and clinical toxicology principles pertaining to bioavailability in therapy and overdosage. Dioscorides, a Greek physician in the court of the Roman emperor Nero, attempted to classify poisons into plant, animal, and mineral poisons. His classification not only remained a standard for 16 centuries but also is still a convenient classification. Dioscorides also dabbled in therapy, recognizing the use of emetics in poisoning and the use of caustic agents and cupping glasses in snakebite. Poisoning with plant and animal toxins was quite common. Expeditious suicide also made use of toxicological knowledge.

The Romans made considerable use of poisons in politics. King Mithridates VI of Pontus 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 antidote concoction. From this tale comes the term "mithridatic," referring to an antidotal or protective mixture.

Poisonings in Rome reached epidemic proportions during the fourth century B.C. and continued until Sulla issued the *Lex Cornelia* (circa 82 B.C.), the first law against poisoning. It later became a regulatory statute directed at careless dispensers of drugs.

MIDDLE AGES

Before the Renaissance, the writings of Maimonides (Moses ben Maimon, A.D. 1135–1204) included a treatise on the treatment of poisonings from insects, snakes, and mad dogs (*Poisons and Their Antidotes,* 1198). Maimonides, like Hippocrates before him, wrote on the subject of bioavailability. It is rumored that alchemists of this period (circa A.D. 1200), in search of the universal antidote, learned to distill fermented products and made a 60% ethanol beverage that had many interesting powers.

In 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. An infamous figure of the time was a woman named Toffana, who peddled specially prepared arsenic-containing cosmetics (*Agua Toffana*). Arsenic-containing cosmetics were responsible for deaths well into the twentieth century.

Among the prominent families engaged in poisoning, the Borgias were the most notorious. The deft application of poisons to men of stature in the Catholic Church swelled the holdings of the papacy, which was their prime heir.

Catherine de Medici exported her skills from Italy to France, where the prime targets of women were their husbands. Under the 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).

AGE OF ENLIGHTENMENT

> All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.
>
> *Paracelsus*

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). A physician-alchemist and the son of a physician, Paracelsus promoted a focus on the "toxicon," the primary toxic agent, as a chemical entity, as opposed to the Grecian concept of the mixture or blend. Paracelsus held that experimentation is essential in the examination of responses to chemicals, that there is a distinction between the therapeutic and toxic properties of chemicals, that these properties are sometimes indistinguishable except by dose and that one can ascertain a degree of specificity of chemicals and their therapeutic or toxic effects. This was the first sound articulation of the dose-response relation, a bulwark of toxicology.

The occupational hazards associated with metalworking were recognized during the fifteenth century. The major work on the subject, *On the Miners' Sickness and Other Diseases of Miners* (1567), published by Paracelsus, addressed the etiology of miners' disease, along with treatment and prevention strategies. Occupational toxicology was further advanced by the work of Bernardino Ramazzini. His classic, *Discourse on the Diseases of Workers* (1700), set the standard for occupational medicine well into the nineteenth century. Ramazzini's work broadened the field by discussing occupations ranging from mining to midwifery and including printing, weaving, and pottery. Furthermore, Percival Pott's (1775) recognition of the role of soot in scrotal cancer among chimney sweeps was the first reported example of polyaromatic hydrocarbon carcinogenicity.

The nineteenth century dawned in a climate of industrial and political revolution. Organic chemistry was in its infancy in 1800, but by 1880 more than 10,000 organic compounds had been synthesized. Determination of the toxicological potential of these newly created chemicals became the underpinning of the science of toxicology as it is practiced today. However, the impact of industrial toxicology discoveries was not felt until the passage of workers' insurance laws, first in Germany (1883), then in England (1897), and later in the United States (1910).

Orfila, a Spanish physician in the French court, was the first toxicologist to use autopsy material and chemical analysis systematically as legal proof of poisoning, the underpinning of forensic toxicology. Magendie, a physician and experimental physiologist, studied the absorption and distribution of compounds in the body. Claude Bernard's treatise, *An Introduction to the Study of Experimental Medicine* (1865), is a classic in the development of toxicology.

Many German scientists contributed greatly to the growth of toxicology in the late nineteenth and early twentieth centuries. Oswald Schmiedeberg made many contributions to the science of toxicology, not the least of which was the training of approximately 120 students. His research focused on the synthesis of hippuric acid in the liver and the detoxification mechanisms of the liver in several animal species. Louis Lewin's contributions on the chronic toxicity of narcotics and other alkaloids remain classic.

MODERN TOXICOLOGY

With the advent of anesthetics and disinfectants and the advancement of experimental pharmacology in the late 1850s, toxicology as it is currently understood got its start. The introduction of ether, chloroform, and carbonic acid led to several iatrogenic deaths, which spurred research into the causes of the deaths.

During this period, the use of "patent" medicines was common, and there were several incidents of poisonings from these medicaments. The adverse reactions to patent medicines, coupled with the response to Upton Sinclair's exposé of the meat-packing industry in *The Jungle,* culminated in the passage of the Wiley Bill (1906), the first of many U.S. pure food and drug laws. The National Safety Council was established in 1911, and the Division of Industrial Hygiene was established by the U.S. Public Health Service in 1914. Major chemical manufacturers established internal toxicology research laboratories to help guide decisions on worker health and product safety. The discovery of vitamins, or "vital amines," led to the use of the first large-scale bioassays (multiple animal studies) to determine whether these "new" chemicals were beneficial or harmful to laboratory animals. These early bioassays were made possible by a major advance in toxicology: the availability of developed and refined strains of inbred laboratory rodents.

The 1920s saw many events that began to mold the fledgling field of toxicology. The use of arsenicals for the treatment of diseases such as syphilis (arsenicals had been used in agriculture since the mid-nineteenth century) resulted in acute and chronic toxicity. Prohibition of alcoholic beverages in the United States opened the door for early studies of neurotoxicology, with the discovery that triorthocresyl phosphate, methanol, and lead (all products of "bootleg" liquor) are neurotoxicants. Mueller's discovery of DDT (dichlorodiphenyltrichloroethane) and several other organohalides, such as hexachlorobenzene and hexachlorocyclohexane, during the late 1920s resulted in wider use of insecticidal agents. Work on the bioactivity of the estrogenic compounds resulted in the synthesis of diethylstilbestrol (DES), hexestrol, and other stilbenes and the discovery of the strong estrogenic activity of substituted stilbenes. The exponential growth of toxicology during this century can be traced to the World War II era, with its marked increase in the production of drugs, pesticides, munitions, synthetic fibers, and industrial chemicals. The discovery of sulfanilamide was heralded as a major event in combating bacterial diseases. However, the drug was sold in glycol solutions, and several patients died of acute kidney failure resulting from the metabolism of the glycol. This led in 1938 to the passage of the Copeland Bill, the second major bill leading to the formation of the U.S. Food and Drug Administration (FDA).

The crisis of World War II caused the next major leap in the development of toxicology. This story commences with the use of uranium for the "bomb" and continues today with research on the role of metals in their interactions with DNA, RNA, and growth factors. The work of the wartime scientists gave the scientific community data that contributed to the early understanding of macromolecular binding of xenobiotics, cellular mutational events, methods for inhalation toxicology and therapy, and toxicological properties of trace metals, along with a better appreciation of the complexities of the dose-response curve.

Another seminal event in toxicology that occurred during the World War II era was the discovery of organophosphate cholinesterase inhibitors, nonbioaccumulating insecticides that were destined to replace DDT and other organochlorine insectides.

Early in the twentieth century, it had been demonstrated experimentally that quinine has a marked effect on the malaria parasite. This discovery led to the development of quinine derivatives for the treatment of the disease and the formulation of the early principles of chemotherapy. However, because it had been noted by Russian scientists that some antimalarial compounds caused retinopathies in humans but did not apparently have the same adverse effect in rodents and dogs, toxicity testing in rhesus monkeys is performed before efficacy studies in people. It also led to the school of thought that nonhuman primates may be one of the best models for humans and the establishment of primate colonies for the study of toxicity.

Experimental pathology developed from bioassays of estrogens and early experiments in chemical- and radiation-induced carcinogenesis. It is from these early studies that hypotheses on tumor promotion and cancer progression have evolved.

Toxicologists today owe a great deal to the researchers of chemical carcinogenesis of the 1940s. Much of today's work can be traced to

Elizabeth and James Miller at Wisconsin, whose seminal research led to the discovery of the role of reactive intermediates in carcinogenicity and that of mixed-function oxidases in the endoplasmic reticulum. These findings, which initiated the great works on the cytochrome P-450 family of proteins, were aided by two other major discoveries: paper chromatography in 1944 and the use of radiolabeled dibenzanthracene in 1948. Seminal research by Bernard Brodie on the metabolism of methyl orange in 1947 led to the examination of blood and urine for chemical and drug metabolites. It became the tool with which one could study the relationship between blood levels and biological action. The classic treatise of R. T. Williams, *Detoxication Mechanisms* (1947), described the many pathways and possible mechanisms of detoxication.

The first major U.S. pesticide act, signed into law in 1947, marked the first time in U.S. history a substance that was neither a drug nor a food had to be shown to be safe and efficacious. Adrian Albert's classic *Selective Toxicity* (1951) presented a concise documentation of the principles of the site-specific action of chemicals.

The mid-1950s witnessed the strengthening of the FDA's commitment to toxicology under the guidance of Arnold Lehman. Lehman and coworkers formalized the experimental program for the appraisal of food, drug, and cosmetic safety in 1955, updated by the FDA in 1982, and the Gordon Research Conferences established a conference on toxicology and safety evaluation. These two events led to close relationships among toxicologists from several groups. The Delaney clause stated broadly that any chemical found to be carcinogenic in laboratory animals or humans could not be added to the U.S. food supply. Delaney resulted in the inclusion of biostatisticians and mathematical modelers in the field of toxicology. It fostered the expansion of quantitative methods in toxicology and served as a starting point for understanding the complexity of the biological phenomenon of carcinogenicity and the development of risk assessment models.

Shortly after the Delaney amendment and after three successful Gordon Conferences, the first American journal dedicated to toxicology was launched by Lehman and others. *Toxicology and Applied Pharmacology* has been the flagship journal of toxicology ever since. The founding of the Society of Toxicology followed shortly afterward, and this journal became its official publication.

Starting with the tragic thalidomide incident, in which several thousand children were born with serious birth defects, and the publication of Rachel Carson's *Silent Spring* (1962), attempts to understand the effects of chemicals on the embryo and fetus and on the environment as a whole gained momentum.

During the latter half of the 1960s, the analytic tools used in toxicology were developed to a level of sophistication that allowed the detection