

Casarett & Doull's Essentials of Toxicology, 2e >

Chapter 1. History and Scope of Toxicology

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Key Points

- Toxicology is the study of the adverse effects of xenobiotics on living systems.
- Toxicology assimilates knowledge and techniques from biochemistry, biology, chemistry, genetics, mathematics, medicine, pharmacology, physiology, and physics.
- Toxicology applies safety evaluation and risk assessment to the discipline.

History of Toxicology

Modern toxicology goes beyond the study of the adverse effects of exogenous agents by assimilating knowledge and techniques from most branches of biochemistry, biology, chemistry, genetics, mathematics, medicine, pharmacology, physiology, and physics and applies safety evaluation and risk assessment to the discipline. In all branches of toxicology, scientists explore the mechanisms by which chemicals produce adverse effects in biological systems. Activities in these broad subjects complement toxicologic research, thereby contributing to the application of this knowledge to the science and art of toxicology.

Antiquity

Knowledge of animal venoms and plant extracts for hunting, warfare, and assassination presumably predate recorded history. One of the oldest known writings, the Ebers Papyrus (circa 1500 b.c.), contains information pertaining to many recognized poisons, including hemlock, aconite, opium, and metals such as lead, copper, and antimony. Whereas the *Book of Job* (circa 1400 b.c.) speaks of poison arrows (Job 6:4), Hippocrates (circa 400 b.c.) added a number of poisons and clinical toxicology principles pertaining to bioavailability in therapy and overdose. 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 the Roman emperor Nero, made the first attempt at classifying poisons into plant, animal, and mineral poisons in his book *De Materia Medica*, which contains reference to some 600 plants.

One legend tells of Roman King Mithridates VI of Pontus, who was so fearful of poisons that he regularly ingested a mixture of 36 ingredients 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. This tale leads to use of the word mithridatic as an antidote or protective mixture. Because poisonings in politics became so extensive, Sulla issued the *Lex Cornelia* (circa 82 b.c.), which appears to be the first law against poisoning and later became a regulatory statute directed at careless dispensers of drugs.

Middle Ages

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 described the subject of bioavailability, noting that milk, butter, and cream could delay intestinal absorption. In the early Renaissance and under the guise of delivering provender to the sick and the poor, Catherine de Medici 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 and site of action), and the complaints of the victim (clinical signs and symptoms).

Renaissance

All substances are poisons; there is none that is not a poison. The right dose differentiates a poison from a remedy.

Paracelsus

Philippus Aureolus Theophrastus Bombastus von Hohenheim-Paracelsus (1493–1541) was pivotal, standing between the philosophy and magic of classic antiquity and the philosophy and science willed to us by figures of the seventeenth and eighteenth centuries. Paracelsus, a physician-chemist, formulated many revolutionary views that remain integral to the structure of toxicology, pharmacology, and therapeutics today. He focused on the primary toxic agent as a chemical entity, and held that (1) experimentation is essential in the examination of responses to chemicals, (2) one should make a distinction between the therapeutic and toxic properties of chemicals, (3) these properties are sometimes but not always indistinguishable except by dose, and (4) one can ascertain a degree of specificity of chemicals and their therapeutic or toxic effects. These principles led Paracelsus to articulate the dose–response relation as a bulwark of toxicology.

Come bitter pilot, now at once run on

The dashing rocks thy seasick weary bark!

Here's to my love! O true apothecary!

Thy drugs are quick. Thus with a kiss I die.

Romeo and Juliet, act 5, scene 3

Although Ellenbog (circa 1480) warned of the toxicity of mercury and lead from goldsmithing and Agricola published a short treatise on mining diseases in 1556, the major work on the subject, *On the Miners' Sickness and Other Diseases of Miners* (1567), was published by Paracelsus. This treatise addressed the etiology of miners' disease, along with treatment and prevention strategies. Occupational toxicology was further advanced by the work of Bernardino Ramazzini when he published in 1700 his *Discourse on the Diseases of Workers*, which discussed occupations ranging from miners to midwives and including printers, weavers, and potters. Percival Pott's (1775) recognition of the role of soot in scrotal cancer among chimney sweeps was the first report of polyaromatic hydrocarbon carcinogenicity. These findings led to improved medical practices, particularly in prevention.

Age of Enlightenment

Experimental toxicology accompanied the growth of organic chemistry and developed rapidly during the nineteenth century. Magendie (1783–1885), Orfila (1787–1853), and Bernard (1813–1878) laid the groundwork for pharmacology, experimental therapeutics, and occupational toxicology.

Orfila, a Spanish physician in the French court, used autopsy material and chemical analysis systematically as legal proof of poisoning. His introduction of this detailed type of analysis survives as the underpinning of forensic toxicology. Orfila published a major work devoted expressly to the toxicity of natural agents in 1815. Magendie, a physician and experimental physiologist, studied the mechanisms of action of emetine and strychnine. His research determined the absorption and distribution of these compounds in the body. One of Magendie's more famous students, Claude Bernard, contributed the classic treatise, *An Introduction to the Study of Experimental Medicine*.

German scientists Oswald Schmiedeberg (1838–1921) and Louis Lewin (1850–1929) made many contributions to the science of toxicology. Schmiedeberg trained approximately 120 students who later populated the most important laboratories of pharmacology and toxicology throughout the world. Lewin published much of the early work on the toxicity of narcotics, methanol, glycerol, acrolein, and chloroform.

Modern Toxicology

Toxicology has drawn its strength and diversity from its proclivity to borrowing from almost all the basic sciences to test its hypotheses. This fact, coupled with the health and occupational regulations that have driven toxicology research since 1900, has made this discipline exceptional in the history of science.

With the advent of anesthetics and disinfectants in the late 1850s, toxicology as it is currently understood began. The prevalent use of “patent” medicines led to several incidents of poisonings from these medicaments, which, when 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 in 1906, the first of many U.S. pure food and drug laws.

During the 1890s and early 1900s, the discovery of radioactivity and the **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.

One of the first journals expressly dedicated to experimental toxicology, *Archiv für Toxikologie*, began publication in Europe in 1930. That same year the National Institutes of Health (NIH) was established in the United States. As a response to the tragic consequences of acute kidney failure after taking **sulfanilamide** in glycol solutions, the Copeland bill was passed in 1938. This was the second major bill involving the formation of the U.S. Food and Drug Administration (FDA). The first major U.S. pesticide act was signed into law in 1947. The significance of the initial Federal Insecticide, Fungicide, and Rodenticide Act was that for 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.

After World War II

You too can be a toxicologist in two easy lessons, each of ten years.

Arnold Lehman (circa 1955)

The mid-1950s witnessed the strengthening of the U.S. FDA's commitment to toxicology. The U.S. Congress passed and the president of the United States signed the additives amendments to the Food, Drug, and Cosmetic Act. 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 U.S. food supply. Delaney became a battle cry for many groups and resulted in the inclusion at a new level of biostatisticians and mathematical modelers in the field of toxicology. Shortly after the Delaney amendment, the first American journal dedicated to toxicology, *Toxicology and Applied Pharmacology*, was launched. The founding of the Society of Toxicology followed shortly afterward.

The 1960s started 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. New legislation was passed, and new journals were founded. Cellular and molecular toxicology developed as a subdiscipline, and risk assessment became a major product of toxicologic investigations.

Currently, many dozens of professional, governmental, and other scientific organizations with thousands of members and over 120 journals are dedicated to toxicology and related disciplines. In addition, the International Congress of Toxicology is made up of toxicology societies from Europe, South America, Asia, Africa, and Australia, which brings together the broadest representation of toxicologists.

Toxicology has an interesting and varied history. Perhaps as a science that has grown and prospered by borrowing from many disciplines, it has suffered from the absence of a single goal, but its diversification has allowed for the interspersion of ideas and concepts from higher education, industry, and government. This has resulted in an exciting, innovative, and diversified field that is serving science and the community at large. Few disciplines can point to both basic sciences and direct applications at the same time. Toxicology—the study of the adverse effects of xenobiotics—may be unique in this regard.

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