9TH EDITION

Casarett & Doull's TOXICOLOGY

THE BASIC SCIENCE OF POISONS

CURTIS D. KLAASSEN

Mc Graw Hill Education

Casarett and Doull's
TOXICOLOGY
The Basic Science of Poisons

> "What is there that is not poison?
> All things are poison and nothing (is)
> without poison. Solely the dose
> determines that a thing is not a poison."

Paracelsus (1493–1541)

Casarett and Doull's
TOXICOLOGY

The Basic Science of Poisons

Ninth Edition

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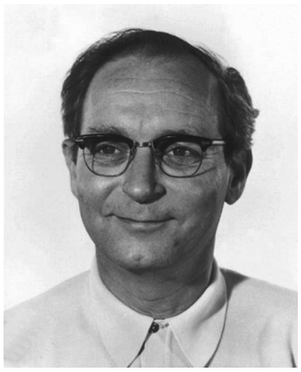
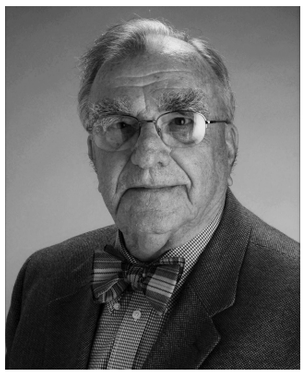
History and Dedication



Louis James Casarett

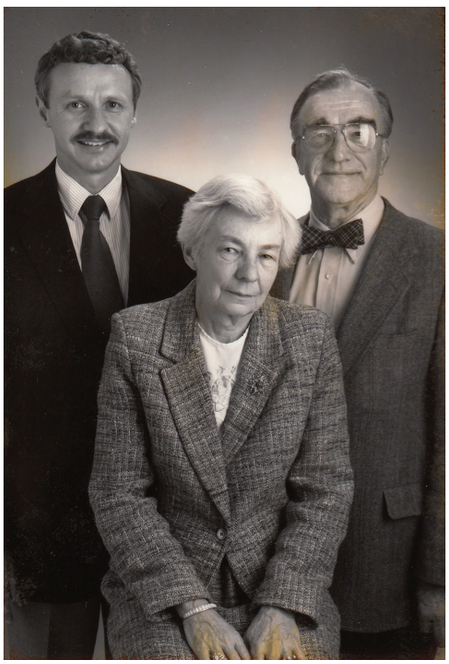


John Doull

Fifty years ago when I started lecturing graduate students there was no comprehensive toxicology textbook, and thus one often needed many hours in the library reading the literature to prepare for a lecture. Thus, I was thrilled when Lou Casarett and John Doull decided to edit a textbook in toxicology because it would enable me to give much better lectures with much less preparation time. The textbook provided a review of the literature on each topic in toxicology written by an expert in the area.

The origin of this textbook started at NIH Toxicology Study Sections meetings in the late 1960s and early 1970s. All members of the Study Sections agreed there was a growing need for a textbook in toxicology, in fact many members of those Study Sections became authors of various chapters in the book.

At the time, Lou Casarett was a professor at the University of Hawaii and John Doull was a professor at the University of Kansas. As a result, Lou spent time in Kansas City with John selecting authors of the book, whereas John and his family spent a summer in Hawaii in finalizing the organization of the book and writing chapters for the first edition. Unfortunately, shortly thereafter and before the first edition was published, Lou died of brain cancer.



Klaassen, Amdur, Doull

The first edition was entitled *Toxicology: The Basic Science of Poisons* and was published in 1975. John Doull asked Mary Amdur, a friend of Lou Casarett, and myself, a younger toxicologist at the University of Kansas, to help him edit the second edition of the textbook. Mary suggested that the names of the two first editors be added to the title of the textbook, and thus the second and all subsequent editions have been entitled *Casarett and Doull's Toxicology: The Basic Science of Poisons.* The second, third, and fourth edition were edited by Doull, Amdur, and Klaassen. Mary Amdur died in 1998 and John Doull in 2017.

This ninth edition is dedicated not only to Lou Casarett, John Doull, and Mary Amdur, but all authors who have contributed to the nine editions of this book. These authors have summarized the knowledge in their area of expertise to help faculty prepare lectures as well as to help students learn the discipline. To emphasize the importance that previous authors have had on the education of toxicologists over the decades, their names are acknowledged in the chapter they previously authored.

Lou Cantilena, MD, PhD, author of the "Clinical Toxicology" chapter of this book and previous editions, was killed, along with his daughter, in an airplane accident in December 2017. Lou was piloting his daughter home for the Christmas holiday from Kansas City, where she was finishing her MD and PhD studies at the University of Kansas. Professionally, Dr. Cantilena will be remembered for his contributions to the Poison Control Centers and for treating poisoned patients, educating physicians for the military, doing clinical trials in order to discover more effective and less addicting treatments for pain, and consulting with the Food and Drug Administration on the management of drug-induced *torsades de pointes*. Lou's positive attitude, enthusiasm, smile, sincerity, and devotion to his family are hallmarks of his legacy.

Curtis D. Klaassen, PhD, DABT, ATS, FAASLD

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Preface

The ninth edition of *Casarett and Doull's Toxicology: The Basic Science of Poisons*, as in previous editions, is meant primarily as a text for, or an adjunct to, graduate courses in toxicology. Because the eight previous editions have been widely used in courses in environmental health and related areas, an attempt has been made to maintain those characteristics that will again provide information on the many facets of toxicology, especially the principles, concepts, and modes of thoughts that are the foundation of the discipline. Mechanisms of toxicity are emphasized. Research toxicologists will find this book an excellent reference source to find updated material in areas of their special or peripheral interests.

The overall framework of the ninth edition is similar to that of the previous editions. The seven units are General Principles of Toxicology (Unit I), Disposition of Toxicants (Unit II), Non-Organ-Directed Toxicity (Unit III), Target Organ Toxicity (Unit IV), Toxic Agents (Unit V), Environmental Toxicology (Unit VI), and Applications of Toxicology (Unit VII).

This edition reflects the progress made in toxicology during the last few years. The examples are the importance of apoptosis, autophagy, cytokines, growth factors, oncogenes, cell cycling, receptors, gene regulation, protective mechanisms, repair mechanisms, transcription factors, signaling pathways, transgenic mice, knock-out mice, humanized mice, polymorphisms, microarray technology, second-generation sequencing, genomics, proteomics, epigenetics, exposome, microbiota, read across, adverse outcome pathways, high-content screening, computational toxicology, innovative test methods, organ-on-a-chip, etc. in understanding the mechanisms of toxicity and the regulation of chemicals. This edition is markedly updated from the previous edition; over one-third of the chapters in this ninth edition are authored by scientists that have not been previously involved with the textbook. References in this edition include not only traditional journal and review articles, but Internet sites too.

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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.

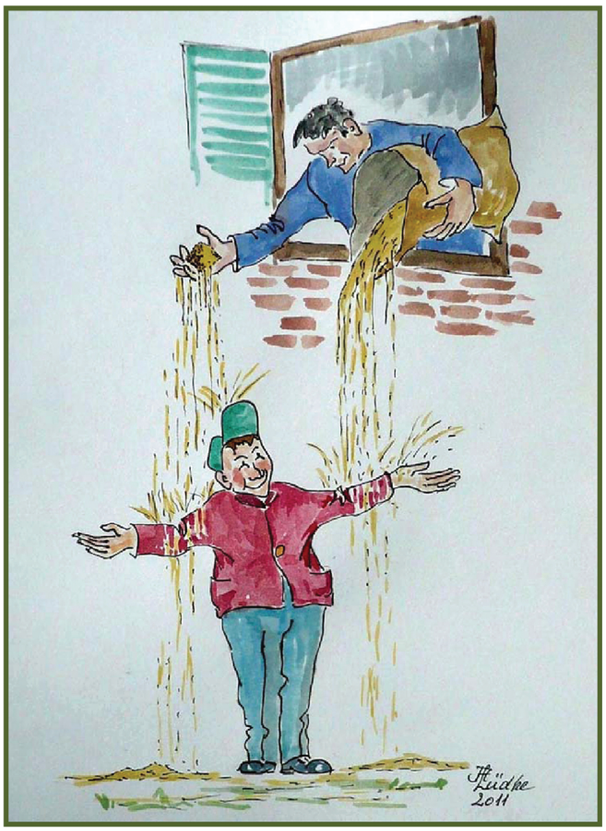
It will be obvious to the reader that the contents of this book represent a compromise between the basic, fundamental, mechanistic approach to toxicology and the desire to give a view of the broad horizons presented by the subject. While it is certain that the editors' selectivity might have been more 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 colleague.

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.

Dose and Dose-Rate matter



Unit I

General Principles of Toxicology

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chapter 1

The Evolving Journey of Toxicology: A Historical Glimpse

Philip Wexler and Antoinette N. Hayes

ABOUT TOXICOLOGY

Humans are smart but vulnerable. We need to be prepared for countless unforeseen events that could compromise our health and well-being. Toxicology arose as a way to understand, prevent, mitigate, and treat the potentially harmful consequences of many of the substances we are exposed to.

According to the Society of Toxicology (SOT) (http://www.toxicology.org/about/vp/vision.asp):

Toxicology is the study of the adverse effects of chemical, physical, or biological agents on living organisms and the ecosystem, including the prevention and amelioration of such adverse effects.

The National Library of Medicine's (NLM) *Collection Development Manual* elaborates by noting:

Toxicology studies the agents responsible for adverse effects, the mechanisms involved, the damage that may ensue, testing methodologies to determine the extent of damage, and ways to avoid or repair it. Toxicology is traditionally associated with chemical exposures, such as the effects of drugs, industrial chemicals, pesticides, food additives, household products, and personal care items. Toxinology, a sub discipline of toxicology, studies biological exposures, such as insect stings, poisonous mushrooms and plants, venomous snakes and aquatic life. The third category of toxicology is concerned with physical hazards, such as radiation and noise.

One of the key points to understand, as noted above, is that although toxicology in the popular mind is confined to chemicals and, probably, in practice most of the research and concern occur in this realm, other agents such as radiation and substances derived from biological organisms are equally relevant to the field.

The word *toxicology* is derived from the Latinized form of the Greek word *toxicon*, meaning "arrow poison." *Poison*, as a noun, dates back to the Old French *poison* or *puison*, meaning, originally, a drink, especially a medical drink, but later signifying more of a magical potion or poisonous drink. Another point of terminology concerns the commonly misused term *toxin*. Despite past and informal uses of the term, it formally should be used to refer to toxic substances produced biologically. Thus, technically, chemicals such as formaldehyde or asbestos, say, would *not* be considered toxins. There are any number of other terms which could be used to delineate the broader category of substances which are toxic, regardless of origin. Examples are *toxicant*, *toxic agent*, and *toxic substance*. *Xenobiotics* is a term referring to substances, whether toxic or not, foreign to a given organism.

Finally, in this brief lesson on toxicology nomenclature, one needs to clarify the use of the words *poisonous* and *venomous* when used as animal adjectives. Though often used interchangeably, they are, in fact, rather distinct. A venom requires a delivery mechanism. Thus, because a snake, for example, injects its venom (or toxin) into its victim, it is considered a *venomous* animal. Instead, a toxic mushroom must be ingested to make its effect felt. Thus, it should instead be deemed *poisonous*.

Toxicology is largely concerned with the interaction of toxicants and biological organisms. While toxicodynamics investigates the effect of the toxicant on the organism, toxicokinetics looks at how the organism affects the toxicant (e.g., absorption, biotransformation, distribution, and elimination). Mechanisms of toxicity at cellular and biochemical levels play a key role in determining why an agent has the effects it does. Toxic responses may be directed to particular organs or systems, for example, kidney, liver, and nervous system. Another way to consider effects is as clastogenic or mutagenic, resulting in carcinogenic or teratogenic effects. Often the focus of research is on a particular chemical or class of chemicals,

such as pesticides, metals, or solvents. Environmental contamination and toxicology are tightly bound fields of study, and toxicology has much to contribute to an understanding of air, water, and soil pollution. Establishing the safety of drugs relies upon toxicology as does ensuring the safety of our water and food supply. Envenomations, whether by snakes, spiders, scorpions, aquatic life, or other creatures, as well as poisoning by plants and fungi are also within toxicology's scope.

Toxicology today is a highly interdisciplinary science that borrows from and intersects with other sciences such as chemistry, biology, pharmacology, medicine, physiology, biochemistry, molecular biology, pathology, and environmental science. Increasingly, it is also appropriating the tools of the computational sciences as one way to improve the precision of safety assessment, screen large numbers of chemicals efficiently, cut costs, and reduce animal use. Toxicology can be parsed into branches in a variety of ways. One such set of groupings follows:

Descriptive Toxicology: The emphasis is on the testing of toxicants, typically on animals. It focuses on the dose–response relationship and extrapolation to humans.

Mechanistic Toxicology: Looks at how the agent induces its biochemical or physiological effect on the organism, that is, modes of action. *Biochemical and Molecular Toxicology* is a synonym for this branch.

Clinical Toxicology: This branch's focus is on the effects of drugs and other chemicals on humans, particularly, but also on other animals. Its work is often involved with drug overdoses and other poisonings, and determining the substance involved and its amount in the body. Sometimes used synonymously with *Medical Toxicology* although technically, in terms of profession, a medical toxicologist tends to have an MD while a clinical toxicologist has a PharmD. A veterinarian who specializes in toxicology, typically, has a DVM.

Forensic Toxicology: Concerned with the cause of death from toxic agents, often in instances of drug abuse or misuse. With a focus on homicides and suicides, this branch of toxicology goes hand-in-hand with the work of the police and medical examiners.

Environmental Toxicology: Investigates the effects of toxicant exposures on the general environment and living organisms therein. Thus, pollution of air, water, and soil, and effects on plants and wildlife would fall within this branch. Ecotoxicology, a more specialized area, is devoted to the effects of toxic chemicals on populations, communities, and terrestrial, freshwater, and marine ecosystems. Environmental toxicologists can further define their work in even more specialized terms, for example, aquatic toxicology.

Occupational Toxicology: Deals with the study of chemical and other agents in the workplace, worker exposures, safety and health, and standard setting. Industrial Hygiene covers a very similar terrain.

Regulatory Toxicology: Focuses on ways in which humans and the environment can be protected from toxic effects, through regulations and standard setting. Considers scientific decision-making within a societal and legal framework. Relies heavily upon risk assessment.

Toxicogenomics: Concerned with the compilation and synthesis of information regarding gene and protein expression in order to understand molecular mechanisms involved in toxicity. Toxicogenomics calls upon proteomics, metabolomics, and transcriptomics to identify biomarkers that predict toxicity and genetic susceptibility to harmful substances. Environmental pollutants, pharmaceuticals, and other potentially toxic substances are all within the scope of toxicogenomics research.

Computational Toxicology: Deals with the use of modern computational approaches and information technologies to elucidate mechanisms of toxicity. May also be referred to as toxicoinformatics.

Virtually every branch of toxicology listed overlaps with at least one other. Other ways to parse the discipline are by agents under consideration, such as venoms, pesticides, metals, solvents, drugs, and radiation. One can also look, instead, at target biological systems which the agent may affect, for example, liver, kidney, skin, and heart. As for toxins, they can be categorized by their biological origin, such as insect-, plant-, reptile-, or marine-derived toxins. Some toxicologists spend their careers focused very tightly on a subject, while others graze across many research fields.

ABOUT HISTORY

History is *about* the past; it is not the past. The past is passive, objective, all encompassing. History is active, subjective, and selective. The further back in time that we look, the more problematic it is for us to reach, in the present, conclusions about what happened in the past. Examples, particularly from ancient eras, described below, will show how tales accepted without question are currently being re-examined and revised, and remind us that history is also relative.

Science begins with observation. In the distant past, our observational skills did not extend beyond our senses. We put our senses, to good use, nevertheless, in assessing toxicity and safety even in prehistorical times (i.e., before the written record). Our hominin ancestors used trial and error extensively to explore their environment. In terms of toxicology, they would make careful note of which substances, particularly potential food sources, were safe and which were hazardous. Although it might very well be after the damage was done, they and their tribe and descendants would quickly learn to differentiate between the safe and toxic. Toxic substances, of course, were to be avoided, although it soon became clear that they could be used against enemies.

There are numerous ways to approach the history of toxicology because there are many histories, such as those of the branches outlined in the previous section. Complicating the presentation of a uniform history is the fact that these individual histories overlap. Given the space limitations of this chapter, we will focus on chemicals and proceed chronologically, taking occasional detours as necessary.

TOXICOLOGY IN ANTIQUITY

Ancient China

Shen Nong, the legendary founder of Chinese Herbal Medicine, also known as the farmer god (for he also taught his people how to farm), and said to live circa 2800 BC, saved his subjects from the worry of trying different potential food plants to decide whether they were poisonous. He was said to have tasted hundreds of herbs daily to differentiate the poisonous from the medicinal or just plain edible. Although the toxins he encountered made him sick frequently, he somehow survived them. He is also considered the author of perhaps the world's first pharmacological compendium, *Divine Farmer's Classic of Materia Medica*. His text, a compilation of oral traditions, was compiled in the 3rd century AD. Legend also has it that Shen Nong discovered tea when, sitting under a Camellia tree, dried leaves fell into the water he was boiling to drink (Wilkinson, 2007; Yang, 1998).

Du (毒) is the standard word for poison or toxicity in Chinese. It was understood by the ancient Chinese that drugs (herbals in this instance) were potentially toxic and dose played a role. Aconite, derived from the plant wolfsbane and possessing extreme potential toxicity, was widely used medicinally in small doses in China over 2000 years ago. It was usually applied externally, often processed in some way or mixed with other drugs, to treat various wounds, but was also ingested as a tonic to restore qi (the vital energy defined by Chinese medicine) and extend life. At the same time, sources from that era show that unadulterated aconite in larger doses was often used to murder (Liu, 2014). Today we know that the alkaloids in aconite have a narrow therapeutic index and their use is not generally recommended. Interestingly, it took several thousand years for the role of dose in toxicity to be firmly articulated in the West by Paracelsus, who is discussed later in this chapter.

The ancient Chinese poison, Gu, is one of many potions residing in that blurry historical space between fact and legend. Presumably, a variety of venomous creatures such as snakes, lizards, scorpions, and insects were confined in a container and left to devour each other until only one was left. This survivor thus concentrated in its body the toxins of all its former cell mates and the venom extracted from it was believed to be superbly potent.

Ancient India

Ancient India was no stranger to the knowledge and uses of poisons. Poisoned weapons of various sorts were well known. A Sanskrit verse reads, "Jalam visravayet sarmavamavisravyam ca dusayet," or "Waters of wells were to be mixed with poison and thus polluted" (Khajja et al., 2011). Sushruta was an Indian surgeon. Volume 5 of his medical and surgical compendium, *Suśrutasaṃhitā*, a foundational work in Ayurveda (traditional Indian medicine), contains several chapters related to poisons and poisoning, including descriptions of vegetable and mineral poisons (Sthavara) and animal poisons (Jangama), as well as advice on medical treatment of snake bites and insect bites (Wisdom Library, n.d.). *Agada Tantra*, one of the eight clinical specialties of Ayurvedic medicine, is specifically associated with toxicology (Manohar, 2014; Wujastyk, 2003).

India also has a long tradition of tales about the so-called "venomous virgin" (visakanya), first mentioned in the *Suśrutasaṃhitā*. This maiden, sometimes referred to as the "poison damsel," would, as a young girl, be fed "tolerably minute, but gradually increasing, amounts of poison or snake venom, and that by the time she was an attractive young woman, the level of toxin in her body would be so high that she could be sent to an enemy king as a gift. Upon kissing her, making love to her, or even just sharing glass of wine with her, he would instantly fall dead" (Slouber, 2015). The Rig Veda itself, one of the four texts sacred to Hinduism, includes hymns related to poisons (Wikisource, n.d.-a).

Ancient Egypt

Ancient Egypt was for nearly 30 centuries one of the world's preeminent civilizations and has left us a legacy of unrivalled art, architecture, and religious traditions. Animals played an important role in its belief systems. Egyptian gods and goddesses often took on a hybrid human–animal physical form.

Venomous snakes and insects were well known and the focus of toxicology as it existed in ancient Egypt. One of the major documents examining snakebite, and surviving in most of its entirety to our time are the Brooklyn Papyri (held by the Brooklyn Museum), 525–600 BC (Sanchez and Harer, 2014). Its two sections describe individual snakes and treatment for snakebites, respectively. Paragraph 15 of the Papyri, for example, describes the snake known by the Egyptians as Apophis which, mythologically, personified evil. Scholars believe this may be the Boomslang (*Dyspholidus typhus*) in the Colubridae family. Symptoms and signs of snake envenomation are presented in the Papyri. The treatments offered could be general, for any snakebite, or specific. Bites by snakes known to be lethal generally received no treatment. Therapeutic measures, overall, were largely symptomatic. One treatment that comes up with frequency is the use of Allii Cepae, the onion, used in various preparations depending on the bite. Often this was used in conjunction with induced vomiting to rid the body of the poison:

Paragraph 41: Very good remedies to be made for those suffering from all snake bites: Onion, ground finely in beer. Eat and spit out for one day. (then follows an incantation)
Paragraph 42: As for the onion, it should be in the hand of the priest of Serqet, wherever he is. It is that which kills the venom of every snake, male or female. If one grinds it in water and one smears a man with it, the snake will not bite him. If one grinds it in beer and sprinkles it all over the house one day in the new year, no serpent male or female will penetrate therein. (Nunn, 1996)

Toxicity is addressed to a lesser extent in other important papyri such as the Berlin, Edwin Smith, and Ebers papyri.

Cleopatra VII, born in 69 BC, is one of the most fascinating personalities to flourish in Egypt when Greece and Rome held sway. During her reign as Pharaoh, Egypt was a Hellenistic (i.e., Greek) province, part of the Ptolemaic dynasty, established after the death of Alexander the Great. After Cleopatra's death, Egypt was annexed by Rome. And while her romantic exploits with Julius Caesar and Mark Anthony have been grist for generations of writers and artists, it is her death that holds toxicological interest for us. After the Battle of Actium (on Greece's west coast), which ended in defeat for the Egyptians, and learning that Marc Anthony killed himself by a self-inflicted sword wound, Cleopatra decided to follow suit. It is said that she had her servants bring her a basket of figs, in which one or more asps (Egyptian cobra) were hidden, and holding one to her breast, she succumbed to its venomous bite. A recent analysis questions the feasibility of a maid capable of carrying a basket of one or more Royal Cobras (9.8–13 ft in length, and weighing some 13 lbs) camouflaged by figs (Tsoucalas and Sgantzos, 2014). Other evidence on the time frame of her dying support this doubt. It has now been suggested that a more likely scenario was that she was murdered, perhaps with a poisonous draught by Octavian, the victor in their battle. He may have then spread the rumor of her suicide to avoid turmoil in the streets (against him) by the subjects who adored her.

Pontus, Mithridates, and Theriacas

The kingdom of Pontus in northeastern Turkey played an interesting role in the history of poisons and antidotes. Mithridates VI, its ruler beginning in 120 BC, was a fierce adversary of Rome, engaging it in battle three times. Ultimately, he succumbed to defeat by Pompey in the third war and committed suicide. Even as a boy, Mithridates experimented with poisons and antidotes, even on himself. Son of a father who was murdered with poison and a mother who would have poisoned him in order to ascend to the throne, he went into hiding for a period of years. He returned to capture his rightful position by likewise using poison, probably arsenic. With a background like that, one could hardly consider it paranoia that he feared assassination by poison and took precautions to avoid it (Mayor, 2010).

His approach was to ingest small doses of toxicants to become immune to them. His lifelong pursuit was to create a universal

antidote, which came to be known as a theriac, his particular one called a Mithridatium, by creating a concoction of tiny amounts of deadly poisons and antidotes. Not as far-fetched as it seems, recent science reveals that exposure over thousands of years to arsenic among certain Andean highland populations may have resulted in a level of resistance in their modern-day descendants (Schlebusch et al., 2013).

There have been many speculations about what the ingredients of the Mithridatium were, but we do not know for certain, and may never know. Returning to Mithridates' defeat by Pompey, legend holds that the ignominy of it led him to want to end his life. He retreated, with a poison, to the highest tower of his castle with his daughters. His daughters insisted that they be administered the poison first. After they died, he drank the balance. He weakened, but did not die, and his disorientation prevented him from stabbing himself with his own sword as he attempted. Instead, at least in one version of his actual death, he appealed to his bodyguard, Bituitus, to impale him with a sword.

Ancient Greece

Nicander of Colophon (fl 130 BC), a Greek poet and physician, is the author of two of the oldest extant works on poisons—*Theriaka* and *Alexipharmaka*—both written in hexameter verse (Gow and Scholfield, 2014; Touwaide, 2014b). The *Theriaka* concerns venomous animals. As such they have a delivery system through which injection of their venom can be harmful to humans and other organisms. A large portion of this volume is devoted to snakes. Among other information, he describes 15 snakes, including several cobras, and the symptoms in humans associated with envenomation, followed by discussion of remedies. Additional narrative is devoted to spiders, scorpions, insects, lizards, and fish. His *Alexipharmaka*, a briefer poem, deals with 21 poisons from the vegetable, mineral, and animal kingdoms. Among them are aconite, white lead, and hemlock. As in his companion work, Nicander describes the poison, its symptoms, and antidotes.

The Greek philosopher, Socrates (469–399 BC), whose wisdom was kept alive through the ages via his disciple, Plato, became an iconic figure in the history of toxicology through his death. Convicted of corrupting the youth of Athens and disrespecting the gods, he was sentenced to death. The received knowledge of the ages, historiographically transmitted, is that his execution was to be carried out in suicidal fashion, with Socrates condemned to drink an extract of hemlock, a poisonous plant (*Conium maculatum*) well known to the ancients. Recently, scientific evidence has called this into question largely because the account provided in Plato's *Phaedo* describes a clinical disorder not caused by hemlock poisoning (Dayan, 2009), although the debate has yet to be resolved and some sources point to a possible mixture of hemlock and opium (Arihan et al., 2014).

Alexander the Great (born 356 BC) plays a role in the history of toxicology in Greece in that the cause of his death is an unsolved mystery as well (Mayor, 2014). He is said to have drunk vast quantities of wine at a banquet in Babylon, after which he suffered severe abdominal pain. Over days, things went from bad to worse and he developed partial paralysis finally dying two weeks later. Rumors of poisoning began circulating in no time. He had enough enemies. Some even thought that Aristotle, his former tutor, poisoned him. Some of his friends guessed that he succumbed to a legendary poison taken from the waterfall of the Styx River, not only the mythological entrance to Hades, but an actual place in the north central Peloponnese. Ancient writers have considered the river poisoned. Though possibilities abound and speculation is widespread, the true cause of Alexander's death has never been confirmed.

Recent discoveries suggest that even the Oracle at Delphi, perhaps the most important and sacred shrine in ancient Greece, is, in a curious fashion, toxicologically significant. Associated with the Greek god Apollo, people would pilgrimage to Delphi with questions usually about what events would occur in the future. They would address their questions to the Pythia, a role filled by various women at different time. Plutarch, the celebrated Greek biographer and essayist, served as one of the priests at the temple of Apollo at Delphi. He noted that *pneuma* (a kind of gas or vapor) was emitted in the *adyton*, a small inner sanctum type area (de Boer, 2014). The Pythia would sit on a tripod-shaped chair, given a chance to inhale the *pneuma*, and go into a trance, after which a priest would address to her the questions asked by the petitioners. Similar accounts appear in ancient texts by others including Plato. Modern-day research attempted to assess the likelihood of an actual gas affecting the mental states of these priestesses. A 2002 paper bringing together the skills of a geologist, archaeologist, and clinical toxicologist reviewed the various research studies, concluding that "the probable cause of the trancelike state used by the Pythia at the oracle of Delphi during her mantic sessions was produced under the influence of inhaling ethylene gas or a mixture of ethylene and ethane from a naturally occurring vent of geological origin" (Spiller et al., 2002).

Toxicology is also heir to a rich mythological tradition. After Hercules, for example, killed the nine-headed sea monster known as the Hydra, as part of his second labor, he cut it open and dipped his arrows in its venom, providing him with what may have been the first biological weapon for use in future battles. Achilles, one of the prominent heroes in Homer's *Iliad* was a victim of just such a poison. Immersed as an infant in the river Styx by his mother to make him immortal, she failed to realize that in holding him by the heel, that very part of the body would make him susceptible to future danger. And so, it was that in the final battle of the Trojan War, he was killed by a poisoned arrow shot into this heel. These are but two examples of how poisons were incorporated into myth and legend in ancient Greece and elsewhere.

Ancient Rome

The Romans of antiquity were also knowledgeable in the principles and practice of toxicology. Interestingly, the Latin word *venenum* can mean either poison or remedy, and one would typically modify the term according to the usage intended (i.e., *bonum venenum* or *malum venenum*).

Dioscorides (born 40 AD), a native of Anazardus, Cilicia, Asia Minor, was a physician who traveled through the Roman Empire with Emperor Nero's army. He would collect samples of local medicinal herbs as he encountered them. The information he gleaned became material for his encyclopedic *De materia medica*, compiled in the 1st century AD, and relied upon for centuries as the most extensive and reliable herbal available. In it he classified poisons as animal, plant, or mineral (Timbrell, 2005). More specifically, *De Venenis* and *De venenosis animalibus*, ascribed to Dioscorides but probably not written by him, covered poisons in general and animal venoms, respectively, and were very influential works in toxicology down through the ages (Touwaide, 2014a).

Galen, another Roman Empire era physician, born (129 AD) in Pergamon, had a monumental impact on the understanding and practice of medicine. He became court physician to Marcus Aurelius. He was a firm subscriber to the theory of the humors (blood, yellow bile, black bile, and phlegm), the origins of which may go back to ancient Egypt but which were first articulated about medicine by Hippocrates. Galen formulated his own Galeni Theriaca and claimed it improved upon the one concocted by Mithridates (Karaberopoulos et al., 2012). He wrote about assorted theriac

compounds in his books *De Antidotis* I and II and *De Theriaca ad Pisonem*. Indeed, he tested them by bringing roosters into contact with snakes.

Poisoning, especially among the ruling classes, was frequently practiced, typically (but not exclusively) by women upon their husbands or other inconvenient relatives. If they did not have the skills to do the deed themselves, they sought professional poisoners, usually women as well. One of the most notorious of the lot was Locusta. As the story is told, she was summoned by Agrippina, the wife of Emperor Claudius, to kill him so that Agrippina's son, Nero, from a previous marriage would become the new Roman emperor. Locusta supplied Agrippina with a batch either of poisoned or poisonous mushrooms. Though taken quite ill, the mushrooms did not kill Claudius outright. Quick thinking (though history is not quite clear by whom) led Agrippina to convince Claudius to let her run a feather down his throat to expel the poison. The feather itself, though, was coated with a lethal dose of poison which killed Claudius and thus Nero assumed the throne. Though Locusta was imprisoned, it was not long before Nero had her released and, in fact, employed her to poison Britannicus, a son of Claudius from a previous marriage and thus a threat to the new emperor. Nero ultimately pardoned Locusta for all past crimes and she was allowed to establish a school to train others in her art.

The legal framework of toxicology is sometimes dated back to the age of the Roman military and political leader Sulla. Under the *lex Cornelia de sicariis et veneficis* (81 BC), punishment was imposed for anyone who prepared, sold, bought, kept, or administered a noxious poison (venenum malum) (Hobenreich and Rizzelli, 2014).

A theory proposed in 1983 by Jerome Nriagu popularized the idea that the metal lead was responsible for the fall of the Roman Empire. It has been stated that the ruling classes, in particular, were exposed to lead contamination in water supplies, cooking, and the production of wine, ultimately decreasing their fertility and reproductive capacity. More recent archaeological investigations have found that although clinical lead poisoning probably did occur, the mean skeletal lead content of populations at the time was less than half that of present-day Europeans in the same regions. The assertion that lead was the primary culprit in Rome's decline and fall has been largely refuted (Cilliers and Retief, 2014a, 2014b).

Lead has continued to plague mankind, in occupational and other exposures, through the ages. Interestingly, in 1921 a global treaty the White Lead (Painting) Convention was adopted. It was meant to largely prohibit the use of white lead as a pigment in paint. With no thanks to the Lead Industries Association, this was never ratified by the United States (Hernberg, 2000). Herbert Needleman, a physician, was instrumental in helping us understand how lead affects children, particularly with his 1979 study in the *New England Journal of Medicine* noting deficits in children with high dental lead levels (Rosner and Markowitz, 2005). Still a concern in inner cities, lead periodically makes the headlines, as in the case of its seepage into the drinking water of Flint, Michigan, in 2016.

THE MIDDLE AGES AND RENAISSANCE

As we transition from antiquity to the Middle Ages at about 400 AD, toxicology continues to have a presence in European society vis-à-vis both poisoning as a means of dispatching enemies but increasingly in trying to establish its scientific foundation. Some of the well-accepted tenets of the toxicology of this time such as the hypothesis that the saliva of rabid dogs was a poison on a par with snake venom would see revision, but the scientific method was at least beginning to take hold.

The Venetian Council of Ten was a governing body in Venice from around 1310 until 1797. They were known for conducting secret tribunals whereby figures perceived as a threat to the state were ordered executed. Many of these executions were carried out by poisoning. There were several attempts on the life of Francesco Sforza of Milan, while Mehmed II, Sultan of the Ottoman Empire, was allegedly ordered to be poisoned by the Council (Jutte, 2015).

Poisoners continued to find steady employment but some reputations, as will be seen in the following paragraphs, were ill-deserved. Poisoning as an assassination method was widespread during the 14th to 16th centuries in Europe. Letters to Grand Duke Cosimo I de'Medici affirm as much. Animal venoms, phytotoxins, and mineral poisons were all employed. Cosimo himself was suspected of poisoning and was in possession of a poison recipe among his confidential documents and his library contained several books in which poisons were discussed. He was also involved in a plot to assassinate Piero Strozzi, part of a rival banking empire, by poisoning his wine. Poisoning was clearly a family affair with the Medicis, and Cosimo's sons Ferdinando and Francesco were equally complicit in it. Despite persistent rumors that Francesco and his wife, Bianca, were poisoned with arsenic by the former's brother, Ferdinando, the official cause of death was listed as malaria. Although recent forensic examinations still do not entirely agree, it now appears most likely that malaria was indeed the culprit (Fornaciari and Bianucci, 2010). Many legends surround Catherine de'Medici who moved to France to marry the future King Henry II. Despite multiple purported victims, there is no definitive evidence that she poisoned anyone. Developing and testing antidotes was also part of the Medicis' stock-in-trade (Pratte et al., 2014; Barker, 2017).

Another powerful and infamous Italian family, originally from Spain, and on whom were pinned numerous heinous crimes, poisoning among them, were the Borgias. There were claims, for example, that Cesare murdered a servant who was a lover of his sister, Lucretia, in front of their father Pope Alexander. Cesare was also said to have poisoned Cardinal Juan Borgia. The reputation of Lucretia herself was stained with allegations, by enemies of the Borgias, that she was a poisoner. Documents uncovered recently in the Vatican archives refute these and other claims concerning the Borgias and it is now thought that, though saints by no means, their undeserved reputation for extensive poisonings and murders stems from rumors spread and repeated by their enemies (Dal Bello, 2012; Cobb, 2017).

In 17th century France, during the reign of Louis XIV there had been a series of poisonings which have not, at least to date, been subject to any of the above revisionism. It became known as *L'affaire des poisons* (the Affair of the Poisons) and originated with the trial of Madame de Brinvilliers, convicted of poisoning her father and two brothers and attempting to poison other family members. Prior to her execution she implicated, without specifically naming them, many others, who were subsequently prosecuted and sentenced to death. One of the most notorious was the celebrated Catherine Deshayes, also known as La Voisin, an acknowledged sorceress, who did a very good business in poisons, abortions, and black masses. La Voisin was finally burned at the stake in 1680 for her crimes (Duramy, 2012; Somerset, 2014).

Giulia Tofana was yet one more notorious 17th century Italian poisoner, thoroughly skilled at her trade. It is thought that two women in Palermo, Francesca la Sarda and Teofania di Adamo, jointly concocted and marked a poison known as "Acqua Tufania" for which they were executed. Some of their associates fled to Rome and, under the leadership of Giulia Tofana, possibly Teofania's daughter, they carried on the business, even after the death of Giulia.

The poison became known as Aqua Tofana. Arsenic was likely a primary ingredient. It was sold throughout Italy to domestically unsatisfied women seeking freedom from their husbands. Aqua Tofana became an almost generic term for particularly potent poisons and the term has appeared in various sources, including medical textbooks, for some two centuries. Although originally producing violent symptoms, it ultimately became associated with a class of toxicants known as "slow poisons," which rather than existing in fact may have simply been a speculative class of agents designed to fuel the imaginations of the easily swayed (Dash, 2015).

As already mentioned, the Middle Ages and Renaissance were times not only of commonplace poisonings, particularly among the aristocracy and ruling classes, but of an increasingly sophisticated understanding of toxicology. Moses Maimonides, the great Jewish philosopher, theologian, and scientist, wrote his *Treatise on Poisons and their Antidotes*, originally in Arabic, in 1198. Part I was concerned with bites from snakes and rabid dogs (toxicology, remember, was still in its formative stage), and stings of scorpions and insects. Part II dealt with poisons in food and minerals, as well as remedies. He made a distinction between "hot" and "cold" poisons which, it has been claimed, may be equivalent to modern-day hemolysins and neurotoxins. Maimonides also emphasized preventive measures (Rosner, 1968; Furst, 2001; Maimonides, 2009).

The study of toxicants was so widespread in Persian and Arabic countries during the Middle Ages that the era has come to be known as the golden age of medieval toxicology. Among prominent toxicologists who wrote noteworthy treatises on the subject were Jābir (Jaber) ibn Hayyān (721–815 AD), Ibn Maāsawyah (Yuhanna ibn Masawyah, Abu Zakariya, 777–857 AD), and Ibn Waḥshīyah al-Nabti (9–10th century AD). Known by his Latin name of Avicenna in the West, Abū ʻAlīAal-Ḥusayn ibn Abd Allāh ibn Sīnā was perhaps the most noteworthy physician/scientist/philosopher of the Islamic world. His celebrated "Canon of Medicine" remained the most popular medical textbook for some six centuries (Nasser et al., 2009). Covering a broad range of topics, it includes detailed descriptions of venoms and other poisons, such as opioids and oleander, as well as instructions related to antidotes (Ardestani et al., 2017). He even explored the effect of alcohol on opium poisoning:

Patients may have concurrent alcohol poisoning. It can have a synergistic effect with opium poisoning and decrease its lethal dose. On the other hand, alcohol may serve as an opium antidote. This effect depends on the amount of ingested alcohol.

Many of his observations have been confirmed by current medical knowledge (Heydari et al., 2013).

On a very practical level, as was seen even in the Roman era, it became clear to ordinary people, especially those whose work entailed significant exposure to certain natural materials such as minerals, that their very occupations could be harmful. Georgius Agricola (1494–1555) born in the kingdom of Saxony, currently part of Germany, studied many subjects and completed his medical education in Padua. He has come to be known as "the father of mineralogy" largely as a result of his best known monograph, *De Re Metallica*, published in 1556.

Inevitably we reach the point where we address the incalculable contributions of the unorthodox medical revolutionary, Theophrastus von Hohenheim, called Paracelsus (1493/94–1541). Born in Einsiedeln, a municipality now in modern-day Switzerland, he was a wanderer and iconoclast, and strongly tied to the alchemical tradition. He theorized that there were four pillars of medicine: natural philosophy, astronomy, alchemy, and medical virtue. He went his own way and was not highly regarded by the medical establishment or local government officials. Indeed, as a lecturer at the University of Basel (as well as the city's municipal physician until being forced to flee), he burned the standard medical textbooks of the day, such as those of Avicenna and Galen (Borzelleca, 1999). History, though, has vindicated many of his teachings. In addition to his medical works, he was a keen observer and investigator of toxic effects of various agents and wrote a treatise about their effects upon miners. He concludes this work with a discussion of metallic mercury and criticizes its use at the time as therapy for people afflicted with syphilis (Gantenbein, 2017).

The most famous toxicological adage associated with Paracelsus is "The dose makes the poison," which is a distillation of what he wrote in his *Seven Defenses*, designed to defend his controversial teachings in the face of his adversaries:

Wenn jhr jedes Gifft recht wolt außlegen/ Was ist das nit Gifft ist? alle ding sind Gifft/ vnd nichts ohn Gifft/ allein die Dosis macht/ dz ein ding kein Gifft ist.
When you want to correctly evaluate a poison, what is there that is not poison? All things are poison and nothing is without poison; only the dose determines that something is not a poison.

This was surely known in various and sundry ways, certainly by experience, long before the time of Paracelsus, but never had it been so well articulated. We may, today, look upon the latter portion of this statement as an oversimplification. After all, what about factors other than dose which influence toxicity—gender, age, pre-existing conditions, genetics, the microbiome, etc.? This is all well and good, and it is not unusual for quite valid eureka moments to be refined over time, but for a concise encapsulation of one of the key components of what and when something is a poison, and which continues to serve as a bedrock of toxicology, Paracelsus deserves the laurel crown and the oft-cited appellation, "Father of toxicology." An understanding of the dose–response relationship is no less significant to our understanding of toxicology today than it was 500 years ago.

It is tempting to declare Paracelsus' legacy as ironclad. However, proponents of a theory originating in the 19th century known as hormesis are today suggesting that substances known to be toxic at elevated doses may actually have a beneficial effect at very low doses. Non-monotonic dose–response (NMDR) curves graphically describe hormesis. Hormesis remains a controversial theory among toxicologists.

Paracelsus was but one example of the tenuous link between alchemy and toxicology. The alchemist Jan Baptist Van Helmont, though once a disciple of Paracelsus, ultimately went his own way. Van Helmont did acknowledge that almost everything in nature is possessed of some secret poison but that somehow it overlay a core of goodness. He referred to the bible and medical alchemical theories to support his views and reveal ways to remove the poison (Hedeson, 2017).

Other key figures were Pietro d'Abano who compiled a treatise devoted to poisons and their remedies, *De venenis*, which sought to return to the pure Greek roots of toxicology; the Paduan physician Girolamo Cardano who offered a careful analysis on the relationship between poison and putrefaction; Gerolamo Mercuriale who focused on reconciling ancient and contemporary definitions of poison; and Andrea Bacci who argued against a universal definition of poison and also said that its unusual powers made it similar to other natural substances such as the magnet (Gibbs, 2017; see http://fredgibbs.net/posts/universals-and-particulars-of-poison).

Interest has always been keen on both preventing and treating poisoning. Various products of biological origin, typically solid and hard, were said to serve in this capacity. They include stones, shark teeth, bezoars, and horns, sometimes embellished and worn as jewelry, and used in table settings or even in some instances found

in graves. A bezoar stone is an indigestible mass found in the gastrointestinal system, especially the stomach. Etymologically, the word derives from the Farsi words, *bāk* (purification) and *zahr* (poison) and, indeed, the stones were described in ancient Arabic medical literature since the 8th century and used as antidotes by Persian, Arab, and Jewish physicians. Belief in bezoars made its way to Europe and is mentioned in Johannes de Cuba's *Hortus Sanitatis* in 1485 and Pietro d'Abano described their use in 1565 (Barroso, 2014, 2017).

Fossil shark teeth (Glossopetrae), as well, have found application as prophylactics, detectors, and neutralizers of poisons. In medieval times, it was said that such teeth mounted in silver announced poisons by "sweating" or changing color. Their ability to detect poison and protect humans from poisoning is cited in Lapidaries such as those of Marbode (11th century), Sloane (16th century), and Jean de Mandeville. Miocence specimens of *Otodus megalodon* from Malta were said to be the most efficacious of the shark's teeth. Due to a 16th century shortage of bezoar stones, a substitute that came to be known as Goa Stones was formulated. In addition to various precious stones, coral, ambergris, and musk, they often contained pulverized fossil shark teeth. Often gold-plated, they could be housed in containers of elaborate silver or gold. Scrapings from these stones mixed in wine, beer, or other beverages could purportedly ward off the effects of any poisons (Duffin, 2017).

Alicorn, that is, the horn of the mythical unicorn, was thought to have medicinal and poison detecting qualities. By the end of the 14th century, the idea became established that it too like shark teeth could detect poison by perspiring in the presence of adulterated food and drink. One of the earliest medieval sources about the medicinal power of unicorns (though the horn per se is not mentioned) is the *Physica b*y Hildegard of Bingen (1098–1179) (Lavers, 2017). James Primrose noted: "It can scarce be said, whether to the Bezaar stone, or to the Unicornes horn the common people attributes greater vertues, for those are thought to be the prime Antidotes of all" (Primrose, 1651). Narwhal teeth or the horns of many another animal were likely passed off as unicorn horns. In 1389, John of Herse made a pilgrimage to Jerusalem and observed, "Near the field Helyon in the Holy Land is the river Mara whose bitter water Moses struck with his staff and made sweet so that the children of Israel could drink thereof. Even now evil and unclean beasts poison it after the going down of the sun; but in the morning the unicorn comes from the sea and dips its horn into the stream and thereby expels the poison so that the other animals can drink of it during the day. The fact which I describe I have seen with my own eyes" (Unitarian Review, 1879). There was not, though, universal acceptance of the anti-toxic legitimacy of unicorn products (including powder). Two respected French authorities, Ambroise Paré (1510–1590), court physician to four French kings, and the pharmacist Laurent Catelan (1568–1590) from Montpellier, had differing views on alicorn, with the former a detractor of its efficacy and the latter a proponent (Gerritsen, 2007). Eventually, as with much else, the antidotal property of unicorn horns was consigned to legend.

18TH AND 19TH CENTURIES

Hermetical traditions such as alchemy did not suddenly disappear come 1700. Isaac Newton himself was a passionate alchemist, as was Robert Boyle, often considered the father of modern chemistry. That said, the scientific method gained increasing prominence in the 18th and 19th centuries as a way of understanding our universe, and toxicology benefited from this more sophisticated and methodical approach. A number of scientists made important contributions to toxicology during this time.

Richard Mead (1673–1754) is the author of the first book in English devoted solely to poisons, *A Mechanical Account of Poisons in Several Essays*. He described the signs and symptoms of snake envenomation, performed chemical tests on venom, and experimented on snakes (to study their venom delivery system) and other animals (Seifert, 2011).

Bernardino Ramazzini, born in Carpi, Italy, and educated at the University of Parma, was a physician whose seminal achievements have earned him the moniker Father of Occupational Medicine (Pope, 2004). While the connection between workers' illnesses and their workplace environment, including materials to which they are exposed, had been noted by the ancients, Ramazzini's analysis of this linkage raised the issue to an entirely new level. The first edition of his most famous book, *De Morbis Artificum Diatriba* (*A Treatise on the Diseases of Workers*), published in 1700, is the first comprehensive and systematic work on occupational diseases (Felton, 1997). It outlined the health hazards of chemicals and other substances, including repetitive motions, encountered by workers in over 50 occupations. Among Ramazzini's many enlightening observations, and one in which he quotes Hippocrates, is the following:

"When you come to a patient's house, you should ask him what sort of pains he has, what caused them, how many days he has been ill, whether the bowels are working and what sort of food he eats." So says Hippocrates in his work Affections. I may venture to add one more question: what occupation does he follow?

The spirit of Ramazzini lives on in the Collegium Ramazzini (CollegiumRazazzini), an independent, international academy founded in 1982 by Irving J. Selikoff and others, to advance the study of occupational and environmental health issues. It holds conferences, symposia, and training courses, and publishes statements and research papers.

Another key figure in occupational toxicology is Percivall Pott (1714–1788), born in London. In 1774 he published an essay, *Chirurgical Observations Relative to the Cataract, the Polypus of the Nose, the Cancer of the Scrotum*. In this he made the link between the profession of chimney sweeps (regarding soot lodging in the folds of scrotal skin) and scrotal cancer (Brown and Thornton, 1957). This was the first occupational link to cancer and Pott's investigations contributed to the science of epidemiology. It wasn't until the 1920s that benzo[a]pyrene was identified as the actual chemical responsible (Dronsfield, 2006).

There were many scientists spanning the 18th and 19th centuries who played significant roles in making toxicology the discipline that it is. The ability to synthesize new chemicals and the added ability to detect their presence, especially in small amounts, marked the beginning of the modern era of toxicology. For centuries, poisonings were confirmed only by confession or eye witness accounts. Making the leap from merely suspecting adulteration or poisoning to irrefutable proof was a major milestone for toxicology. Four scientists who made remarkable advances in the area of chemical detection were Karl Wilhelm Scheele, Christian Friedrich Samuel Hahnemman, Johann Daniel Metzger, and Valentine Rose. Scheele discovered oxygen before Joseph Priestley, although he published his results later. He is also credited with the discovery of hydrofluoric, hydrocyanic, and arsenic acids, and devised methods for detecting arsenic in body fluids and corpses. Hahnemman discovered a test for arsenic oxide. Rose and Metzger discovered the first methods for detecting elemental arsenic and arsenic oxides in fluids and tissues (Farrell, 1994). In 1836, the English chemist

James Marsh developed what came to be known as the Marsh test, a groundbreaking method for detecting arsenic.

The medical celebrity Mathieu Joseph Bonaventure Orfila (1787–1853) is often claimed by Spain (where he was born and studied) and France (where he continued his studies, worked, and died) (Bertomeu-Sanchez and Nieto-Galan, 2006; Bertomeu-Sanchez, 2009). While very influential in applying the concepts of chemistry to medicine, it was in toxicology that he excelled and for which he is best known. He became Dean of the Paris Medical Faculty and was a founding member of the Academy of Medicine. At a time when animal experimentation was somewhat less frowned upon, he experimented widely with dogs, varying the amount of poison (such as arsenic) administered and the route of administration, and tested antidotes and treatments. He authored *Traite des poisons*, one of the most popular textbooks of the first half of the 19th century (Orfila, 1814–1815). He subsequently extracted the sections on antidotes and treatments and published them in a compact free-standing volume designed not only for physicians but also for lay audiences that may not have access to medical care but need to know what to do in the event of a poisoning emergency.

Orfila was called to act as a medical expert in various criminal cases. He is best known for a case involving Marie Lafarge, charged with poisoning her husband. Eyewitnesses had seen her buying arsenic (used to exterminate rats) and stirring a white powder into her husband's food. Upon his exhumation, no evidence of arsenic was found using the newly improved test for arsenic devised by James Marsh, although doubts remained whether the physicians were performing the test properly. Orfila was summoned and found definite traces of arsenic in the body, and demonstrated that it did not come from the surrounding soil. Marie Lafarge was found guilty of murder and received a death sentence, later commuted to life in prison. The case cemented Orfila's reputation as the greatest toxicologist of the day.

And yes, indeed, not only Paracelsus, but also Orfila has been called "Father of Toxicology," but of course representing a different era, and for different reasons. "Father of Forensic Toxicology," or "Father of Modern Toxicology," might be more precise. Let's hope that all these "Father of Toxicology" claims don't result in any paternity suits.

In France, Francois Magendie (1783–1855) was best known for his pioneering contributions in neuroscience and neurosurgery, and experimental physiology. His studies on the effects of drugs on different parts of the body though led to the introduction of compounds such as strychnine and morphine into medical practice (Tubbs et al., 2008). His research into the mechanisms of toxicity of these and other alkaloids furthered the science of toxicology.

Claude Bernard (1813–1878), Magendie's most celebrated pupil, made several physiological discoveries including the role of the pancreas in digestion, the regulation of the blood supply by vasomotor nerves, and the glycogenic function of the liver. His work also led to an understanding of the self-regulating process of living organisms we now refer to as homeostasis. He won acclaim for his book *Introduction à l'Etude de la Médecine Expérimentale* (*An Introduction to the Study of Experimental Medicine*), a classic in the field. He stressed the importance of starting with a hypothesis and having results which are reproducible, thereby furthering the paradigm of the modern scientific method. In the realm of toxicology, Bernard demonstrated that the mechanism of action of curare resulted from its interference in the conduction of nerve impulses from the motor nerve to skeletal muscle. The sensory nerves were left intact. In addition to curare, he studied the toxicological properties of other neuroactive compounds such as opium, atropine, strychnine, and nicotine (Bernard, 1857; Conti, 2002). He was also the first to describe the hypoxic effects of carbon monoxide. Bernard was attuned to how the perturbation of biological systems by toxic agents can be of value to basic science. He stated:

Poisons can be employed as means for the destruction of life or as agents for the treatment of the sick but in addition there is a third of particular interest to the physiologist. For him the poison becomes an instrument which dissociates and analyses the most delicate phenomena of living structures and by attending carefully to their mechanism in causing death he can learn indirectly much about the physiological processes of life …

While Orfila, as we have seen, also experimented on dogs, and was one of many scientists, including Magendie, to subscribe to animal experimentation, Bernard established it as part of the scientific method. He stated:

Experiments on animals are entirely conclusive for the toxicology and hygiene of man. The effects of these substances are the same on man as on animals, save for differences in degree.

Bernard, though an acknowledged seminal figure in experimental medicine, was criticized over his vivisection experiments on unanesthetized animals. The debate over the moral ramifications of animal experimentation gained steam during his lifetime. Interestingly, his wife was appalled by this part of his work. She left him, took their daughters, and with them became ardent antivivisectionists (Cavan, n.d.).

Greatly influenced by Orfila, Robert Christison (1797–1882), a Scottish physician, was interested in underpinning medical jurisprudence, especially toxicology, with a scientific foundation. Early on, he investigated the detection and treatment of oxalic acid poisoning and followed this up with investigations on arsenic, lead, opium, and hemlock. His celebrated book, *Treatise on Poisons,* first published in 1829, went through four editions. In addition to his work on poisons, he made important contributions in nephrology (Wikisource, n.d.-b).

Substance abuse, dependence, and addiction have plagued people throughout all time. Published in 1821, Thomas De Quincey's penetrating *Confessions of an English Opium Eater* is an autobiographical account of his opium (more properly laudanum, for he took his opium with alcohol) addiction. His book covers both *The Pleasures of Opium* and *The Pains of Opium*. This may have been the first look at drug addiction but was followed by countless others, fact and fiction, in numerous artistic genres, literary, visual, and even musical: to name a few (some made into movies) Aldous Huxley (*The Doors of Perception*), Hunter S. Thompson (*Fear and Loathing in Las Vegas*), William S. Burroughs (*Naked Lunch* and *Junky*), and Irvine Welsh (*Trainspotting*). Billy Wilder's film, *The Lost Weekend* (1945), featuring Ray Milland, is a classic about alcoholism and Frank Sinatra stars as a heroin addict in *The Man with the Golden Arm* (1955).

THE MODERN ERA

Radiation

The late 19th century is about the time when an understanding of radiation and its potentially hazardous effects began to surface. As is the case with chemicals and biological agents, radiation can be and has been of enormous benefit to society in general and has resulted in countless positive health outcomes via diagnosis and therapy. Nonetheless, precautions are necessary because radiation hazards can be devastating. In 1895, Wilhelm Röntgen discovered x-rays, electromagnetic energy waves with wavelengths

some 1000 times shorter than those of light. He also learned that x-rays could penetrate human flesh. In 1896, Nikola Tesla intentionally exposed his fingers to x-rays and reported burns. In that same year Henri Becquerel discovered that uranium salts naturally emitted similar rays. Marie Curie, a student of Becquerel, named the phenomenon "radioactivity." She went on to discover thorium, polonium, and radium, and received the Nobel Prize twice (once with her husband and Becquerel in physics and later in chemistry). Tragically, her death was attributed to aplastic anemia, likely contracted from her extensive work with radioactive materials (Jorgensen, 2016).

Soon after radium's discovery, it was manufactured synthetically and was believed to have almost magical healing properties. It appeared in food products such as bread, chocolate, toys (because of its luminescence), toothpaste, cosmetics, suppositories, and products to treat impotence. One of the first revelations about the true potency of radioactivity and the scope of its potential danger concerned the unfortunate girls who became radium watch dial painters in the early 1900s. These "radium girls" were hired by the U.S. Radium Corporation to apply radium paint to watch and clock faces so they would glow in the dark. They were instructed to use their lips to shape the brushes to a fine point. By 1927, over 50 women died due to radium paint poisoning, and many of the survivors suffered significant health problems (Mullner, 1999).

The detonation of the world's first atomic bomb in 1945, the Trinity Test, an outgrowth of the Manhattan Project, took place in the New Mexico desert where the nuclear age literally burst upon the scene. There were no doubts, at this point, about the damage such a bomb could inflict and did. On August 6, 1945, while World War II was raging, an American B-20 aircraft dropped an atomic bomb over the city of Hiroshima, killing nearly 100,000 people on impact and decimating virtually the entire city. Maybe half of that number of people were killed when a second atomic bomb was dropped on Nagasaki. Tens of thousands of people in both cities would later die of radiation exposure or otherwise suffer devastating injuries (Blow, 2015). The Treaty on the Non-Proliferation of Nuclear Weapons (NPT), which entered into force in 1970 and was extended indefinitely in 1995, seeks to "prevent the spread of nuclear weapons and weapons technology, to promote cooperation in the peaceful uses of nuclear energy and to further the goal of achieving nuclear disarmament and general and complete disarmament" (UNODA, n.d.).

Although nuclear weapons were developed and used to intentionally wreak destruction and havoc, nuclear power plants are designed to harness the force of the atom for peaceful purposes, that is, to generate energy. However, things do not always go as planned. In 1979, the Three Mile Island plant in Pennsylvania suffered a malfunction that led cooling water to escape from the reactor, and the nuclear fuel rods suffered a partial meltdown. Thankfully, there were no detectable health effects in the population at large. In contrast, the people in the area of the Ukraine where the Chernobyl plant was located experienced a dramatic meltdown in 1986 and were not so fortunate. There was no containment structure and a plume of radioactive material was sent skyward. An estimated 30 people died from radiation poisoning over a period of weeks and several thousand more were put at risk for cancer. In 2011, a massive earthquake and tsunami disabled the power supply and cooling of three Fukushima Daiichi reactors in Japan. All three cores melted within days. No deaths from radiation sickness was reported but over 100,000 people were evacuated from their homes (NPR, n.d.; World Nuclear Association, 2017).

Food and Drugs

The science of qualitative and quantitative chemical detection was applied most effectively to the detection of chemicals in body fluids, drugs, and food. In modern society, we have grown so accustomed to regulations that ensure high standards of purity for most commercial products that it is difficult to remember a time when there were no such protections in place. The realization that there was indeed a need for them evolved gradually. Events leading up to the passage of the Pure Food and Drug Act of 1906 are a good place to start since much of what we consider the modern era of toxicology occurred in and around early efforts to regulate the commerce of food and drugs.

Toxicology has developed and continues, to some extent, to develop as a reactive (rather than proactive) field. Thus, chemical laws and regulations often are enacted in reaction to major or widespread exposure incidents. An early demonstration of this phenomenon is in the efforts to ensure the safety of certain substances to which virtually everyone was exposed, that is, food and drugs. As early as 1848, chemical analyses of agricultural products were carried out in the U.S. Patent office under the Department of the Interior by Lewis Caleb Beck, an American physician and chemist who researched the adulterants in many drugs commonly prescribed by physicians of the time (Kinch, 2016). In 1846 he published *Adulterations of Various Substances Used in Medicine and the Arts with Means of Detecting Them: Intended as a Manual for the Physician, the Apothecary, and the Artisan*. His publication helped promote the Drug Importation Act of 1848. At the time, there were six major ports of entry within the United States, namely New York, Boston, Baltimore, Philadelphia, New Orleans, and Charleston, where pharmaceuticals entered the American market. The 1848 law required the U.S. Customs Service to inspect and stop any adulterated drugs from entering the U.S. market. Inspectors were typically experienced physicians and pharmacists who could more easily detect a counterfeit substance. They were also armed with the added ability to conduct qualitative tests, such as those detailed in Beck's publication, to determine if a drug was adulterated.

The Department of Agriculture, which would eventually give rise to the Food and Drug Administration (FDA), was established under Abraham Lincoln in 1862. The Division of Chemistry rested within this department and employed a single chemist Charles Mayer Wetherill. In 1883, Harvey W. Wiley, who was to play a highly influential role in safeguarding the country's food and drugs, took over as the Division's fourth chemist. The Division of Chemistry became the Bureau of Chemistry in 1901 and in 1902 Wiley was granted $5000 to administer what came to be called the "Poison Squad" experiments. These experiments involved asking healthy volunteers to consume measured amounts of preservatives routinely added to food items to determine whether they were safe for human consumption. The experiments were carried out in a controlled setting with meals prepared by a designated cook and chemist William R. Carter (Pray, 2003). Although cringeworthy by today's ethical standards, some of the chemicals fed to these young men were borax, benzoic acids, and formaldehyde. While many still question the validity of these sensational experiments, the publicity helped to enlighten consumers about the potential dangers of adulterated foods and the importance of accurate labeling.

Wiley was not alone in his pursuit to rid the market of impure foods and drugs. Journalists as well took up the cause of exposing quack medicines and adulterated food staples thereby fueling Wiley's efforts. The so-called muckraking journalists of the early 20th century exposed hundreds of patent medicines as misleading, harmful, and sometimes deadly. One example (of many) was the

case of acetanilide, a nonsteroidal anti-inflammatory drug used to treat pain and reduce fever, but highly toxic. In 1905, Samuel Hopkins Adams published, in *Collier's Weekly*, "The Great American Fraud," a sensational article exposing the hoax of patent medicines (Adams, 1905). Upton Sinclair's 1906 book, *The Jungle*, detailed unsanitary conditions of workers in the meat packing industry. "The Jungle" was published as a serial in 1905 and then as a book in 1906. Despite the many efforts to pass legislation to ensure food and drug safety prior to 1906, nothing seemed to get through both the House and Senate and, unfortunately, many bills languished for years. Wiley worked tirelessly to institute food and drug legislation throughout his tenure at the FDA (1883–1912) and during this time over 100 food and drug bills were introduced in Congress with nearly all failing to gain any traction.

The Pure Food and Drugs Act and the Meat Inspection Act were passed on the very same day in 1906 by the then president Theodore Roosevelt. The former law became known as the "Wiley Bill" due to Harvey Wiley's efforts. The Bureau of Chemistry was reorganized in 1927 into the Food, Drug, and Insecticide Administration, later renamed the Food and Drug Administration and ultimately moved out of the Department of Agriculture entirely and into what is now the Department of Health and Human Services.

To backtrack a bit in time, England's attention to the adulteration of food and drugs actually preceded that of the United States by a half century. Friedrich Accum, Wiley's counterpart in the United Kingdom, published a book in the 1820s titled *A Treatise on the Adulterations of Food, and Culinary Poisons* with the subtitle *There Is Death in the Pot*. Accum wrote about hundreds of poisonous additives commonly used in food products to either sweeten, color, or bulk up foods. He also pointed a finger at the perpetrator, giving the names and addresses of the offending manufacturers, which was unprecedented at the time (Accum, 1820; Oser, 1987). Accum became extremely unpopular among wealthy shop owners and he eventually left the country. Friedrich Accum and, later, Thomas Wakley and Arthur Hill Hassall were the figures most responsible for the campaign to prevent food adulteration which eventually resulted in food and drug legislation in the United Kingdom (Oser, 1987).

The 1906 Pure Food and Drug Act in the United States did not have the broad impact that was intended. Wiley and other supporters were hopeful that the law would have far reaching implications and broadly protect the food supply. However, as written, its main purpose was to ban foreign and interstate traffic of adulterated, falsely advertised, or mislabeled food and drug products. It empowered the U.S. Bureau of Chemistry to inspect products and refer offenders to prosecutors, but gave no prosecutorial power to the agency itself. For example, during the Jamaican Ginger poisonings detailed in the next paragraph, the FDA was not involved in the investigation or prosecution of the crime until well after the case was resolved by a judge. The law required that the active ingredients be placed on the label of a drug's packaging and that drugs could not fall below purity levels established by the United States Pharmacopeia (USP) or the National Formulary. The USP and National Formulary guidelines were established some years earlier by a group of physicians and pharmacists, and served as a foundation for the Pure Food and Drugs Act. Although the law was popular, it was virtually impossible to enforce. The 1906 law prevented the manufacture, sale, or transportation of adulterated, misbranded, poisonous, or deleterious foods, drugs, medicines, and liquors. The new law led to the establishment of government-run analytical laboratories, and the conditional removal of certain ingredients such as ethanol, herbal mixtures, and coloring agents in most but not all cases. Many sections of the Act were overturned by the then Associate Justice Oliver Wendell Holmes and the U.S. Supreme Court in 1911. Wiley left the Bureau of Chemistry in 1912. The 1906 Act was not perfect, but it was a perfect jump start to the subsequent food and drug reform laws in the United States.

Prohibition in the United States ran from 1920 to 1933. During this time, there were very few legal means for obtaining alcohol. One of the few remaining options for alcohol consumption was via a doctor's prescription which would allow one to procure whiskey or rum from a pharmacist. Meanwhile, it was legal to purchase over-the-counter patent medicines or elixirs containing alcohol. Some disreputable drug companies began increasing the alcoholic content of their medicines or inventing new ones composed almost entirely of alcohol. One infamous concoction was Jamaica Ginger, which contained between 70% and 80% alcohol by weight. The U.S. Treasury Department required changes to the ingredients of Jamaica Ginger to discourage its abuse. The minimum requirement of ginger solids per cubic centimeter of alcohol resulted in a bitter concoction that was not palatable. Inspectors would often boil down the liquid and weigh the solids to ensure that the concoction was formulated appropriately. Two bootleggers (Harry Gross and his brother-in-law Max Reisman) developed an alternative recipe that could pass the inspection and taste well enough to sell by adding tri-ortho-cresyl phosphate (TOCP) to the mixture. In early 1930 reports began to pour in detailing strange paralysis of the legs, arms, and wrists with little to no recovery in large numbers of people throughout the midwest. By 1931 the disease, which had come to be known colloquially as Ginger Jake paralysis, had reached epidemic proportions affecting an estimated 10,000 people across the country from New York to California. Doctors eventually traced the illness back to the Jamaica Ginger elixir, but since the typical ingredients (as listed in the U.S. Pharmacopeia) were not known to cause disease they immediately suspected a contaminant was responsible. The matter was taken up by the Public Health Service's National Institutes of Health (NIH), which was newly formed from the Hygienic Laboratory in 1930. It was there that the adulteration with tri-ortho-cresyl phosphate was discovered. There were over 35,000 members of the United Victims of Ginger Paralysis Association (Morgan and Penovich, 1978). The Ginger Jake episode and other cases of false therapeutic claims made it clear that change needed to come to the 1906 law, and change it did, propelled by the sulfanilamide poisonings of 1937–1978.

Sulfa drugs were a 20th century miracle for the treatment of bacterial and fungal infections. The first sulfa drug, Protonsil, showed no effect in vitro with bacterial assays but was extremely effective in vivo. It was later discovered that Protonsil is metabolized to sulfanilamide in vivo and the science of the bioactivation of drugs was revealed. The discovery of sulfanilamide was heralded as a major event in combating bacterial diseases. However, for a drug to be effective there needed to be an equally effective delivery system. Sulfanilamide is highly insoluble in an aqueous solution. Originally prepared as an elixir in ethanol, chemists discovered that the drug was more soluble in diethylene glycol. Therefore, the latter solvent replaced it, and a sweet syrup was added to make it more palatable to children. The new preparation was labeled an "elixir." Many patients, most of whom were children, died of acute kidney failure resulting from metabolism of the glycol to oxalic acid and glycolic acid. The drug and its metabolites crystallized in the kidney tubules, leading to renal failure (Wax, 1994). This tragedy led to the passage of the 1938 Food, Drug, and Cosmetic (FD&C) Act, also known as the Copeland Bill, named for Senator Royal S. Copeland. It contained provisions for both misbranding and adulteration. A cosmetic was deemed to be adulterated if it "contains any poisonous or deleterious substance that may render it injurious to users

under customary conditions of use." The misbranding provisions prohibited labeling that is "false or misleading in any particular." The law also required that a package's ingredients and their amounts, as well as the name and address of the manufacturer, packer, or distributor, be clearly displayed on the label. To enforce the statute, the FDA was given search, seizure, and prosecutorial powers.

The sulfanilamide disaster played a critical role in the development of toxicology and inspired the research of Eugene Maximillian Geiling in the Pharmacology Department of the University of Chicago that elucidated the mechanism of toxicity of the sulfanilamide elixir (diethylene glycol). These studies began at the heart of the investigations in the late 1930s (Geiling et al., 1938). Studies of the glycols were simultaneously carried out at the FDA by a group led by Arnold Lehman, another legendary modern toxicologist.

Frances Oldham Kelsey was a research assistant in Geiling's lab at the University of Chicago during the sulfanilamide investigations and was responsible for conducting the animal toxicity testing with sulfanilamide. She earned a PhD from the University of Chicago in 1938 and graduated from Chicago's medical school in 1950. She started working at the FDA in 1960 where she was tasked with reviewing new drug applications for U.S. approval. Among her first assignments was a new drug thalidomide (Kevadon), an anti-nausea medication, also used to alleviate morning sickness in pregnant women, recently licensed by the William S. Merrell drug company based in Cincinnati, Ohio. The company had already distributed the drug to over 1200 U.S. doctors with the expectation that it would be approved quickly. Drugs could go on the market 60 days after the manufacturer filed an application with the FDA. It was often the practice of pharmaceutical companies to supply doctors with the new drugs and they were encouraged to test them on patients. Kelsey held up the application and asked Merrell for more information regarding its safety. By 1961 it became clear that thalidomide posed a serious safety risk. Infant deaths and deformities were occurring at an alarming rate across Europe and the German manufacturer began pulling the drug from the market in late 1961. By 1962 the application for approval in the United States was withdrawn completely. Though never licensed in the United States, physicians distributed the drug as samples to patients. The government estimated that more than 2 million tablets were distributed to around 20,000 patients in the United States and by late 1962 there were at least 17 babies with thalidomide-related defects. Worldwide, there were more than 10,000 babies born with thalidomide-related defects and countless pregnancies that ended in miscarriage (the exact number is unknown). The tragedy could have been far worse in the United States if not for the efforts of Frances Kelsey. The thalidomide tragedy led to the 1962 Kefauver-Harris Amendments to the FDA signed by the then President John F. Kennedy. With these amendments, the FDA was given the authority to require proof of efficacy (rather than just safety) before a new drug could gain approval. The amendments created the groundwork for the multi-phased approval process involving clinical trials, which is still very much in use today. Interestingly, under strict controls, in recent years thalidomide has been reintroduced as a treatment for certain symptoms of leprosy.

Even with the current laws in place, occasionally a drug must be highly regulated, recalled, or removed from the open market for reasons such as toxicity, impurities, lack of efficacy, or abuse potential. Clinical trials are conducted on populations significantly smaller than those eventually using the drug. Side effects not detected prior to approval often become apparent in the larger population. All other factors being equal, many effects are harder to detect in a small sample size. Increasing the sample size enhances the statistical power of a test which is the situation after approval when the drug is taken by many more people. Although drugs are often voluntarily removed from the market, there are cases where the FDA orders a drug to be recalled or removed. Mylotarg (gemtuzumab ozogamicin), for example, was approved under an accelerated approval process in 2000 for the treatment of acute myelogenous leukemia. In 2010 the drug was voluntarily withdrawn from the market by its manufacturer Pfizer. A phase 3 comparative controlled clinical trial demonstrated an increase in mortality. Additionally, the drug was not considered to be more effective over conventional cancer therapies available at the time. Vioxx (rofecoxib) was one of the largest worldwide (by Merck) recalls ever. This nonsteroidal, anti-inflammatory medication for arthritis was responsible for perhaps over 27,000 heart attacks and cardiac deaths. These effects did not emerge in the original clinical trials but subsequent trials confirmed the danger.

From around 1938 to 1971, millions of pregnant women were prescribed diethylstilbestrol (DES) as a hormone-replacement therapy and to prevent miscarriages and premature births. Research during the 1950s showed it was not effective. Before long it was discovered that DES caused a rare vaginal cancer (clear cell adenocarcinoma) in girls and young women who had been exposed to DES in the womb (Herbst et al., 1971). It was recalled from the market in 1971.

In some cases, a drug may be removed from the market temporarily to protect consumers. In 1982, there were several deaths eventually linked to Tylenol brand acetaminophen capsules. The capsules were laced with potassium cyanide (Wolnik et al., 1984). Several copycat crimes followed this incident; most notably, the conviction of Stella Nickell in 1987. Stella Nickell laced Excedrin capsules with cyanide, killing both her husband and a woman who purchased the tampered product. Crimes such as these made clear the need for tamper-evident packaging and led to the passage of the Federal Anti-Tampering Act of 1983. Tamper-evident packaging created visual evidence for the consumer that a product was opened or damaged prior to purchase. The new packaging didn't provide 100% protection against tampering but made it much more difficult to tamper.

The FDA is routinely scrutinized by Congress, the public, drug companies, and consumer advocacy groups. Amendments and other changes are issued as the need arises according to the changing landscape of drug use, discovery, and development.

Among the latest of these changes is the process by which the FDA plans to review applications for new drugs in the future. The FDA implemented an initiative to harmonize the review and approval process for new drugs with the SEND initiative in 2016. SEND stands for the Standard for Exchange of Nonclinical Data and is an implementation of the Clinical Data Interchange Standards Consortium (CDISC) Standard Data Tabulation Model (SDTM) for nonclinical studies. The primary purpose of SEND is to present nonclinical data consistently regardless of the source of the data.

Pesticides Research and Chemical Warfare: A Surprising Alliance

Naturally derived pesticides have been used to protect crops for thousands of years. The first recorded use of insecticides took place some 4500 years ago with the Sumerians who dusted elemental sulfur on their crops. Three thousand two hundred years ago, the Chinese used mercury and arsenic compounds to control body lice (Unsworth, 2010). Synthetic pesticide development and use is a product of the 20th century. The histories of synthetic pesticide use and chemical warfare agents go at least partially hand in hand. Their research and development was widespread throughout the

United States and Europe during the early 20th century. Many of the chemical warfare agents manufactured during World War I and II were discovered while conducting pesticide research. The chemicals under investigation were typically noxious chlorine derivatives and were discovered to be mildly to extremely toxic to humans. Not surprisingly, the peacetime attention to pesticide research was diverted to weaponizing many of these fortuitous discoveries during wartime. The effort behind the wartime manufacture of these agents was immense and after the war there was a surplus of what may arguably be considered the deadliest chemicals ever invented. The post-war effort was primarily geared toward disposal of these agents, although many were merely transferred and stockpiled in various countries outside of Germany. From 1946 through 1948 large amounts of various chemical weapons confiscated during World War II were dumped into the Baltic Sea after the war in a military campaign known as "Operation Davy Jones' Locker" (Kaffka, 1995). These materials continue to contaminate the waters and poison fishermen and wildlife as they are slowly released from their containers. The containers were not suitable for long-term storage and degraded over time.

Germany was responsible for much of the large-scale production of pesticides and warfare gases used in the early to mid-1900s. Fritz Haber, a German scientist, sought a way to capture nitrogen in the air for use in large-scale fertilizer production. His success, with further contributions from Carl Bosch, at nitrogen fixation (the Haber-Bosch process), garnered him the Nobel Prize in 1918. The Haber-Bosch process was instrumental in the manufacture of nitrogen-based explosives for the German Army during World War I (Hager, 2009). Some argue that the Germans would have run out poisonous gases if not for Fritz Haber and Carl Bosch. Bosch also researched the weaponization of toxic substances such as chlorine, phosgene, and mustard gas, leading to the largest deployment of chemical weapons in modern history. During World War I, the Germans launched a chemical attack using chlorine gas in Ypres, Belgium in 1915. Phosgene, which is now used in the manufacture of pesticides and plastics, was employed extensively by the Germans during World War I and accounted for nearly 85% of all gas-related fatalities during that war (Marrs et al., 2007). Tabun was the first nerve agent to be synthesized in 1937 by the IG Farben scientist Gerhard Schrader during his research to discover new organophosphate insecticides. The human toxicity of tabun was realized by accident during its development in 1935. Tabun causes acetylcholinesterase inhibition in the peripheral and central nervous systems. The symptoms that result include trembling, convulsions, and respiratory paralysis. During World War II, tabun was manufactured as a part of the Grün 3 program in Brzeg Dolny, Poland in 1942. The plant was seized by the Soviet Army and moved to Russia. The production and stockpiling of chemical warfare agents continued throughout World War II. In the 1930s Willy Lange (a German biochemist) and Gerhard Schrader also discovered organophosphate cholinesterase inhibitors including sarin, soman, cyclosarin, and other less potent organophosphate insecticides. This class of chemicals was destined to become a driving force in the study of neurophysiology and toxicology for several decades (Sneader, 2006).

The United States embarked upon an active research program to study the effects of exposure to these nerve agents and to develop a means of defense. Much of this early research occurred at the University of Chicago. The growth of toxicology in academia grew out of these studies of organophosphate pesticides. Eugene Geiling and Kenneth Dubois at the University of Chicago in the 1940s were instrumental in these early studies. Their dedication to fostering the education of so many other scientists in the field of toxicology was pivotal to the development of toxicology programs around the country.

It should also be noted that, pesticides aside, the spread of toxicology through academic development of eager scientists was accomplished decades earlier through the work of Oswald Schmiedeberg (1838–1921) and Louis Lewin (1850–1929) at the University of Strasbourg and Berlin in Germany, respectively. Schmiedeberg trained approximately 120 students in toxicology and Lewin, who trained under Matthias Eugen Oscar Liebreich at the Pharmacological Institute of Berlin (1881), studied the chronic toxicity of narcotics and other alkaloids. Lewin also published much of the early research on the toxicity of methanol, glycerol, acrolein, and chloroform (Lewin, 1920, 1929). Lewin wrote in his book *Gifte und Vergiftungen* (1929) of the causal connection between dental amalgam fillings and illness. One of his famous patients was the well-known chemistry professor Alfred Stock (1876–1946), who suffered from mercury poisoning due to chronic exposure to mercury vapors which was common among chemists at the time. Lewin informed Stock of the toxicity of mercury exposure from dental amalgams. In 1926 in an article in *Zeitschrift für Angewandte Chemie* (*Journal of Applied Chemistry*), Stock sided with the claim that mercury released from amalgam fillings caused poisoning and demanded that the use of mercury for this purpose be stopped.

Though Schmiedeberg and Lewin had a 60- to 70-year head start, the efforts at the University of Chicago were no less significant. Geiling and Dubois's toxicology lab there investigated the effects of chemical warfare agents synthesized by chemists working at the National Defense Research Council's Office of Scientific Research and Development. This organization (NDRC/OSRD) was founded in 1940 by Franklin Delano Roosevelt to manage and conduct scientific research related to the problems underlying the development, production, and use of devices and materials used for warfare. The university had a very large smokestack on the grounds making it an ideal place on campus to study the effects of poisonous gases. The toxicology lab at the University of Chicago was active for about 30 years, dissolving in the late 1960s (Doull, 2001). The lab produced many scientists who became leaders in the field of toxicology. These scientists went to other academic institutions, government agencies, and industrial laboratories and were instrumental in establishing many toxicology laboratories and programs throughout the United States, consequently spreading their knowledge and influence and lending credibility to the discipline. Members of Geiling and DuBois's group were the leaders in organophosphate toxicology. DuBois's colleagues, principally Sheldon Murphy, continued to be in the forefront of this special area of study for many years. Geiling and Dubois wrote the first undergraduate toxicology text, *Textbook of Toxicology*, in 1959 (DuBois and Geiling, 1959). In 1975, Louis Casarett and John Doull (1923–2017) followed with what has become the most widely accepted toxicology text in academic programs—*Toxicology: The Basic Science of Poisons*, currently in its ninth edition and edited by Curtis D. Klaassen of the University of Kansas. John Doull was a revered scientist and mentor who remained active in toxicology through most of the first quarter of the 21st century.

The importance of the early research on the organophosphates has taken on special meaning in the years since 1960. Organophosphate insecticides are typically short-lived and do not persist in the environment or bioaccumulate up the food chain. For this reason, many were used as a replacement for DDT and other persistent organochlorine insecticides. Today, a third generation of insecticides, mainly pyrethroids, has replaced many of the organophosphates formerly used.

DDT was recognized as an insecticide by Paul Hermann Müller in 1939, a discovery which won him the Nobel Prize in Physiology in 1972. DDT was extremely effective in preventing the spread of

malaria in developing countries. It was the chemical of choice for controlling insect populations in the United States as well. Not long after its introduction, it was discovered to have detrimental effects on wildlife, particularly on certain species of birds. The chemical caused fragility in eggshells and thus many birds didn't reproduce effectively and populations diminished over time. The work and research of Rachel Carson brought this to the attention of environmental scientists and to the public when she published her findings in the book *Silent Spring* in 1962 (Carson, 1962). Although she encountered considerable opposition from those in the research community, her conclusions could not be refuted. The subsequent 1972 ban of DDT was a milestone in toxicological history for several reasons. For one, it was the first ban of a chemical based upon its effects on wildlife. Further, the grassroots effort surrounding the desire to ban DDT joined other environmental advocacy movements, which together were instrumental in influencing the government to create the Environmental Protection Agency (EPA) in 1970. Although DDT can still be legally manufactured in the United States, its use is prohibited. However, it is still used on some continents such as South America and South Africa and has effectively decreased the incidence of certain diseases such as malaria, typhus, and bubonic plague.

Another popular and critically important book which has had a strong influence on toxicology as it relates to pesticides and other chemicals (such as DES discussed above) is Theo Colburn's *Our Stolen Future* published in 1996 with a foreword by the then Vice President Al Gore. It brought the concept of endocrine disruption, while not a new one, to the public and scientific forefront. The book argued that endocrine active (or estrogen mimicking) compounds may be eliciting effects at doses considerably lower than toxicities caused by other mechanisms, and that reproductive and developmental risks can be significant. U.S. federal agencies have since funded a multitude of research projects related to endocrine disruption.

The Poison Control Center Movement and High Profile Poisonings

Pesticides were not the only class of chemicals synthesized and used in great quantities in the mid-20th century. Many other potentially harmful industrial chemicals flooded the market. Poisoning in the home increased principally in young children with the advent and widespread use of laundry and cleaning agents. In the 1950s the American Academy of Pediatrics formed a special committee to consider the problem of poisoning in children. Louis Gdalman had already begun the first poison information services, however modest, in the 1930s at Saint Luke's Hospital in Chicago. He kept a detailed card index of the most common poisons along with their treatments and antidotes and maintained and answered a call line or hotline for emergencies as well. By 1953 the Chicago Area Poisoning Control Program was established with Saint Luke's at its epicenter in Chicago and Louis Gdalman as its head. Today this poison control center is known as the Chicago and Northeastern Illinois Regional Poison Control Center. Poison control centers were founded in Boston and New York soon after the one in Chicago, and by 1955 there were a total of 17 centers. There were 661 poison control centers in 1978 at the height of the poison control center movement. The number of active centers since then has dramatically decreased due, largely, to federal and state funding cuts (Institute of Medicine Committee on Poison Prevention and Control, 2004). There were approximately 54 active poison control centers nationwide in 2014 and they provided telephone guidance for nearly 2.2 million human poison exposures. Most poison control centers are also able to handle queries related to companion animals, and the ASPCA (American Society for the Prevention of Cruelty to Animals), founded in 1866, manages its own specialized Animal Poison Control Center, established in 1996. It operates 24 hours a day, 365 days a year. The invention of child-safety-lock packaging reduced many accidental pediatric ingestions and the iconic figure Mr. Yuk taught children to identify hazardous substances in the home. Ways to protect consumers from chemical products in the home was one issue that was fervently addressed with numerous campaigns geared toward education and prevention.

Poisonings, even apart from their irregular use in chemical warfare or inadvertent household exposures, have continued unabated from ancient times forward. Several of these have been of high profile personalities and some have been suicides. In 1978, Jim Jones, founder of the Peoples Temple, led over 900 of his followers, one third of them children, to their deaths, by ordering them to drink a cyanide-laced punch drink in Jonestown, Guyana. An umbrella outfitted with a firing mechanism was used to administer the poison ricin to the leg of Georgi Markov, a Bulgarian dissident and writer. He died several days later. Nazi leaders such as Hitler, Himmler, and Goering committed suicide with cyanide and were responsible for the poisoning deaths of millions of Jews during World War II. In 1995, five plastic bags of liquid sarin were punctured with metal-tipped umbrellas in Tokyo subway cars during rush hour releasing the deadly nerve gas. The Aum Shinrikyo religious cult, led by Shoko Asahara, was found responsible. In 2004, prior to his election as President of Ukraine, Viktor Yuschchenko was poisoned with dioxin, resulting in severe facial disfigurement due to chloracne. In 2006, Alexander Litvinenko, a former officer of the Russian state security organization FSB was poisoned by, and died from, radioactive polonium-210. In February 2017, Kim Jong Nam, the half-brother of North Korean Leader Kim Jong Un, was assassinated at a Malaysian airport when two women rubbed his face with the lethal nerve agent VX. It is clear that poisons continue to be a weapon of choice in politics and in society (Famous Deaths).

Mass Environmental Exposures, the U.S. EPA, and Environmental Legislation

Years prior to the advent of a full-fledged grassroots environmental movement, a variety of events made clear the fragility of our environment. The Donora Smog, for example, was a historic air inversion in Pennsylvania that killed 20 people and sickened 7000 more in 1948. In 1952, during the so-called Great Smog of London, over 5 days, more than normal coal emissions mixed with fog in a temperature inversion resulted in thousands of deaths and tens of thousands of hospitalizations. Recent research has determined that Londoners were breathing in the fog equivalent of acid rain. Sulfate was a big contributor to the fog, and sulfuric acid particles were formed from sulfur dioxide released by coal-burning for residential use and power plants (Wang et al., 2016). It was the Great Smog that led to passage of the 1956 Clean Air Act in the United Kingdom. In Cleveland, the Cuyahoga River is remembered as the body of water polluted from decades of industrial waste which infamously caught fire in 1969 (and, in fact, on earlier occasions as well). One seminal event, a harbinger of environmental awareness, was the celebration of the first Earth Day on April 22, 1970, an ongoing annual event.

More direct cause–effect incidents involving chemicals also began coming to light. Most companies didn't originally have built-in strategies for removing the waste they created. A common modus operandi was to create landfills for dumping the chemical byproducts that accumulated because of the manufacturing process.

The increase in the manufacture of chemicals translated to both an increase in direct human exposure via ingestion of products kept in the home, and an increase in indirect human exposure via leaching of dumped chemicals into the ground water, air, and food supply. One of the earliest and most pivotal demonstrations of the issue of chemical dumping in the United States that is, and one that would influence the course of toxicology, was the environmental disaster that came to be known as Love Canal. Epidemiological and other scientific studies confirmed the tragedy.

Love Canal in Niagara Falls, New York was used as a dump site by the Hooker Chemical Company for over a decade. In the 1970s, long after it was capped and an entire community built on top of it, weather patterns forced chemical waste into the groundwater and at surface. The entire area was found to be contaminated with a variety of toxic chemicals, which led to a cluster of illnesses among the residents living in the area. The activism around the contamination and subsequent cleanup led to legislation that would ensure that other chemically contaminated sites would receive government funding for cleanup and move families to prevent further exposure. This law, the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), commonly known as Superfund, was enacted by Congress on December 11, 1980. Administered by the EPA, it authorizes the cleanup of uncontrolled or abandoned hazardous-waste sites as well as accidents, spills, and other emergency releases of pollutants and contaminants into the environment.

Love Canal paved the way for other communities and sites to be cleaned up as well. Contaminated communities were found, for example, in Times Beach, Missouri where dioxin was discovered, and in Woburn, Massachusetts, where the primary contaminant of concern was trichloroethylene. Hexavalent chromium was discovered in Hinkley, California, and asbestos contamination in Libby, Montana. The EPA was given the responsibility to develop risk assessment methodology to determine health risks from exposure to effluents and to attempt to remediate these sites. Exposure to chemicals from these waste sites tend to be highly variable and unpredictable because they typically involve exposure to a mixture of chemicals. The effort behind the Love Canal incident led to broad-based support for research into the mechanisms of action of individual chemicals and complex mixtures.

Regrettable as it is that the consequences of toxic environmental exposure fall upon anyone, it is even more unfortunate that the burden is often borne by communities otherwise disadvantaged or in the minority, be it as a result, for example, of poverty, race, or education. Environmental justice, which advocates for the fair treatment of people of all persuasions with regard to the development, implementation, and enforcement of environmental laws, regulations, and policies, is but one example. The National Environmental Justice Advisory Council (NEJAC), a federal advisory committee to the EPA, was established in 1993.

Superfund was amended as a virtually direct result of the release of methyl isocyanate from a Union Carbide insecticide plant in Bhopal, India, in 1984. With an immediate death toll of some 4000, a final death toll of many thousands more, and even more victims who suffered and are still suffering lingering effects, Bhopal disaster remains probably the worst industrial accident in history. An important law authorized by Title III of the 1986 Superfund Amendments and Reauthorization Act (SARA) is the Emergency Planning and Community Right-to-Know Act (EPCRA). It requires public records of chemicals managed at facilities, and provides the EPA with the authority to work with states and localities to prevent accidents and develop emergency plans in case of dangerous releases of chemicals ("EPA Superfund"). The EPA's Toxics Release Inventory (TRI), a publicly accessible online database, is an outgrowth of EPCRA. It lists, among other annually collected data, the numbers of pounds of certain potentially hazardous chemicals released to the environment.

Outside of this fairly straight line to regulations protecting the American public from chemical releases, there was no shortage of other disasters throughout history. For decades in the early part of the 20th century, one of Japan's Chisso Corporation plants began releasing methylmercury in industrial wastewater to Minamata Bay. It bioaccumulated in the aquatic life in the Bay and was eaten by the local populace, as well as animals. With the situation not discovered until 1956, it took a severe toll on the population. Over 2000 victims suffered from severe nervous system symptoms, and many of those died (Hachiya, 2006). Referencing this disaster as well as many other health concerns of the chemical, the 2013 Minamata Convention on Mercury is a global treaty to protect human health and the environment from the adverse effects of the chemical and its compounds ("Mercury Convention"). Itai-itai, another disease outbreak in Japan, was caused by cadmium poisoning, resulting from the release of large quantities of this chemical into the Jinzū River from mining operations. Weak and brittle bones are among the main effects. Again, it took decades for this to come to light and investigations were not undertaken in earnest by the Toyama Prefecture until 1961. In Italy, the 1976 Seveso disaster was the result of an industrial accident. Named after the Italian town of Seveso, it resulted in the exposure of thousands of people to dioxin. Chloracne was among the main sequelae and there was an excess risk of lymphatic and hematopoietic tissue neoplasms in the most exposed zones (Pesatori et al., 2009). Man-made as well as naturally occurring environmental accidents involving chemicals have occurred throughout the world. Some of these exposures were avoidable and some were not. When natural phenomenon leads to chemical exposures we are often left without a clear understanding of the cause. On August 15, 1984, Lake Monoun in West Province, Cameroon exploded in a limnic eruption, in which dissolved carbon dioxide suddenly erupted from deep lake waters, forming a gas cloud with suffocating potential. The gas killed 37 people. At that time, such eruptions involving volcanic lakes were unknown. It was still unclear how to deal with this type of disaster 2 years later when on August 21, 1986 a similar and even more deadly eruption occurred at Lake Nyos, about 100 km (62 mi) NNW. The Lake Nyos eruption killed approximately 1746 people and more than 3000 livestock. Lake Monoun, Lake Nyos, and Lake Kivu are the only known volcanic lakes in the world to have high concentrations of gas dissolved deep below the surface (Kling et al., 2005). The buildup of these gases can result in a limnic eruption. Currently efforts are underway to understand these volcanic lakes and devise ways to safely degas them without harming humans or surrounding plant and animal life. With each new environmental mishap or disaster, we are reminded of the fragility of human life and the ecosystem. We can learn by understanding how and why these exposures occur and either prevent or prepare for the next incident.

The Toxic Substances Control Act (TSCA) is a U.S. law passed by the United States Congress in 1976 and administered by the United States Environmental Protection Agency. The law regulates the introduction of new or already existing chemicals. When the TSCA was put into place, all existing chemicals were considered to be safe for use. There were, however, some 62,000 chemicals that were never tested by the EPA because they were "grandfathered" in and statutorily not considered an "unreasonable" risk. The TSCA did not require any toxicity testing before submitting a Pre-Manufacturing Notice (PMN). No safety information was required to be included in the PMN. The EPA had to rely on

computer modeling to determine whether the new chemical "could" present an unreasonable risk. The 2013 reform to the law aimed to fix the key flaws in TSCA's safety standard. These flaws led to the EPA's inability to ban asbestos. The new changes allowed the EPA to order testing without first having to show potential risk, and making more information about chemicals available to states, health professionals, and the public by limiting trade-secret allowances. The Frank R. Lautenberg Chemical Safety for the 21st Century Act revised the standard TSCA used to determine whether regulatory control of a certain chemical is warranted. If a chemical presents an unreasonable risk of injury to health or the environment, TSCA requires the EPA to initiate rulemaking to reduce risks to a reasonable level. The bill requires that standard to be based on exposure to a chemical under its conditions of use.

A sampling of other significant environmental legislation administered by the EPA includes the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (1947), which regulates pesticides, the Clean Air Act (1970), the Clean Water Act (1972), the Safe Drinking Water Act (1974), and the Resource Conservation and Recovery Act (RCRA) (1976), giving the agency the authority to control hazardous waste from "cradle to grave," all strengthened in various ways with amendments since their initial implementation.

The Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) is a European Union regulation dated December 18, 2006. REACH requires all companies manufacturing or importing chemical substances into the European Union in quantities of one ton or more per year to register these substances with the European Chemicals Agency (ECHA) in Helsinki, Finland. Since REACH applies to some substances that are contained in products ("articles" in REACH terminology), any company importing goods into Europe could also be affected.

Occupational Safety and Health and Industrial Toxicology

As we have seen, concerns about occupational safety date back to antiquity. Modern industrial toxicology in the United States, though, was born out of the Bureau of Labor Statistics (BLS) in the early 1900s with the first report on industrial hygiene commissioned in 1903 by Carroll D. Wright, the Bureau's first commissioner. Charles P. Neill, Commissioner of the Bureau when the 1906 Meat Inspection Act and Food and Drug Act were passed, was responsible for inspecting the meat packing factories just prior to the passage of these laws. Neill was an advocate for industrial health and safety issues and made them a priority for the Bureau. After the Federal Employees' Compensation Act of 1908, Neill began to put even greater emphasis on industrial hygiene and safety. He was aware of and impressed by Alice Hamilton, Chief Medical Examiner for the Illinois State Commission on Occupational Diseases, and convinced her to work for the BLS. She was given the official title of "Special Investigator of Industrial Diseases" and one of her first assignments was to investigate companies in the United States that manufactured white lead. She discovered 358 cases of lead poisoning between 1910 and 1911, 16 of which were fatal. She also discovered incidents of lead poisoning in the pottery making industry and in the painter's trade. Alice Hamilton was a modern-day pioneer of occupational safety comparable to Ramazzini in his day. She traveled the country documenting the diseases associated with various occupations, and while not officially employed by the government during her early excursions, her research and reports were respected and procured by the government. She conducted surveys throughout the United States and abroad. She read extensively on worker protection. While the subject was documented and recognized as an official branch of medicine in Europe, workplace-related diseases and preventive measures received scant attention in the United States. Government officials at that time were unconcerned, and assured her that the working conditions in the United States were better than those in other countries so there was no need for industrial safety. However, a survey conducted by the BLS under Carroll Wright proved otherwise. Investigations of the match-making industry revealed hundreds of workers suffering from "phossy jaw" after being exposed to phosphorous dust particles. The disease caused painful swelling of the gums and jaw. Abscesses in the jaw that resulted in partial or total removal of the jawbone were common. Often the condition led to organ failure and death. Phossy Jaw was well known in both Europe and the United States at the time. European industrial medicine experts warned of this occupational disease in their countries, but the United States did little to protect or warn its workers. Hamilton was determined to document and make public information about these diseases so that something could be done to protect workers. During her surveys, she gained entry into countless factories, becoming well informed of the manufacturing processes for various trades. She was the leading authority on lead poisoning and reported on the high mortality rates of workers in the lead industries. Her reports undoubtedly invigorated the laws that were passed, as many were a direct response to tragedies or diseases she uncovered in workplaces across the country. The seed for occupational safety was planted by a small group of concerned officials, but it was cultivated by Hamilton who became the eyes and ears of the movement (Hamilton, 1943).

The BLS was not the only organization to address occupational health and safety concerns. The Bureau of Mines, for example, was created in 1910, within the Department of the Interior, and health and safety were within its purview. The National Safety Council was established in 1911. An Office of Industrial Hygiene and Sanitation was established within the Public Health Service in 1914. The *Journal of Industrial Hygiene* started publication in 1918. By the late 1940s many of the country's largest companies (such as Dow, Du Pont, and Union Carbide) began to establish internal toxicology laboratories to help ensure worker safety. Frank A. Patty who served as Director of Industrial Hygiene for General Motors authored *Industrial Hygiene and Toxicology* in 1948. His book, now known as *Patty's Industrial Hygiene and Toxicology* has gone through many editions and is a standard of the field. The Occupational Safety and Health Administration (OSHA) was founded in 1971 with the first guidelines for standards of safety following in 1972. Hamilton published *Industrial Hygiene* in 1925, the first American textbook in the field. She published *Industrial Toxicology* in 1934.

Harriet Hardy was a physician from Massachusetts. She became interested in industrial toxicology and began working for the Massachusetts Division of Occupational Medicine. She began studying the diseases of workers in the fluorescent bulb industries in Ipswich, Lynn and Salem, Massachusetts around 1945 (Castleman, 1994). She discovered that many of the workers contracted berylliosis. Berylliosis is caused by the inhalation of dust or fumes containing beryllium. The disease presents itself with coughing, weight loss, shortness of breath, and scarring of the lungs. While beryllium was a main area of study for Dr. Hardy throughout her career, she also studied anthrax and mercury poisoning. Alice Hamilton invited Hardy to update *Industrial Toxicology*. *Hamilton and Hardy's Industrial Toxicology*, now in its 6th edition, is another classic of the field. The OSHA passed in 1970 by President Nixon also created the National Institute for Occupational Safety and Health (NIOSH). Although OSHA is the regulatory agency that establishes limits to

chemical exposures in the workplace and investigates workplace hazards, NIOSH conducts research to help to reduce workplace illnesses and accidents.

MISCELLANEOUS ORGANIZATIONS

While organizations are discussed throughout this chapter in the context of the particular subject under consideration, we gather together here several additional professional societies, governmental organizations, and other bodies that been influential in toxicology.

The discipline and profession of toxicology has grown enormously in the past century. There are numerous scholarly societies, professional and government organizations, conferences, textbooks, and educational programs, all dedicated to toxicology. The Society of Toxicology (SOT) was founded in 1961 by Fredrick Coulston, William Deichmann, Kenneth DuBois, Victor Drill, Harry Hayes, Harold Hodge, Paul Larson, Arnold Lehman, and C. Boyd Shaffer (Hays, 1986). There were 108 charter members who joined SOT the first year. There are now thousands of members of SOT in addition to members of affiliate organizations who attend the annual conference. To name just a few other groups devoted to more specialized areas of toxicology, consider the International Society of Toxinology (est. 1962), the American Academy of Clinical Toxicology (est. 1968), the Society of Forensic Toxicology (est. 1970), the Society of Toxicologic Pathology (est. 1971), the Society of Environmental Toxicology and Chemistry (est. 1979), the American College of Toxicology (est. 1979), the Society of Risk Analysis (est. 1980), and the International Society for the Study of Xenobiotics (est. 1981).

The FDA continues to play a primary role in toxicology research and regulations. The National Center for Toxicological Research (NCTR), founded in 1971 to support FDA's ability to make science-based decisions, is considered its research arm. The National Institute of Environmental Health Sciences (NIEHS) is a branch of the National Institutes of Health (NIH) and was founded in 1969 to study the effects of the environment on human disease. NIEHS is home to the National Toxicology Program, an interagency program of the Department of Health and Human Service (DHHS), and dedicated to testing and evaluating substances in the environment. Other U.S. government agencies, although their mission does not focus on toxicology, are in fact involved in it to one extent or another. Examples are the Department of Transportation, which regulates hazardous materials, and the Department of Housing and Urban Development, which considers toxic chemicals in dwellings. The Consumer Product Safety Commission is a regulatory agency charged with protecting the public from unreasonable risks of injury or death associated with the use of consumer products, including household chemicals. Certainly, state and local jurisdictions also must deal with issues relating to toxicology and environmental health.

The Gordon Research Conferences "provide an international forum for the presentation and discussion of frontier research in the biological, chemical, and physical sciences, and their related technologies" (Gordon Research Conferences, n.d.). They have played a key role in the history of toxicology and in furthering its research. A series of conferences were held on toxicology and safety evaluation, beginning with one chaired by Bernard Oser in 1956. Indeed, it was at the conference in 1961 at Kimball Union Academy in Meriden, New Hampshire that the first organizational meeting for SOT was held. There continue to be several Gordon Research Conferences of toxicological relevance each year.

There are also several organizations that offer certification in toxicology. The American Board of Toxicology is considered the "gold standard" in the field for many and its diplomats receive the "DABT" designation upon successful completion of the exam. The Academy of Toxicological Sciences, the American Board of Medical Toxicology, the American Board of Forensic Toxicology, and the American Board of Veterinary Toxicology are also among the main certifying organizations within the various toxicology disciplines.

The Federation of European Toxicologists and European Societies of Toxicology, or EUROTOX, fosters the science and teaching of toxicology throughout Europe. On an even broader global level, the International Union of Toxicology, founded in 1980, has as its members toxicology societies from around the world, and hosts the triennial International Congress of Toxicology (ICT) in addition to the Congress of Toxicology in Developing Countries (CTDC).

INTERNATIONAL ENVIRONMENTAL CONVENTIONS AND OTHER GLOBAL EFFORTS

Given that toxic agents do not respect national borders, it is important to seek, where possible, international agreements on controlling them. Globally, there are treaties that have had, and continue to have, a strong component related to chemicals management. Multilateral Environmental Agreements (MEAs) is the broad term used to encompass such agreements, some of which are directly relevant to toxicology in terms of managing potentially hazardous chemicals. While such international conventions were signed even in the early years of the 20th century, most of them are an outgrowth of several United Nations conferences, that is, the UN Conference on the Human Environment (Stockholm, 1972), the UN Conference on Environment and Development, aka the Earth Summit (Rio de Janeiro, 1992), and the UN World Summit on Sustainable Development (Johannesburg, 2002). The big three MEAs particularly relevant to chemicals management are the Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal (adopted 1989; entered into force 1992), the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade (adopted 1998; entered into force 2004), and the Stockholm Convention on Persistent Organic Pollutants (adopted 2001; entered into force 2004).

Complementing the treaties above is the Strategic Approach to International Chemicals Management (SAICM), a non-binding policy framework to promote chemical safety around the world. Its overall objective is "the achievement of the sound management of chemicals throughout their life cycle so that by the year 2020, chemicals are produced and used in ways that minimize significant adverse impacts on the environment and human health." SAICM's objectives are grouped into five themes: risk reduction; knowledge and information; governance; capacity-building and technical cooperation; and illegal international traffic. SAICM's final decision-making meeting before the 2020 goal, the fourth session of the International Conference on Chemicals Management, was held in Geneva in 2015.

ANIMAL ALTERNATIVES, RISK ASSESSMENT, AND GREEN CHEMISTRY

While we have already seen how poisoning incidents and environmental accidents can spur legislation and consequently influence and advance the course of toxicological science, another issue has

played a major role as well. The practice of using animals in scientific experiments with the ultimate aim of advancing biomedical research and safeguarding human health has had a long and checkered history. Greeks such as Aristotle and Erasistratus performed experiments on living animals as early as the 4th century BC (Hajar, 2011). Though animal experimentation was generally well intentioned and has resulted in significant breakthroughs in improving health, there have always been ethical concerns and continued questions about relevance and cost. Over the years, more and more, the public advocated for, and toxicologists employed, alternative means to assess the toxicity and safety of toxicants. The need for less expensive, and more efficient and germane, means of testing were spurs to the search for animal alternatives, in support of the significant argument of compassion.

W.M.S. Russell and R.L. Burch first proposed the concept of the Three Rs, standing for Replacement, Reduction, and Refinement, in 1959 (Russell and Burch, 1959). These ethical principles are widely adhered to throughout the world as a way to significantly limit the number of animals used in scientific experimentation. The term *alternatives*, as an approximate synonym for the Three Rs, was coined by the distinguished physiologist David Smyth in 1978 (Smyth, 1978). The U.S. Animal Welfare Act, signed into law in 1966, regulates the treatment of animals in research and exhibition, and was a good first step in addressing the issues of animal use but it wasn't until the technology advanced sufficiently that true inroads were made into alternatives to animal testing, which in turn were an impetus to strengthen the framework of risk assessment.

The EPA defines human health risk assessment as "the process to estimate the nature and probability of adverse health effects in humans who may be exposed to chemicals in contaminated environmental media, now or in the future." In 1983, the National Research Council (NRC), in its publication, *Risk Assessment in the Federal Government* (also known as the Red Book), set forth a critical paradigm for assessing risks consisting of four steps: (1) hazard identification, (2) dose–response assessment, (3) exposure assessment, and (4) risk characterization. They also drew a distinction between this scientifically grounded process and the process of risk management, which ideally relies upon it, but brings into play economic, legal, social, technological, and political factors, as well as public values (National Research Council, 1983). A complementary NRC publication in 2009 focused on improving both the technical analysis supporting risk assessment and the utility of risk assessment, that is, making it more relevant to and useful for risk-management decisions and offered several recommendations (National Research Council, 2009). An NRC companion volume of another sort urged strengthening activities in exposure science (National Research Council, 2012). Given that exposure assessment is a critical step in the risk assessment process, it has been surprisingly underemphasized as a scientific companion to toxicology. The committee preparing this report "envisions a shift toward a toxicologic assessment program that has an interface with exposure science and is influenced by and responsive to human and environmental exposure data." Most recently, in 2017, the National Academies issued the report, "Using 21st Century Science to Improve Risk-Related Evaluations" (https://www.nap.edu/catalog/24635/using-21st-century-science-to-improve-risk-related-evaluations). It considers advances in molecular and cellular biology, omics technologies, analytical methods, bioinformatics, and computations tools, looking as well at exposure science, and makes recommendations for integrating these new scientific approaches into risk-based evaluations.

The Precautionary Principle is a relatively recent means of integrating ethical and common sense concerns into the risk assessment process. The 1998 Wingspread Statement on the Precautionary Principle summarizes it as follows:

When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. In this context the proponent of an activity, rather than the public, should bear the burden of proof.

While not new conceptually (e.g., better safe than sorry), formalizing it has helped incorporate the principle into various policies and laws. Although not scientifically grounded, it invokes common sense for many people, scientists included. The Stockholm Treaty on Persistent Organic Pollutants, for example, invokes the Precautionary Principle to govern genetically modified organisms and some toxic chemicals (http://sehn.org/wingspread-conference-on-the-precautionary-principle/).

Tied in with both modern approaches to non-animal testing and bringing risk assessment into the 21st century is the concept of "Green Chemistry." The term was coined in 1991 by Paul Anastas, at the time an EPA staff chemist, who also developed and launched the EPA's Green Chemistry Program (Anastas, 2009). It was after publication of his 1998 groundbreaking book *Green Chemistry: Theory and Practice* that this approach to creating safer chemical products was better appreciated by toxicologists (Anastas and Warner, 2000). Sometimes called "sustainable chemistry," its focus is on the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances and applies across the life cycle of such products. Sustainability itself has become one of the early 21st century's buzzwords. There is no universal definition of sustainable development, but one of the most widely quoted and earliest comes from the 1987 Brundtland Commission Report, also known as *Our Common Future*: "Development that meets the needs of the present without compromising the ability of future generations to meet their own needs" (Brundtland Commission, 1987). This very broad definition easily encompasses green chemistry and the direction toxicology should be taking in the future.

INFORMATION RESOURCES

Often overlooked in discussions, historical or otherwise, of any science, is its informatics framework. The National Library of Medicine (NLM), currently a component of the National Institutes of Health (NIH), began life in 1836 in the office of the U.S. Army Surgeon General. The Index Catalogue to its collection of monographs and periodicals was launched in 1880 and Index Medicus, the first comprehensive index of journal articles, in 1879. Toxicology papers have been in scope since those early years. The Toxicology Information Program was established at NLM in 1967 at the behest, a year earlier, of the President's (i.e., Lyndon Johnson) Science Advisory Committee. The Committee concluded that "there exists an urgent need for a much more coordinated and more complete computer based file of toxicological information than any currently available and, further, that access to this file must be more generally available to all those legitimately needing such information" (PSAC, 1966). The program was renamed the Toxicology and Environmental Health Information Program (TEHIP) in 1994.

The TOXLINE database, intended to be a comprehensive bibliographic resource for scientific literature on toxicology, started operation in 1972 and ultimately was incorporated into the larger TOXNET system ("Toxnet"). Today, TEHIP offers an extensive array of free online databases including TOXLINE, the Hazardous Substances Data Bank (HSDB), the chemical dictionary ChemIDplus, the Household Products Database, Haz-Map, an

occupational health and toxicology database, EPA's Toxics Release Inventory, and many more.

The EPA's Aggregated Computational Toxicology Online Resource (ACToR), with data on over 500,000 chemicals, is another major portal as is the OECD's eChemPortal, initiated in 2004 in response to the request by the World Summit on Sustainable Development to improve the availability of hazard data on chemicals. Finally, the European Chemicals Agency (ECHA) offers a unique source of information on well over 100,000 chemicals (https://echa.europa.eu/information-on-chemicals).

WHERE ARE WE HEADED?

Looking to the future, toxicology, no differently than other sciences, will continue to rely heavily upon the knowledge gained from basic research. New techniques and technologies have only improved the field of toxicology. The sequencing of the human and other genomes has markedly affected all biological sciences. Toxicology is no exception. Today new animal models, especially zebrafish, *Caenorhabditis elegans*, and *Drosophila melanogaster* (all of which have orthologs of human genes), are widely used in toxicology. The understanding of epigenetics is opening novel approaches to the fetal origin of adult diseases including cancers, diabetes, and neurodegenerative diseases and disorders. The discovery of micro RNAs and siRNAs has significantly improved our ability to understand the function of certain genes. The 21st century genome editing tool CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) will likely find its way into a variety of toxicological applications.

Small interfering RNA (siRNA) or short interfering RNA is a class of double-stranded RNA molecules ranging from 20 to 25 base pairs in length. Small interfering RNA functions through the RNA interference (RNAi) pathway and works by blocking the expression of specific genes with a complementary nucleotide sequence. The result of this interaction prevents translation of the target mRNA. David Baulcombe and Andrew Hamilton discovered these inhibitory elements in plants, and later the phenomenon was discovered in *C. elegans* by Craig Mello and Andrew Fire (Fire et al., 1998; Hamilton and Baulcombe, 1999). Their discoveries gave rise to a new tool for biomedical research and drug discovery. Significant therapeutic advances have been made in rare genetic diseases, infectious diseases, and other more common illnesses based on the siRNA platform. RNAi-based therapeutics include drugs targeting age-related macular degeneration (AMD), respiratory syncytial virus (RSV), hepatitis C, cancer, and renal failure. The development of these unique and specific therapies and the platform around gene silencing is responsible for the increase in pharmaceutical companies and academic centers devoted to this area of research. The number of new and existing companies and academic programs with RNAi programs is too numerous to list here, but they are the platform from which new advances in research and drug discovery will mature.

Contemporary toxicology is spreading its research tentacles in a variety of directions. The toxicological study of nanomaterials promises to yield significant findings based upon quantum size effects and large surface area to volume ratios. They may pose unique threats to the environment and humans. The recently articulated concept of the exposome, in a sense of the environmental equivalent of the human genome, considers the many complex exposures we are subjected to throughout our lives, including diet, lifestyle, and social influences. Systems biology is increasingly being used to identify biomarkers of toxicant exposure and to understand molecular mechanisms of toxic pathways. Researchers are uncovering the significant role of the microbiome in affecting toxicity. Meanwhile, organs-on-chips are a new technology which may, in the future, revolutionize toxicity testing.

Few disciplines can point to both basic sciences, direct applications, and societal influences at the same time. Toxicology may be unique in this regard. The mechanisms of action of the xenobiotics studied by toxicologists, in the tradition of Claude Bernard, continue to be the tools of modern biology. Adverse outcome pathways (AOPs), today, are being recognized as a new construct for organizing biological information. Data, its generation and application, have always been a critical element in science. Today, big data, open data, and data science are all the rage, even though there seem to be no uniform definitions. In general terms, though, *big data* refers to data sets that are extremely large and require advanced computation to reveal patterns and trends. *Open data* refers to data that can be shared freely by all. One of the primary objectives is to accommodate interoperability to allow different data sets to work in tandem. *Data science* is an even more generic term encompassing big data, open data, and more. The 2017 annual conference of the Society of Toxicology convened an informational session on "Supporting Open Data in Toxicology." Its goals were "to provide basic conceptual frameworks to increase open access to toxicological data, encourage cross-discipline collaboration, link existing toxicological research data with computational toxicology and Tox21, and ensure long-term sustainability for toxicological data resources into the future."

Tox21 (Toxicology in the 21st Century) is a federal collaboration among the EPA and various NIH branches aiming to develop better toxicity assessment methods to quickly and efficiently test whether certain chemical compounds have the potential to disrupt processes in the human body that may lead to negative effects (https://www.epa.gov/chemical-research/toxicology-testing-21st-century-tox21). Since its inception in 2008, it has focused its chemical screening initiatives on two themes: (1) generating fit-for-purpose cellular models for secondary screening, and (2) developing a high-throughput gene expression core facility. In a related vein, Evidence-based Toxicology took a cue from Evidence-based Medicine to more coherently adapt assessment and validation of toxicological test methods and testing strategies (Hoffmann et al., 2016). The Evidence-based Toxicology Collaboration (EBTC), founded in 2011 at the Johns Hopkins Bloomberg School of Public Health, sees itself as "guided by the themes of transparency, objectivity and consistency."

One of the great challenges remaining is the issue of mixtures. While most research focuses on single chemicals, we are, in fact, exposed to many chemicals at a time and over time. Learning how they interact with each other in causing their effects upon organisms is a critical question. Related to this is the issue of the effects of chemicals or combinations thereof in common household products including furniture, cars, electronics, and baby products.

The history of toxicology is rich with fascinating narratives that span many scientific disciplines. There are few fields which have interacted so widely and intimately with its sister sciences. Toxicologists are shaped in academia where they learn and develop the primary skillset to conduct basic research to understand mechanisms of chemical interaction and biological processes. Graduate and undergraduate programs continue to develop and improve. Toxicology is taught in schools of public health, medical schools, and schools of pharmacy inside and outside of the United States. Toxicologists from academic laboratories continue to seed other academic institutions, government organizations, and private industries, as the guardians of human, animal, and environmental health.

The upward trajectory of toxicology continues unabated. Its scientific foundation is becoming more assured, precise, and relevant.

Challenges will remain and part of the drag on its thrust will be intermittent funding and political constraints but these will not be powerful enough to interfere with long-term progress. Toxicology will continue to build upon its history, and build a trail of new history. A better understanding of toxicant exposures, individual and combined, and their effects upon living organisms will lead to an era when the global environment will be significantly safer and the world's populace healthier. Reaching this goal will take time and labor but it is achievable as we look toward the future and learn from the past.

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REFERENCES

Accum F. *A Treatise on Adulteration of Food, and Culinary Poisons, Exhibiting the Fraudulent Sophistications of Bread, Beer, Wine, Spirituous Liquors, Tea, Oil, Pickles, and Other Articles Employed in Domestic Economy and Methods of Detecting Them*. London: Longman, Hurst, Rees, Orme, and Brown; 1820.

Adams S. *The Great American Fraud*. New York: Collier and Son; 1905.

Anastas P. *Green Chemistry? He Invented the Term*. New York: New York Academy of Sciences; 2009.

Anastas PT, Warner JC. *Green Chemistry: Theory and Practice*. New York: Oxford University Press; 2000.

Ardestani MM, Rahimi R, Esfahani MM, Habbal O, Abdollahi M. The golden age of Medieval Islamic toxicology. In: Wexler P, ed. *History of Toxicology and Environmental Health. Toxicology in the Middle Ages and Renaissance*. Academic Press; 2017:11–30.

Arihan O, Arihan SK, Touwaide A. The case against Socrates and his execution. In: Wexler P, ed. *History of Toxicology and Environmental Health*; Vol. 1: Toxicology in Antiquity. Academic Press; 2014:69–82:chap 8.

Barker S. Poisons and the prince: toxicology and statecraft at the Medici Grand Ducal Court. In: Wexler P, ed. *History of Toxicology and Environmental Health. Toxicology in the Middle Ages and Renaissance*. Academic Press; 2017:71–81.

Barroso MS. Animal stones and the dark age of Bezoars. In: Wexler P, ed. *History of Toxicology and Environmental Health. Toxicology in Middle Ages and Renaissance*. Academic Press; 2017:115–124.

Barroso MS. The Bezoar stone: a princely antidote, the Tavora Sequeir Pinto Collection—Oporto. *Aca Med-Hist Adriat*. 2014;12(1):77–98.

Bernard C. *Leçons sur les Effets des Substances Toxiques et Medicamenteuses*. Paris: Baillière; 1857.

Bertomeu-Sanchez JR. Popularizing controversial science: a popular treatise on poisons by Mateu Orfila (1818). *Med Hist*. 2009;53(3):351–378.

Bertomeu-Sanchez JR, Nieto-Galan A, eds. *Chemistry, Medicine, and Crime (Mateu J.B. Orfila (1787-1853) and His Times*. Sagamore Beach, MA: Science History Publications; 2006.

Blow M. *The Atomic Bomb*. New Word City, Inc.; 2015.

Borzelleca JF. Paracelsus: herald of modern toxicology. *Toxicol Sci*. 1999;53(1):2–4.

Brown JR, Thornton JL. Percivall Pott (1714–1788) and chimney sweepers' cancer of the scrotum. *Br J Ind Med*. 1957;14(1):68–70.

Brundtland Commission. *Our Common Future*. New York: Oxford University Press; 1987.

Carson R. *Silent Spring*. Boston, MA: Houghton Mifflin; 1962.

Castleman B. Remembering Harriet Hardy, M.D. *New Solut*. 1994;4(3):33–34.

Cavan S. Animal experimentation: the tragic legacy of science; n.d. Available at: http://userwww.sfsu.edu/kazbeki/animexper.html. Accessed August 8, 2017.

Cilliers L, Retief F. Lead poisoning and the downfall of Rome: reality or myth? In: Wexler P, ed. *History of Toxicology and Environmental Health*; Vol. 1: Toxicology in Antiquity. Academic Press; 2014a:118–126:chap 11.

Cilliers L, Retief F. Poisons, poisoners, and poisoning in ancient Rome. In: Wexler P, ed. *History of Toxicology and Environmental Health*; Vol. 1: Toxicology in Antiquity. Academic Press; 2014b:127–137:chap 12.

Cobb C. The case against the Borgias. In: Wexler P, ed. *History of Toxicology and Environmental Health. Toxicology in the Middle Ages and Renaissance*. Academic Press; 2017:53–62.

Conti F. Claude Bernard's Des Fonctions du Cerveau: an ante litteram manifesto of the neurosciences? *Nat Rev Neurosci*. 2002;3(12):979–985.

Dal Bello M. La leggenda nera. I Borgia (a TV series). Città Nuova. 2012.

Dash M. Aqua Tofana: slow poisoning and husband-killing in 17th century Italy. A blast from the past; 2015. Available at: https://mikedashhistory.com/2015/04/06/aqua-tofana-slow-poisoning-and-husband-killing-in-17th-century-italy/.

Dayan AD. What killed Socrates? Toxicological considerations and questions. *Postgrad Med J*. 2009;85:34–37.

de Boer JZ. The oracle at Delphi: the Pythia and the pneuma, intoxicating gas finds, and hypotheses. In: Wexler P, ed. *History of Toxicology and Environmental Health*; Vol. 1: Toxicology in Antiquity. Academic Press; 2014:83–91.

Doull J. Toxicology comes of age. *Annu Rev Pharmacol Toxicol*. 2001:41:1–21.

Dronsfield A. Percival Pott, chimney sweeps and cancer. Education in Chemistry. Royal Society of Chemistry; 2006. Available at: https://eic.rsc.org/feature/percival-pott-chimney-sweeps-and-cancer/2020205.article.

DuBois K, Geiling EMK. *Textbook of Toxicology*. New York: Oxford University Press; 1959.

Duffin CJ. Fossil sharks' teeth as alexipharmics. In: Wexler P, ed. *History of Toxicology and Environmental Health. Toxicology in the Middle Ages and Renaissance*. Academic Press; 2017:125–134.

Duramy BF. Women and poisons in 17th century France. *Chi-Kent L Rev*. 2012;87(2):347–370.

Farrell M. Pioneer forensic toxicologists: Marsh, Orfila and their predecessors. *Criminologist*. 1994;18(1):33–36.

Felton JS. The heritage of Bernardino Ramazzini. *Occup Med (Lond)*. 1997;47(3):167–179.

Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature*. 1998;391(6669):806–811.

Fornaciari G, Bianucci R. I e Bianca: Una Scomoda Verita [Francesco I and Bianca: An inconvenient truth]. *Paleopatologia.It*; 2010. Available at: http://www.paleopatologia.it/attivita/pagina.php?recordID=24.

Furst A. Moses Maimonides. *Toxicol Sci*. 2001;59(2):196–197.

Gantenbein UL. Poison and its dose: Paracelsus on toxicology. In: Wexler P, ed. *History of Toxicology and Environmental Health. Toxicology in the Middle Ages and Renaissance*. Academic Press; 2017:1–10.

Geiling EMK, Paul MD, Cannon MD. Pathologic effects of elixir of sulfanilamide (diethylene glycol) poisoning: a clinical and experimental correlation: final report. *JAMA*. 1938;111(10):919–926.

Gerritsen SP. Gewina. 2007;30(1):1–20.

Gibbs F. http://fredgibbs.net/posts/universals-and-particulars-of-poison; 2017. Accessed August 8, 2017.

Gordon Research Conferences. https://www.grc.org; n.d.

Gow ASF, Scholfield AF. *Nicander: The Poems and Poetical Fragments*. London: Cambridge University Press; 2014.

Hachiya N. The history and the present of Minamata disease: entering the second half a century. *Jpn Med Assoc J*. 2006;49(3):112–118.

Hager T. *The Alchemy of Air: A Jewish Genius, a Doomed Tycoon, and the Scientific Discovery That Fed the World but Fueled the Rise of Hitler*. New York: Broadway Books; 2009.

Hajar R. Animal testing and medicine. *Heart Views*. 2011;12(1):42.

Hamilton A. *Exploring the Dangerous Trades*. Boston, MA: Little, Brown; 1943. [Reprinted by Northeastern University Press, Boston, MA; 1985.]

Hamilton AJ, Baulcombe D. A species of small antisense RNA in posttranscriptional gene silencing in plants. *Science*. 1999;286(5441):950–952.

Hays HW. *Society of Toxicology History, 1961–1986*. Washington, DC: Society of Toxicology; 1986.

Hedeson GD. Jan Baptist Van Helmont and the medical-alchemical perspectives of poison. In: Wexler P, ed. *History of Toxicology and Environmental Health. Toxicology in the Middle Ages and Renaissance*. Academic Press; 2017:91–100.

Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med*. 1971;284:878–881.

Hernberg S. Lead poisoning in a historical perspective. *Am J Ind Med*. 2000;38(3):244–254.

Heydari M, Hashempu MH, Zargaran A. Medicinal aspect of opium as described in *Avicenna's Canon of Medicine*. *Acta Medico-Historica Adriatica*. 2013;11(1):101–112.

Hobenreich E, Rizzelli G. Poisoning in ancient Rome: the legal framework, the nature of poisons, and gender stereotypes. In: Wexler P, ed. *History of Toxicology and Environmental Health*; Vol. 2: Toxicology in Antiquity. Academic Press; 2014:42–51:chap 12.

https://echa.europa.eu/information-on-chemicals.

https://www.epa.gov/chemical-research/toxicology-testing-21st-century-tox21.

https://www.nap.edu/catalog/24635/using-21st-century-science-to-improve-risk-related-evaluations.

http://sehn.org/wingspread-conference-on-the-precautionary-principle/.

http://www.toxicology.org/about/vp/vision.asp.

Hoffmann S, Hartung T, Stephens M. Evidence-based toxicology. *Adv Exp Med Biol*. 2016;856:231–241.

Institute of Medicine Committee on Poison Prevention and Control. Historical context of poison control. In: *Forging a Poison Prevention and Control System*. Washington, DC: National Academies Press, 2004:80–105:chap 4.

Jorgensen TJ. *Strange Glow: The Story of Radiation*. Princeton, NJ: Princeton University Press; 2016.

Jutte D. *The Age of Secrecy: Jews, Christians, and the Economy of Secrets, 1400–1800*. New Haven, CT: Yale University Press; 2015:56–57.

Kaffka A. *Sea-Dumped Chemical Weapons: Aspects, Problems, and Solutions*. Boston, MA: Kluwer Academic; 1995.

Karaberopoulos D, Karamanou M, Androutsos G. The art of medicine: the theriac in antiquity. *Lancet*. 2012;376:1942–1943.

Khajja BS, Sharma M, Singh R, Mathur GK. Forensic study of Indian toxicological plants as botanical weapon (BW): a review. *J Environ Anal Toxicol*. 2011;1(3):112.

Kinch M. *A Prescription for Change: The Looming Crisis in Drug Development*. Chapel Hill, NC: University of North Carolina Press; 2016.

Kling GW, Evans WC, Tanyileke G, Kusakabe M, Ohba T, Yoshida Y, Hell JV. Degassing lakes Nyos and Monoun: defusing certain disaster. *Proc Natl Acad Sci USA*. 2005;102(40):14185–14190.

Lavers D. Origin of myths related to curative, antidotal and other medicinal properties of animal "horns" in the Middle Ages. In: Wexler P, ed. *History of Toxicology and Environmental Health*; *Toxicology in the Middle Ages and Renaissance*. Academic Press; 2017:101–114.

Lewin L. *Die Gifte in der Weltgeschichte: Toxikologische, allgemeinverstandliche Untersuchungen der historischen Quellen*. Berlin: Springer; 1920.

Lewin L. *Gifte und Vergiftungen*. Berlin: Stilke; 1929.

Liu Y. Poisonous medicine in ancient China. In: Wexler P, ed. *History of Toxicology and Environmental Health*; Vol. 2: Toxicology in Antiquity. Academic Press; 2014:89–97.

Maimonides M. *On Poisons and the Protection against Lethal Drugs: A Parallel Arabic-English Edition*. Gerrit Bos, ed. McVaugh MR, trans. Provo, UT: Brigham Young University; 2009.

Manohar PR. Toxicity of Ayurveda medicines and safety concerns: the need to revive the branch of toxicology in Ayurveda. *Anc Sci Life*. 2014;34(1):1–2.

Mayor A. *The Poison King: The Life and Legend of Mithradates, Rome's Deadliest Enemy*. Princeton, NJ: Princeton University Press; 2010.

Mayor A. Alexander the Great: a questionable death. In: Wexler P, ed. *History of Toxicology and Environmental Health*; Vol. 1: Toxicology in Antiquity. Academic Press; 2014:52–59.

Marrs TT, Maynard RL, Sidell F. *Chemical Warfare Agents: Toxicology and Treatment*. West Sussex, England: Wiley; 2007.

Morgan JP, Penovich P. Jamaica ginger paralysis. Forty-seven-year follow-up. *Arch Neurol*. 1978;35(8):530–532.

Mullner R. *Deadly Glow: The Radium Dial Worker Tragedy*. Washington, DC: American Public Health Association; 1999.

Nasser M, Tibi A, Savage-Smith E. Ibn Sina's Canon of Medicine: 11the century rules for assessing the effects of drugs. *J R Soc Med*. 2009;102(2):78–80.

National Research Council. *Risk Assessment in the Federal Government: Managing the Process*. Washington, DC: National Academy Press; 1983.

National Research Council. *Science and Decisions: Advancing Risk Assessment*. Washington, DC: National Academies Press; 2009.

National Research Council. *Exposure Science in the 21st Century: A Vision and a Strategy*. Washington, DC: National Academies Press; 2012.

NPR. http://www.npr.org/2011/03/17/134568383/japan-three-mile-island-chernobyl-putting-it-all-in-perspective; n.d.

Nunn JF. *Ancient Egyptian Medicine*. Norman, OK: University of Oklahoma Press; 1996:144.

Orfila MJB. *Traite des Poisons Tires des Regnes Mineral, Vegetal et Animal, ou, Toxicologie Generale Consideree sous les Rapports de la Physiologie, de la Pathologie et de la Medecine Legale*. Paris: Crochard; 1814–1815.

Oser B. Toxicology then and now. *Regul Toxicol Pharmacol*. 1987; 7:427–433.

Pesatori AC, et al. Cancer incidence in the population exposed to dioxin after the "Seveso accident" twenty years of follow-up. *Environ Health*. 2009;8:30.

Pope MH. Bernardino Ramazzini: the father of occupational medicine. *Spine*. 2004;29(20):2335–2338.

Pratte ELH, Bryant S, Handley C, Hall M. Pick your poison. *The Chemist*. 2014;87(2):19–29.

Pray S. *A History of Nonprescription Product Regulation*. New York: Pharmaceutical Product Press; 2003.

PrimroseJ.https://quod.lib.umich.edu/e/eebo2/A91017.0001.001?view=toc.

PSAC (President's Science Advisory Committee). *Handling of Toxicological Information*. Washington, DC: White House; 1966.

Rosner D, Markowitz G. Standing up to the lead industry: an interview with Herbert Needleman. *Public Health Rep*. 2005;120:330–337.

Rosner F. Moses Maimonides' treatise on poisons. *JAMA*. 1968; 205(13):914–916.

Russell WMS, Burch RL. *The Principles of Humane Experimental Technique*. London: Methuen; 1959.

Sanchez GM, Harer WB. Toxicology in ancient Egypt. In: Wexler P, ed. *History of Toxicology and Environmental Health*; Vol. 1: Toxicology in Antiquity. Academic Press; 2014:2–10:chap 1.

Schlebusch CM, et al. Possible positive selection for an arsenic-protective haplotype in humans. *Environ Health Perspect*. 2013;121(1):53–58.

Seifert S. Richard Mead: one for the ages. *Clin Toxicol (Phila)*. 2011;49(1):53–55.

Slouber M. The venomous virgin: fact or fantasy? In: Wexler P, ed. *History of Toxicology and Environmental Health*; Vol. 2: Toxicology in Antiquity. Academic Press; 2015:98–103.

Smyth D. *Alternatives to Animal Experiments*. Scolar Press in Association with The Research Defence Society; 1978.

Sneader W. *Drug Discovery: A History*. Wiley; 2006. Available at: http://onlinelibrary.wiley.com/book/10.1002/0470015535.

Somerset A. *The Affair of the Poisons: Murder, Infanticide, and Satanism at the Court of Louis XIV*. St. Martin's Press; 2014.

Spiller HA, Hale JR, De Boer JZ. The Delphic oracle: a multidisciplinary defense of the gaseous vent theory. *J Toxicol Clin Toxicol*. 2002;40(2):189–196.

The Unitarian Review and Religious Magazine, Boston: Office of the Unitarian Review, 1879;12:130.

Timbrell J. *The Poison Paradox*. Oxford, MI: Oxford University Press; 2005.

Touwaide A. Harmful botanicals. In: Wexler P, ed. *History of Toxicology and Environmental Health*; Vol. 1: Toxicology in Antiquity. Academic Press; 2014a:60–68:chap 7.

Touwaide A. Nicander, Thêriaka, and Alexipharmacka: venoms, poisons, and literature. In: Wexler P, ed. *History of Toxicology and Environmental Health*; Vol. 1: Toxicology in Antiquity. Academic Press; 2014b:44–51:chap 5.

Tsoucalas G, Sgantzos M. The death of Cleopatra: suicide by snakebite or poisoned by her enemies? In: Wexler P, ed. *History of Toxicology and Environmental Health*; Vol. 1: Toxicology in Antiquity. Academic Press; 2014:12–20:chap. 2.

Tubbs RS, et al. Francois Magendie (1783–1855) and his contributions to the foundations of neuroscience and neurosurgery. *J Neurosurgery*. 2008;108:1038–1042.
UNODA (United Nations Office for Disarmament Affairs). https://www.un.org/disarmament/wmd/nuclear/npt/; n.d.
Unsworth J. History of pesticide use; 2010. http://agrochemicals.iupac.org/index.php?option=com_sobi2&sobi2Task=sobi2Details&catid=3&sobi2Id=31. Accessed August 8, 2017.
Wang G, et al. Persistent sulfate formation from London fog to Chinese haze. *Proc Natl Acad Sci USA*. 2016;113(48):13630–13635.
Wax PM. Elixir sulfanilamide-Massengill revisited. *Vet Hum Toxicol*. 1994;36(6):561–562.
Wikisource. Rig Veda; n.d.-a. Available at: https://en.wikisource.org/wiki/The_Rig_Veda/Mandala_1/Hymn_191. Accessed August 8, 2017.
Wikisource. Christison, Robert (DNBoo). Dictionary of National Biography, 1885–1900, Volume 10; n.d.-b. Available at: https://en.wikisource.org/wiki/Christison,_Robert_(DNB00). Accessed August 8, 2017.
Wilkinson P. *Chinese Myth: A Treasury of Legends, Art, and History (The World of Mythology)*. New York: Routledge; 2016.
Wisdom Library. http://www.wisdomlib.org/hinduism/book/sushruta-samhita-volume-5-kalpasthana/d/doc142971.html; n.d. Accessed August 8, 2017.
Wolnik KA, Fricke FL, Bonnin E, Gaston CM, Satzer RD. The Tylenol tampering incident-tracing the source. *Anal Chem*. 1984;56(3):466a–470a, 474a.
World Nuclear Association. http://www.world-nuclear.org/information-library/safety-and-security/safety-of-plants/fukushima-accident.aspx; 2017.
Wujastyk D. *The Roots of Ayurveda: Selections from Sanskrit Medical Writings*. London: Penguin; 2003:144.
Yang S, ed. *The Divine Farmer's Materia Medica: A Translation of the Shen Nong Ben Cao*. Boulder, CO: Blue Poppy Press; 1998.

SUPPLEMENTAL READING

Adams F, trans. *The Genuine Works of Hippocrates*. Baltimore, MD: Williams & Wilkins; 1939.
Albert A. *Selective Toxicity*. London: Methuen; 1951.
Beeson BB. Orfila—pioneer toxicologist. *Ann Med Hist*. 1930;2:68–70.
Bernard C. Analyse physiologique des proprietes des systemes musculaire et nerveux au moyen du curare. *C R Acad Sci (Paris)*. 1856;43:325–329.
Bryan CP. *The Papyrus Ebers*. London: Geoffrey Bales; 1930.
Clendening L. *Source Book of Medical History*. New York: Dover; 1942.
Gaddum JH. *Pharmacology.* 5th ed. New York: Oxford University Press; 1959.
Garrison FH. *An Introduction to the History of Medicine*. 4th ed. Philadelphia, PA: Saunders; 1929.
Holmstedt B, Liljestrand G. *Readings in Pharmacology*. New York: Raven Press; 1981.
http://www.ranker.com/list/death-by-poison-list-of-famous-poison-victims/notable-famous-deaths.
http://www.theaic.org/pub_thechemist_journals/Vol-87-No-2/Vol-87-No2-Article-4.pdf.
Hutt PB, Hutt PB II. A history of government regulation of adulteration and misbranding of food. *Food Drug Cosmet J*. 1984;39:2–73.
Leung AY. Traditional toxicity documentation of Chinese Materia Medica—an overview. *Toxicol Pathol*. 2006; 34:319–326.
Orfila MJB. *Secours a Donner aux Personnes Empoisonees et Asphyxiees*. Paris: Feugeroy; 1818.
Poland A, Knutson JC. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and related halogenated aromatic hydrocarbons, examination of the mechanism of toxicity. *Annu Rev Pharmacol Toxicol*. 1982;22:517–554.
Ramoutsaki IA, Ramoutsakis YA, Tsikritzis MD, Tsatsakis AM. The roots of toxicology: an etymological approach. *Vet Hum Toxicol*. 2000;42:111.
Unschuld PU. *Medicine in China: A History of Pharmaceutics*. Berkeley, CA: University of California Press; 1986.
US FDA. *Toxicologic Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food*. Washington, DC: U.S. Food and Drug Administration, Bureau of Foods; 1982.
Williams RT. *Detoxication Mechanisms*. 2nd ed. New York: Wiley; 1959.

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chapter 2

Principles of Toxicology

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INTRODUCTION TO TOXICOLOGY

Toxicology is the study of the adverse effects of chemical, biological, or physical agents on living organisms and the environment. These toxic substances include naturally occurring harmful chemicals, or *toxins,* as well as foreign substances called *xenobiotics.* Toxins are poisons that originate from plants and microbial organisms and also include venoms released by animals in order to injure predators. Aflatoxin is an example of a toxin; it is produced and released from the fungus *Aspergillus* that grows on foods such as corn and nuts. Exposure to aflatoxin is associated with an increased risk of liver cancer. By comparison, xenobiotics include a variety of synthetic chemicals with different intended purposes. Pharmaceuticals are xenobiotics developed to treat disease, whereas pesticides are used to deter pests. In addition, a large number of chemicals are used in manufacturing and industrial processes. For example, the chemical "dioxin" (2,3,7,8-tetrachlorodibenzo-*p*-dioxin [TCDD]) is generated during the production and/or combustion of certain chlorinated organic chemicals. A unique skin toxicity, called chloracne, has been observed in individuals exposed to dioxin. Some toxic substances can be produced by both natural and anthropogenic activities. For example, polyaromatic hydrocarbons are produced by the combustion of organic matter through ordinary processes (e.g., forest fires) and human activities (e.g., combustion of coal for energy production and cigarette smoking). Arsenic, a toxic metalloid, largely appears in groundwater as a natural contaminant, but also enters groundwater from other sources as well. Generally, such toxic chemicals are referred to as toxicants, rather than toxins, because, although they may be naturally produced, they are not produced by biological systems.

Toxic chemicals may also be classified in terms of their physical state (gas, dust, liquid, size; e.g., nanoparticles); their chemical stability or reactivity (explosive, flammable, corrosive); general chemical structure (aromatic amine, halogenated hydrocarbon, etc.); or ability to cause significant toxicity (extremely toxic, very toxic, slightly toxic, etc.). Classification of toxic chemicals on the basis of their biochemical mechanisms of action (e.g., alkylating agent, cholinesterase inhibitor, and endocrine disruptor) is usually more informative than classification by general terms such as irritants and oxidizers. However, more descriptive categories such as air pollutants, occupation-related exposures, and acute and chronic poisons may be useful to associate toxic chemicals that result in similar adverse events or are encountered under particular conditions. There is no single classification that is applicable to the entire spectrum of toxic chemicals. Instead, a combination of classification systems is generally needed to best characterize toxic substances. In this textbook, for example, toxic chemicals are discussed in terms of their target organs (liver, kidney, hematopoietic system, etc.), use (pesticide, solvent, food additive, etc.), source (animal and plant toxins), and adverse effects (cancer, mutation, etc.).

Virtually every known chemical has the potential to produce injury or death if it is present in a sufficient quantity. Paracelsus (1493 to 1541), a Swiss/German/Austrian physician, scientist, and philosopher, phrased this well when he noted, "What is there that is not poison? All things are poison and nothing [is] without poison. Solely the dose determines that a thing is not a poison." This principle is often summarized with the phrase that "the dose makes the poison."

Chemicals differ in their ability to produce serious injury or death. Table 2-1 shows the dose of chemicals needed to produce death in 50% of treated animals (lethal dose 50 [LD_{50}]). Some chemicals produce death in microgram doses and are commonly denoted as extremely poisonous. Other chemicals may be relatively harmless after doses in excess of several grams. It should be noted, however, that measures of acute lethality such as LD_{50} do not accurately reflect the full spectrum of toxic responses, or hazards, associated with exposure to a chemical. For example, some chemicals may have carcinogenic, teratogenic, or neurobehavioral effects at doses that produce no evidence of acute or immediate injury. In addition, there is a growing recognition that a number of factors can account for an individual's susceptibility to a range of responses. These include age, genetics, diet, underlying diseases, and concomitant exposures among many other factors. Finally, it should be recognized that, for a particular chemical, multiple different effects can occur in a given organism, each with its own "dose–response relationship."

Table 2-1

Approximate Acute LD_{50} Values of Some Representative Chemicals

CHEMICAL	LD_{50} (MG/KG)*
Ethyl alcohol	10,000
Glyphosate	5,600
Sodium chloride	4,000
Ferrous sulfate	1,500
Morphine sulfate	900
Phenobarbital sodium	150
Chlorpyrifos	18
Picrotoxin	5
Strychnine sulfate	2
Nicotine	1
VX nerve gas	1
D-Tubocurarine	0.5
Hemicholinium-3	0.2
Tetrodotoxin	0.10
Dioxin (TCDD)	0.001
Botulinum toxin	0.00001

**LD_{50} is the dose (mg/kg body weight) causing death in 50% of exposed animals.*

A *toxicologist* is an individual trained to examine and communicate the nature of a toxicant's properties and identify approaches to prevent or mitigate harm done to human, animal, and environmental health. Toxicological research identifies the cellular, biochemical, and molecular mechanisms of action of toxic chemicals and determines the extent to which these actions cause functional perturbations in critical organ systems. Using these data, a toxicologist then assesses the relationship between toxicant exposure (or dose) to the response (or outcome) and in turn the probability of an adverse event to occur. This determination requires an assessment of *risk* which is the quantitative estimate of the potential effects of a chemical on human and environmental health at particular exposure levels (e.g., pesticide residues in food and chemical contaminants in drinking water). The variety of potential adverse effects and the diversity of chemicals in the environment make toxicology a broad applied science that draws upon multiple disciplines including chemistry, biology, physiology, pathology, pharmacology, molecular biology, physics, statistics, and more. Because of the many facets that require toxicological examination, the field is often divided into subdisciplines that require specialization in particular areas. Our society's dependence on chemicals and the need to assess potential hazards have made toxicologists an increasingly important part of the decision-making processes.

SUBDISCIPLINES OF TOXICOLOGY

The professional activities of toxicologists fall into three main categories: mechanistic, hazard assessment, and regulatory. Although all three categories have distinctive characteristics, each contributes to the others, and all are vitally important to chemical risk assessment (see Chap. 4).

A *mechanistic toxicologist* identifies the cellular, biochemical, and molecular mechanisms by which chemicals exert toxic effects on living organisms (see Chap. 3 for a detailed discussion of mechanisms of toxicity). The results of mechanistic studies have implications in many areas of toxicology. In risk assessment, mechanistic data may be useful in determining whether an adverse outcome (e.g., cancer and birth defects) observed in laboratory animals may occur in humans. For example, the relative toxic potential of most organophosphorus (OP) insecticides in humans, rodents, and insects can be somewhat predicted on the basis of an understanding of common mechanisms (inhibition of acetylcholinesterase) and differences in biotransformation and accumulation of these insecticides among the three species. Similarly, mechanistic data may be very useful in identifying adverse responses in experimental animals that may not be relevant to humans. For example, the propensity of the widely used artificial sweetener saccharin to cause bladder cancer in rats has been demonstrated to be irrelevant to humans at normal dietary intake rates. This is because mechanistic studies have