9TH EDITION

Casarett & Doull's TOXICOLOGY

THE BASIC SCIENCE OF POISONS

Mc Graw Hill Education

CURTIS D. KLAASSEN

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)*

Notice

Casarett and Doull's TOXICOLOGY

The Basic Science of Poisons

Ninth Edition

Editor

Curtis D. Klaassen, PhD, DABT, ATS, FAASLD
University Distinguished Professor and Chair (Retired)
Department of Pharmacology, Toxicology and Therapeutics
School of Medicine
University of Kansas
Kansas City, Kansas

Mc Graw Hill Education

New York Chicago San Francisco Athens London Madrid Mexico City
Milan New Delhi Singapore Sydney Toronto

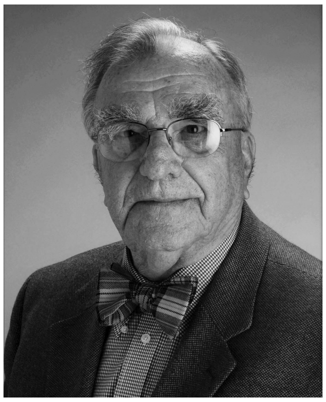
ISBN: 978-1-25-986375-2
MHID: 1-25-986375-1

The material in this eBook also appears in the print version of this title: ISBN: 978-1-25-986374-5, MHID: 1-25-986374-3.

eBook conversion by codeMantra
Version 1.0

History and Dedication

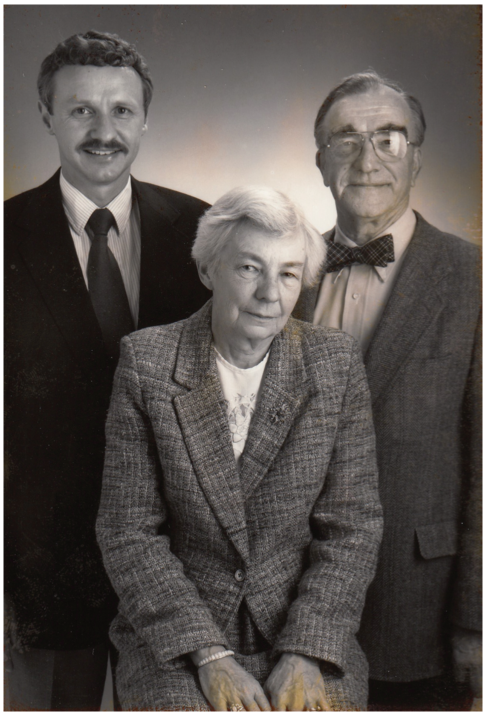

Louis James Casarett


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

This page intentionally left blank

Contents

Contributors

Lauren M. Aleksunes, PharmD, PhD, DABT
Associate Professor
Department of Pharmacology and Toxicology
Rutgers University
Piscataway, New Jersey
Chapter 2

S. Satheesh Anand, PhD, DABT
Manager, Safety Assessment
Life Science Research
Battelle
West Jefferson, Ohio
Chapter 24

Michael Aschner, PhD
Professor
Department of Molecular Pharmacology
Albert Einstein College of Medicine
Bronx, New York
Chapter 16

Thomas M. Badger, PhD
Professor Emeritus
Department of Pediatrics
University of Arkansas for Medical Sciences
Little Rock, Arkansas
Chapter 28

Aaron Barchowsky, PhD
Professor
Department of Environmental and Occupational Health
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, Pennsylvania
Chapter 23

Donald V. Belsito, MD
Leonard C. Harber Professor
Department of Dermatology
Columbia University Medical Center
New York, New York
Chapter 19

Aaron B. Bowman, PhD
Associate Professor
Department of Pediatrics
Vanderbilt University Medical Center
Nashville, Tennessee
Chapter 16

William K. Boyes, PhD
Environmental Health Scientist
Toxicity Assessment Division/Neurotoxicology Branch
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina
Chapter 17

Scott C. Brown, PhD
Principal Scientist
The Chemours Company
Wilmington, Delaware
Chapter 29

James V. Bruckner, PhD
Professor Emeritus
Department of Pharmaceutical & Biomedical Sciences
College of Pharmacy
University of Georgia
Athens, Georgia
Chapter 24

David B. Buckley, PhD, DABT
Director, DMPK
Roivant Sciences, Inc
Durham, North Carolina
Chapter 6

Matthew J. Campen, PhD, MSPH
Regent's Professor
Department of Pharmaceutical Sciences
College of Pharmacy
University of New Mexico
Albuquerque, New Mexico
Chapter 18

Louis R. Cantilena, Jr., MD, PhD*
Professor of Medicine and Pharmacology
Director, Division of Clinical Pharmacology and Medical Toxicology
Uniformed Services University
Bethesda, Maryland
Chapter 33

*Deceased

Ronald F. Chanderbhan, PhD
Supervisory Toxicologist
Division of Biotechnology and GRAS Notice Review, Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
College Park, Maryland
Chapter 27

Supratim Choudhuri, PhD
Toxicologist
Division of Biotechnology and GRAS Notice Review, Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
College Park, Maryland
Chapter 27

Daniel L. Costa, ScD, DABT
Office of Research and Development (Emeritus)
U.S. Environmental Protection Agency
Adjunct Professor
Chapel Hill, University of North Carolina
Chapter 31

Lucio G. Costa, PhD, ATS
Department of Environmental and Occupational Health Sciences
University of Washington
Seattle, Washington
Chapter 22

Richard T. Di Giulio, PhD
Sally Kleberg Professor of Environmental Toxicology
Nicholas School of the Environment
Duke University
Durham, North Carolina
Chapter 30

David L. Eaton, PhD, DABT, ATS, NASEM
Dean and Vice Provost
University of Washington
Seattle, Washington
Chapter 2

Elaine M. Faustman, PhD, DABT
Professor and Director
Institute for Risk Analysis and Risk Communication
Department of Environmental and Occupational Health Sciences
University of Washington
Seattle, Washington
Chapter 4

Jodi A. Flaws, PhD
Professor
Department of Comparative Biosciences
University of Illinois
Urbana, Illinois
Chapter 20

Paul M.D. Foster, PhD, ATS
Senior Scientist; Chief, Toxicology Branch
Division of the National Toxicology Program (NTP), (retired)
National Institute of Environmental Health Sciences (NIEHS)
Fuquay-Varina, North Carolina
Chapter 21

Donald A. Fox, PhD, ATS, ARVO Fellow
Toxicology and Pharmacology Expert
Robson Forensic
Austin, TX
Chapter 17

Bruce A. Goldberger, PhD, F-ABFT
Chief, Director and Professor
Departments of Pathology, Immunology and Laboratory Medicine
College of Medicine, University of Florida
Gainesville, Florida
Chapter 32

B. Bhaskar Gollapudi, PhD
Senior Managing Scientist
Health Sciences Center
Exponent, Inc.
Alexandria, Virginia
Chapter 9

Terry Gordon, PhD
Professor
Department of Environmental Medicine
New York University School of Medicine
New York, New York
Chapter 31

L. Earl Gray, Jr., PhD
Research Biologist
Office of Research and Development
National Health and Environment Effects Research Laboratory
Reproductive Toxicology Branch
Environmental Protection Agency
Durham, North Carolina
Chapter 21

Helen G. Haggerty, PhD
Distinguished Research Fellow
Immuno and Molecular Toxicology
Drug Safety Evaluation
Bristol-Myers Squibb
New Brunswick, New Jersey
Chapter 12

Antoinette N. Hayes, MS, DABT
Lead Associate Scientist
Nonclinical Drug Safety and Bioanalytical
Alnylam Pharmaceuticals
Cambridge, Massachusetts
Chapter 1

David G. Hoel, PhD
Distinguished University Professor
Department of Public Health Sciences
Medical University of South Carolina
Charleston, South Carolina
Chapter 25

Michael P. Holsapple, PhD, ATS
Professor
Michigan State University
MPH Toxicology Consulting, LLC
East Lansing, Michigan
Chapter 12

Patricia B. Hoyer, PhD
Professor Emeritus
Department of Physiology
College of Medicine
The University of Arizona
Tucson, Arizona
Chapter 20

Robert H. Hurt, PhD
Professor of Engineering
Brown University
Providence, Rhode Island
Chapter 29

Hartmut Jaeschke, PhD, ATS
Professor and Chair
Department of Pharmacology, Toxicology and Therapeutics
University of Kansas Medical Center
Kansas City, Kansas
Chapter 13

Norbert E. Kaminski, PhD
Professor, Pharmacology & Toxicology
Director, Institute for Integrative Toxicology
College of Human Medicine
Michigan State University
East Lansing, Michigan
Chapter 12

Agnes B. Kane, MD, PhD
Professor
Department of Pathology and Laboratory Medicine
Brown University
Providence, Rhode Island
Chapter 29

Barbara L.F. Kaplan, PhD
Assistant Professor
Center for Environmental Health Sciences
Department of Basic Sciences
College of Veterinary Medicine
Mississippi State University
Mississippi State, Mississippi
Chapter 12

Faraz Kazmi, PhD
Scientist
Pharmacokinetics, Dynamics and Metabolism
Janssen Research and Development
Spring House, Pennsylvania
Chapter 6

Joanna Klapacz, PhD
Senior Toxicologist
Toxicology and Environmental Research & Consulting
The Dow Chemical Company
Midland, Michigan
Chapter 9

Rebecca D. Klaper, PhD
Professor and Director of the Great Lakes Genomics Center
School of Freshwater Sciences
University of Wisconsin-Milwaukee
Milwaukee, Wisconsin
Chapter 29

James E. Klaunig, PhD
Professor
Department of Environmental Health
Indiana University
Bloomington, Indiana
Chapter 8

Kannan Krishnan, PhD, DABT, FATS, FCAHS
Chief Scientific Officer
Institut de recherche Robert-Sauvé en santé et en sécurité du travail
Montreal, Quebec, Canada
Chapter 7

Dayong Lee, PhD, F-ABFT
Houston Forensic Science Center
Houston, Texas
Chapter 32

Lois D. Lehman-McKeeman, PhD, ATS
Vice President
Pharmaceutical Candidate Optimization
Bristol-Myers Squibb Company
Princeton, New Jersey
Chapter 3

George D. Leikauf, PhD
Professor
Department of Environmental and Occupational Health
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, Pennsylvania
Chapter 15

James P. Luyendyk, PhD
Associate Professor
Department of Pathobiology and Diagnostic Investigation
Michigan State University
East Lansing, Michigan
Chapter 13

Gary E. Marchant, PhD, JD
Regents' Professor
Sandra Day O'Connor College of Law
Arizona State University
Phoenix, Arizona
Chapter 35

Antonia Mattia, PhD
Senior Science Advisor
Senior Science and Policy Staff, Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
College Park, Maryland
Chapter 27

Cliona M. McHale, PhD
Senior Researcher
School of Public Health
University of California, Berkeley
Berkeley, California
Chapter 11

Virginia C. Moser, PhD
Retired
Division of Toxicity Assessment
National Health and Environmental Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina
Chapter 16

Michael C. Newman, PhD
A. Marshall Acuff, Jr. Professor of Marine Science
College of William & Mary
Virginia Institute of Marine Science
Gloucester Point, Virginia
Chapter 30

Günter Oberdörster, PhD
Professor of Toxicology
University of Rochester Medical Center
Rochester, New York
Chapter 29

Brian W. Ogilvie, PhD
Vice President of Scientific Consulting
Sekisui XenoTech, LLC
Kansas City, Kansas
Chapter 6

Andrew Parkinson, PhD
CEO
XPD Consulting
Shawnee, Kansas
Chapter 6

Oliver Parkinson, PhD
Consultant
XPD Consulting
Shawnee, Kansas
Chapter 6

Jason R. Richardson, PhD
Professor
Pharmaceutical Sciences
Northeast Ohio Medical University
Rootstown, Ohio
Chapter 16

Rudy J. Richardson, ScD
Professor of Toxicology
Environmental Health Sciences
University of Michigan
Ann Arbor, Michigan
Chapter 16

John M. Rogers, PhD
Director, Toxicity Assessment Division
National Health and Environmental Effects Research Laboratory
Office of Research and Development
United States Environmental Protection Agency
Research Triangle Park, North Carolina
Chapter 10

Martin J.J. Ronis, PhD
Professor
Department of Pharmacology & Experimental Therapeutics
Louisiana State University Health Sciences Center
New Orleans, Louisiana
Chapter 28

Robert A. Roth, PhD, DABT
Department of Pharmacology and Toxicology
Institute for Integrative Toxicology
Michigan State University
East Lansing, MI

Rick G. Schnellmann, PhD
Professor and Dean
Department of Pharmacology and Toxicology
School of Pharmacy
University of Arizona
Tucson, Arizona
Chapter 14

Kartik Shankar, PhD, DABT
Associate Professor
Department of Pediatrics
University of Arkansas for Medical Sciences
Little Rock, Arkansas
Chapter 28

Angela L. Slitt, PhD
Associate Professor
Department of Biomedical and Pharmaceutical Sciences
College of Pharmacy
University of Rhode Island
Kingston, Rhode Island
Chapter 5

Martyn T. Smith, PhD
Professor of Toxicology
School of Public Health
University of California, Berkeley
Berkeley, California
Chapter 11

Courtney E.W. Sulentic, PhD
Associate Professor
Department of Pharmacology & Toxicology
Boonshoft School of Medicine
Wright State University
Dayton, Ohio
Chapter 12

Peter S. Thorne, MS, PhD
Professor and Head
Department of Occupational & Environmental Health
Director
Environmental Health Sciences Research Center
University of Iowa College of Public Health
Iowa City, Iowa
Chapter 34

Alexander C. Ufelle, MBBS, MPH, PhD
Assistant Professor
Department of Public Health and Social Work
Slippery Rock University
Slippery Rock, Pennsylvania
Chapter 23

Zemin Wang, MD, PhD, DABT
Research Assistant Professor
Department of Environmental Health
Indiana University
Bloomington, Indiana
Chapter 8

David B. Warheit, PhD, DABT, ATS
Technical Fellow
Chemours Company
Wilmington, Delaware
Chapter 29

D. Alan Warren, PhD
Academic Program Director
Program in Environmental Health Sciences
University of South Carolina Beaufort
Bluffton, South Carolina
Chapter 24

John B. Watkins, III, PhD, DABT
Professor Emeritus of Pharmacology and Toxicology
Indiana University School of Medicine
Medical Sciences
Bloomington, Indiana
Chapter 26

Philip Wexler, MLS
Technical Information Specialist (retired)
Toxicology and Environmental Health Information Program
National Library of Medicine
Bethesda, Maryland
Chapter 1

Diana G. Wilkins, PhD, MT(ASCP)
Professor and Division Chief of Medical Laboratory Sciences
Department of Pathology
School of Medicine
University of Utah
Salt Lake City, Utah
Chapter 32

This page intentionally left blank

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.

This page intentionally left blank

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

This page intentionally left blank

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 'AlīAal-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 by* 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