Goldfrank's TOXICOLOGIC EMERGENCIES

11TH EDITION

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GOLDFRANK'S TOXICOLOGIC EMERGENCIES

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GOLDFRANK'S TOXICOLOGIC EMERGENCIES

Eleventh Edition

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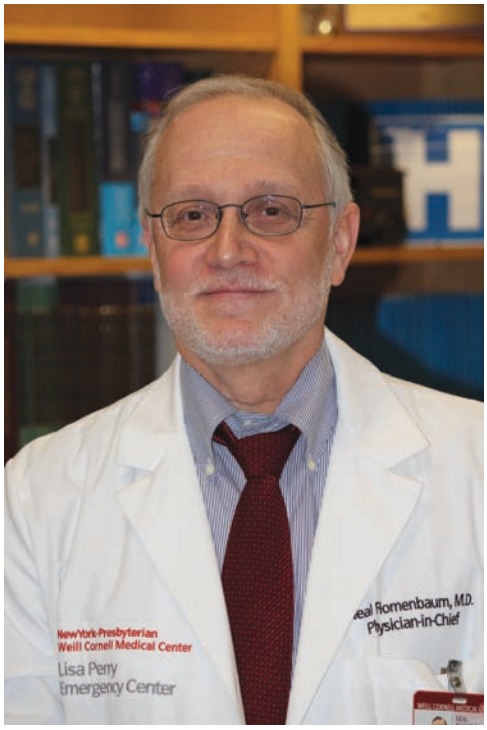
Neal E. Flomenbaum, MD, FACP, FACEP

Editor Emeritus



With the publication of the ninth edition of *Goldfrank's Toxicologic Emergencies*, Neal Flomenbaum informed us of his decision to step down as an editor in order to be able to devote more time to his growing interests in geriatric emergency medicine and prehospital care, while continuing to fulfill his clinical and administrative responsibilities as Chief of Emergency Medicine at New York Presbyterian Hospital-Weill Cornell Medical Center and as Medical Director of its extensive prehospital care system.

In 1979, Dr. Flomenbaum accepted an offer from Lewis Goldfrank to join him at New York University Bellevue Hospital as Associate Director of Emergency Services and Consultant (later, Chief Consultant) to the New York City Poison Control Center, and their subsequent collaborations resulted in many of the outstanding features of this textbook. Frequently, ideas and concepts Neal and Lewis developed for presenting clinical toxicology were recognized for their value to the textbook and then developed further by both, with considerable input and efforts by Neal Lewin, Richard Weisman, Mary Ann Howland, Robert Hoffman, and Lewis Nelson. Thus, an idea for a 1984 review article entitled "Newer Antidotes and Controversies in Antidotal Therapy," written to familiarize clinicians with the appropriate use of antidotes in patient management, became "Antidotes in Depth," a signature feature of this book.

Similarly, the idea for an organ system track in the NYU postgraduate toxicology courses that Neal and Lewis codirected in the early 1980s became "The Pathophysiologic Basis of Medical Toxicology: The Organ System Approach" in the textbook. This section, in turn, suggested another section entitled "The Biochemical and Molecular Basis of Medical Toxicology."

Additional ideas followed for making *Goldfrank's Toxicologic Emergencies* more accessible both as a teaching and a reference resource. A monthly case-based consultants' meeting at the New York City Poison Control Center was modeled after the successful format originated in the first edition of this book, and many of the cases discussed there were adapted for the text and related review books. Placing essential reference tables on the inside front and back covers of the textbook proved to be another useful feature, and Neal is particularly proud of the unique way the textbook acknowledges previous authors at the end of chapters. In addition to his ideas and his organizational and editorial contributions, Neal has written, coauthored, or contributed to dozens of chapters since 1982, including those on salicylates, rodenticides, and managing the acutely poisoned or overdosed patient.

In 1996, Neal Flomenbaum became the first Emergency Physician-in-Chief at New York Presbyterian Hospital/Weill Cornell Medical Center and built a multidisciplinary emergency department of over 50 attending emergency physicians, residents, nurses, nurse practitioners, physician assistants, paramedics, and EMTs. He created, developed, and supported traditional and nontraditional subspecialties and fellowships in pediatric emergency medicine, medical toxicology, prehospital care, global emergency medicine, geriatric emergency medicine, wilderness and environmental emergency medicine, and EM/critical care, each of which was heavily infused with the knowledge and information of age-specific poisonings, overdoses, adverse effects and drug interactions, polypharmacy, and environmental hazards found in these pages. Many of the faculty, in turn, have contributed to chapters in this textbook and peer-reviewed research papers in medial toxicology. These activities culminated in the establishment of an academic department of emergency medicine at Weill Cornell in early 2016. That same year, Neal received the Lifetime Achievement award from his alma mater, the Albert Einstein College of Medicine and, in 2015, the annual "Neal Flomenbaum, MD Prize for Excellence in Emergency Medicine" was established at Weill Cornell commencements.

Neal Flomenbaum first became interested in medical toxicology because of the clinical challenges it presented to emergency physicians, internists, and pediatricians, and he has remained focused on these clinical aspects. His creative energies, talents, and contributions to the second through ninth editions of this book have helped transform a case-based introduction to clinical toxicology into the 2000-page textbook it is today, and these contributions will remain an important part of future editions.

The cover image is the *Papaver somniferum* and is the source of opium. The plant is native to Southwestern Asia, but now grown around the globe. Its products have been used medicinally and recreationally for thousands of years. The beautiful flowers lose their petals with a resultant green capsule, which when lanced exudes the highly viscous opium. Opium contains numerous alkaloids of which morphine, codeine, papaverine, and thebaine are the most medically consequential. Morphine is an opioid agonist analgesic, which when diacetylated produces heroin. Naloxone, a pure opioid antagonist and derivative of thebaine, reverses most of the clinical effects of opioid agonists. Opioids in almost all forms are used with remarkable success for acute pain and conversely, misused and abused with tragic implications for patients, families, and society. The safe and appropriate use of the products and derivatives of *Papaver somniferum* will define much of the work of toxicologists in the twenty-first century.

DEDICATION

To the staffs of our hospitals, emergency departments, intensive care units, and outpatient sites, who have worked with remarkable courage, concern, compassion, and understanding in treating the patients discussed in this text and many thousands more like them.

To the Emergency Medical Services personnel who have worked so faithfully and courageously to protect our patients' health and who have assisted us in understanding what happens in the home and the field.

To the staff of the New York City Poison Control Center, who have quietly and conscientiously integrated their skills with ours to serve these patients and prevent many patients from ever requiring a hospital visit.

To all the faculty, fellows, residents, nurses, nurse practitioners, physician assistants, and medical and pharmacy students who have studied toxicology with us, whose inquisitiveness has helped us continually strive to understand complex and evolving problems and develop methods to teach them to others. (Editors)

To my wife Laura for her unwavering support; to my children Daniel, Adina, and Benjamin for their fresh perspective, youthful insight, and appreciation of my passion; to my parents Myrna of blessed memory and Dr. Irwin Nelson for the foundation they provided; and to my family, friends, and colleagues who keep me focused on what is important in life. (L.N.)

To my husband Bob; to my children Robert, Marcy and Doug and my grandchildren Joey and Mackenzie; to my mother and to the loving memory of my father; and to family, friends, colleagues, and students for all their help and continuing inspiration. (M.A.H.)

To my wife Gail Miller; my sons Jesse Miller Lewin, MD and Justin Miller Lewin, MD and my daughters-in-law Alana Amarosa Lewin, MD and Alice Tang, MD; my granddaughter Isabelle Rose Lewin; and in memory of my parents. To all my patients, students, residents, fellows, and colleagues who constantly stimulate my being a perpetual student. (N.L.)

To my wife Helen, for her resolute support and understanding; to my children Addison and Alston, for their boundless enthusiasm and inquisitiveness; and to my parents. (S.W.S.)

To my children Rebecca and Ryan, Jennifer, Andrew and Joan, Michelle and James; to my grandchildren Benjamin, Adam, Sarah, Kay, Samantha, Herbert, Jonah, Susie, and Sasha, who have kept me acutely aware of the ready availability of possible poisons; and to my wife, partner, and best friend Susan (deceased) whose support was essential to help me in the development of the first ten editions and whose contributions continue to inspire me and will be found throughout the text. (L.G.)

To my wife Ali; my children Casey and Jesse; my parents; and my friends, family, and colleagues for their never-ending patience and forgiveness for the time I have spent away from them; to the many close colleagues and committee members who have helped me understand the fundamentals of evidence-based medicine and challenged me to be clear, precise, and definitive when making treatment recommendations. (R.S.H.)

To the memory of Louis R. Cantilena, MD, PhD. Lou was a wonderful collaborator, thoughtful intellectual, clinical pharmacologist and medical toxicologist who was a critical author for the previous five editions of our textbook. His warmth, enthusiasm and intellect will be missed.

ANTIDOTES IN DEPTH

Editors: Mary Ann Howland and Silas W. Smith

Readers of previous editions of *Goldfrank's Toxicologic Emergencies* are undoubtedly aware that the editors have always felt that an emphasis on general management of patients who are poisoned or overdosed coupled with sound medical management is as important as the selection and use of a specific antidote. Nevertheless, there are some instances when nothing other than the timely use of a specific antidote is an essential lifesaving intervention. For this reason, and also because the use of such strategies are often problematic, controversial, or unfamiliar to the practitioner as new therapeutic approaches continue to emerge and old standards are reevaluated, we have included a section (or sections) at the end of appropriate chapters in which an in-depth discussion of such material is relevant.

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Chapter 32, "Geriatric Principles"
Antidotes in Depth: A1, "Activated Charcoal"
Antidotes in Depth: A2, "Whole-Bowel Irrigation and Other Intestinal Evacuants"
Antidotes in Depth: A3, "N-Acetylcysteine"
Antidotes in Depth: A4, "Opioid Antagonists"
Antidotes in Depth: A7, "Deferoxamine"
Antidotes in Depth: A9, "Octreotide"
Antidotes in Depth: A10, "L-Carnitine"
Antidotes in Depth: A11, "Physostigmine Salicylate"
Antidotes in Depth: A12, "Folates: Leucovorin (Folinic Acid) and Folic Acid"
Antidotes in Depth: A15, "Pyridoxine"
Antidotes in Depth: A18, "Vitamin K_1"
Antidotes in Depth: A19, "Protamine"
Antidotes in Depth: A20, "Glucagon"
Antidotes in Depth: A22, "Digoxin-Specific Antibody Fragments"
Antidotes in Depth: A25, "Flumazenil"
Antidotes in Depth: A26, "Benzodiazepines"
Antidotes in Depth: A28, "Dimercaprol (British Anti-Lewisite or BAL)"
Antidotes in Depth: A29, "Succimer (2,3-dimercaptosuccinic acid) and DMPS (2,3-dimercapto-1-propanesulfonic acid)"
Antidotes in Depth: A30, "Edetate Calcium Disodium ($CaNa_2EDTA$)"
Antidotes in Depth: A32, "Calcium"
Antidotes in Depth: A33, "Fomepizole"
Antidotes in Depth: A34, "Ethanol"
Antidotes in Depth: A35, "Atropine"
Antidotes in Depth: A36, "Pralidoxime"
Antidotes in Depth: A41, "Hydroxocobalamin"
Antidotes in Depth: A42, "Nitrites (Amyl and Sodium) and Sodium Thiosulfate"
Antidotes in Depth: A43, "Methylene Blue"
Special Considerations: SC1, "Principles of Antidote Stocking"

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Chapter 4, "Principles of Managing the Acutely Poisoned or Overdosed Patient"
Chapter 10, "Chemical Principles"
Chapter 17, "Dermatologic Principles"
Chapter 36, "Opioids"
Chapter 57, "Antidysrhythmics"
Chapter 77, "Alcohol Withdrawal"
Chapter 92, "Copper"
Chapter 118, "Plants"
Chapter 121, "Simple Asphyxiants and Pulmonary Irritants"
Antidotes in Depth: A4, "Opioid Antagonists"
Antidotes in Depth: A26, "Benzodiazepines"
Special Considerations: SC3, "Transdermal Toxicology"

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Chapter 119, "Native (US) Venomous Snakes and Lizards"
Antidotes in Depth: A39, "Antivenom for North American Venomous Snakes (Crotaline and Elapid)"

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Chapter 87, "Bismuth"
Chapter 140, "Postmortem Toxicology"
Special Considerations: SC7, "Intrathecal Administration of Xenobiotics"
Special Considerations: SC12, "Organ Procurement from Poisoned Patients"

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Antidotes in Depth: A44, "Potassium Iodide"
Antidotes in Depth: A45, "Pentetic Acid or Pentetate (Zinc or Calcium) Trisodium (DTPA)"

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Special Considerations: SC9, "Diethylene Glycol"

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Antidotes in Depth: A2, 'Whole-Bowel Irrigation and Other Intestinal Evacuants"
Antidotes in Depth: A6, "Botulinum Antitoxin"
Antidotes in Depth: A9, "Octreotide"
Antidotes in Depth: A12, "Folates: Leucovorin (Folinic Acid) and Folic Acid"
Antidotes in Depth: A13, "Glucarpidase (Carboxypeptidase G_2)"
Antidotes in Depth: A14, "Uridine Triacetate"
Antidotes in Depth: A16, "Magnesium"
Antidotes in Depth: A20, "Glucagon"
Antidotes in Depth: A22, "Digoxin-Specific Antibody Fragments"
Antidotes in Depth: A32, "Calcium"
Special Considerations: SC1, "Principles of Antidote Stocking"

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Chapter 104, "Hydrofluoric Acid and Fluorides"
Chapter 130, "Poison Control Centers and Poison Epidemiology"
Antidotes in Depth: A17, "Prothrombin Complex Concentrates and Direct Oral Anticoagulant Antidotes"

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Antidotes in Depth: A24, "Dantrolene Sodium"

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PREFACE

Goldfrank's Toxicologic Emergencies is a multiauthored text of approximately 2,000 pages prepared by using the educational and management principles we apply at the New York City Poison Control Center, New Jersey Poison Information & Education System, and at our clinical sites. In this eleventh edition of *Goldfrank's Toxicologic Emergencies*, we proudly offer readers an approach to medical toxicology using evidence-based principles viewed through the lens of an active bedside clinical practice.

Some would ask why create textbooks and e-books in an era when podcasts and blogs appear so successful. We still believe that the slow, thoughtful, rigorous investigation of all available information by a team of authors and editors required to create and revise this text is essential to analyze the complex problems that challenge our daily practices. Although in our field we have made great progress, the level of uncertainty remains substantial. We have attempted to integrate the collaborative wisdom of experts from diverse backgrounds in order to provide the information necessary to achieve excellence. We offer our readers the evidence, shared thoughts, and structured analysis necessary to arrive at a decision. Evidence is created not only with randomized clinical trials, observational studies, case control studies, and case reports, but also with the insights of six toxicologists who work together continuously, along with the gifted scholars we selected as authors. We have worked together defining and redefining the scope and context of chapters, Antidotes in Depth, and Special Considerations. We then shared our ideas with many respected local, national, and international toxicologists, thus creating new chapters that these toxicologists have revised by adding information and insight that has come to light since the publication of the tenth edition of the text. In this way, knowledge from their experience as toxicologists and related disciplines is merged with ours, allowing us to create chapters that represent our collective thoughts. This iterative process is continued until the authors and editors are satisfied that we have closely approximated the best strategy to evaluate and care for poisoned or overdosed patients. This is a fascinating process. In this edition, we have tried to enhance our rigor focusing on as precise an analysis of the literature as we can all do and an attempt to tell you as clearly as possible what we and our authors think and how we practice. Because we occasionally disagree, we then reread, research, look for special cases, and reflect on a final version with our authors.

In this edition, we have asked Rana Biary, MD to expand the concept of the patient narrative in the Case Studies section. These are the patients who challenge us to be vigilant as toxicologists. Such patients, whose signs and symptoms are related to the whole book or to several chapters, serve to return us to focus on the unknown, the differential diagnosis, and problem solving and include contextual cases representative of our work. Patients with a pesticide exposure, bradycardia, metabolic acidosis, medication error, seizures, coma or agitation, and hyperthermia are offered as examples for contemplation. We believe that analyzing the care of these complex, undifferentiated patients will help you as much as they have helped us and those who read the first edition of this book. These cases act as the building blocks for chapters in this edition and represent provocative introductions to several sections of this text. We have demonstrated our thought processes so that you can understand our approach to patient management. This classic Socratic development of knowledge and improvement of clinical decision making will improve problem solving, stimulate creative investigation, and enhance care. We hope to facilitate your participation in the intellectual processes that we believe to be essential in order to create a fine book for thoughtful readers who desire to render excellent attention to their patients. The cases serve as the transition between the patient and population as you diminish the gap between your roles as a medical or clinical toxicologist at the bedside and that of a toxicologist serving the needs of the community. Our hope is that these cases re-create the clinicians' thoughts prior to, during, and after care is initiated.

In this eleventh edition, Silas W. Smith, MD, became an editor reflecting his superior work on prior editions. We are sure that his knowledge and thoughtfulness will be appreciated by all.

The Editors

ACKNOWLEDGMENTS

We are grateful to Joan Demas, who worked extensively with the local, national, and international authors to ensure that their ideas were effectively expressed. She has assisted all of us in checking the facts, finding essential references, and improving the structure and function of our text, while dedicating her efforts to ensuring the precision and rigor of the text for her fifth consecutive edition. She has helped authors new and old achieve their commitment with the skill of an exceptional publishing professional. The authors' and editors' work is better because of her devotion to excellence, calm demeanor in the face of editorial chaos, and consistent presence throughout each stage of the production of this text. We are deeply appreciative of the wonderful effort she provides for our readers and colleagues.

The many letters and verbal communications we have received with the reviews of the previous editions of this book continue to improve our efforts. We are deeply indebted to our friends, associates, residents, fellows, and students, who stimulated us to begin this book with their questions and then faithfully criticized our answers.

We appreciate the assistance of Dorice Vieira, Associate Curator, Medical Library, and Clinical Outreach and Graduate Medical Education Librarian, in her commitment to helping us find essential information.

We thank the many volunteers, students, librarians, and particularly the St. John's University College of Pharmacy and Health Sciences students and drug information staff who provide us with vital technical assistance in our daily attempts to deal with toxicologic emergencies.

No words can adequately express our indebtedness to the many authors who worked on earlier editions of many of the chapters in this book. As different authors write and rewrite topics with each new edition, we recognize that without the foundational work of their predecessors this book would not be what it is today.

We appreciate the creative skills in design and scientific art that the McGraw-Hill team, led by Armen Ovsepyan, have added to the text. The devotion to the creation of high-quality art graphics and tables is greatly appreciated. The support for excellence in this edition was facilitated by the constant vigilance of our longstanding collaborator Senior Content Acquisitions Editor Karen Edmonson whose thoughtful, and cooperative spirit persists after all these years. Her intelligence and ever vigilant commitment to our efforts has been wonderful. We are pleased with the creative developmental editorial efforts of Robert Pancotti. The organized project management by Revathi Viswanathan has found errors hiding throughout our pages. Her carefully posed questions have facilitated the process of correcting the text. It has been a pleasure to have her assistance. We greatly appreciate the compulsion that Maria van Beuren has applied to make the index of this edition one of unique value. She demonstrated exceptional rigor with a twist of copy editing to find many unseen errors, saving the reader confusion and us embarrassment. We appreciate the work of Catherine Saggese in ensuring the quality of production in the finished work.

1 HISTORICAL PRINCIPLES AND PERSPECTIVES

Paul M. Wax

The term *poison* first appeared in the English literature around 1225 A.D. to describe a potion or draught that was prepared with deadly ingredients.[8,155] The history of poisons and poisoning, however, dates back thousands of years. Throughout the millennia, poisons have played an important role in human history—from political assassination in Roman times, to weapons of war, to contemporary environmental concerns, and to weapons of terrorism.

This chapter offers a perspective on the impact of poisons and poisoning on history. It also provides a historic overview of human understanding of poisons and the development of toxicology from antiquity to the present. The development of the modern poison control center, the genesis of the field of medical toxicology, and the increasing focus on medication errors are examined. Chapter 2 describes poison plagues and unintentional disasters throughout history and examines the societal consequences of these unfortunate events. An appreciation of past failures and mistakes in dealing with poisons and poisoning promotes a keener insight and a more critical evaluation of present-day toxicologic issues and helps in the assessment and management of future toxicologic problems.

POISONS, POISONERS, AND ANTIDOTES OF ANTIQUITY

The earliest poisons consisted of plant extracts, animal venoms, and minerals. They were used for hunting, waging war, and sanctioned and unsanctioned executions. The *Ebers Papyrus*, an ancient Egyptian text written circa 1500 B.C. that is considered to be among the earliest medical texts, describes many ancient poisons, including aconite, antimony, arsenic, cyanogenic glycosides, hemlock, lead, mandrake, opium, and wormwood.[102,155] These poisons were thought to have mystical properties, and their use was surrounded by superstition and intrigue. Some agents, such as the Calabar bean (*Physostigma venenosum*) containing physostigmine, were referred to as "ordeal poisons." Ingestion of these substances was believed to be lethal to the guilty and harmless to the innocent.[130] The "penalty of the peach" involved the administration of peach pits, which we now know contain the cyanide precursor amygdalin, as an ordeal poison. Magicians, sorcerers, and religious figures were the toxicologists of antiquity. The Sumerians, in circa 4500 B.C., were said to worship the deity Gula, who was known as the "mistress of charms and spells" and the "controller of noxious poisons" (Table 1–1).[155]

Arrow and Dart Poisons

The prehistoric Masai hunters of Kenya, who lived 18,000 years ago, used arrow and dart poisons to increase the lethality of their weapons.[20] One of these poisons appears to have consisted of extracts of *Strophanthus* species, an indigenous plant that contains strophanthin, a digitalislike substance.[102] Cave paintings of arrowheads and spearheads reveal that these weapons were crafted with small depressions at the end to hold the poison.[156] In fact, the term *toxicology* is derived from the Greek terms *toxikos* ("bow") and *toxikon* ("poison into which arrowheads are dipped").[6,156]

References to arrow poisons are cited in a number of other important literary works. The ancient Indian text *Rig Veda*, written in the 12th century B.C., refers to the use of *Aconitum* species for arrow poisons.[20] In the *Odyssey*, Homer (ca. 850 B.C.) wrote that Ulysses anointed his arrows with a variety of poisons, including extracts of *Helleborus orientalis* and snake venoms. The writings of Ovid (43 B.C.–18 A.D.), describe weapons poisoned with the blood of serpents.[164]

Classification of Poisons

The first attempts at poison identification and classification and the introduction of the first antidotes took place during Greek and Roman times. An early categorization of poisons divided them into fast poisons, such as strychnine, and slow poisons, such as arsenic. In his treatise, *Materia Medica*, the Greek physician Dioscorides (40–80 A.D.) categorized poisons by their origin—animal, vegetable, or mineral.[156] This categorization remained the standard classification for the next 1,500 years.[156]

Animal Poisons

Animal poisons usually referred to the venom from poisonous animals. Although the venom from poisonous snakes has always been among the most commonly feared poisons, poisons from toads, salamanders, jellyfish, stingrays, and sea hares are often as lethal. Nicander of Colophon (204–135 B.C.), a

TABLE 1–1 Important Early People in the History of Toxicology

Person	*Date*	*Importance*
Gula	ca. 4500 B.C.	First deity associated with poisons
Shen Nung	ca. 2000 B.C.	Chinese emperor who experimented with poisons and antidotes and wrote treatise on herbal medicine
Homer	ca. 850 B.C.	Wrote how Ulysses anointed arrows with the venom of serpents
Aristotle	384–322 B.C.	Described the preparation and use of arrow poisons
Theophrastus	ca. 370–286 B.C.	Referred to poisonous plants in *De Historia Plantarum*
Socrates	ca. 470–399 B.C.	Executed by poison hemlock
Nicander	204–135 B.C.	Wrote two poems, "Theriaca" and "Alexipharmaca," that are among the earliest works on poisons
King Mithridates VI	ca. 132–63 B.C.	Fanatical fear of poisons; developed mithridatum, one of the universal antidotes
Sulla	81 B.C.	Issued *Lex Cornelia,* the first antipoisoning law
Cleopatra	69–30 B.C.	Committed suicide with deliberate cobra envenomation
Andromachus	37–68 A.D.	Refined mithridatum; known as the Theriac of Andromachus
Dioscorides	40–80 A.D.	Wrote *Materia Medica,* which classified poisons by animal, vegetable, and mineral
Galen	ca. 129–200 A.D.	Prepared "nut theriac" for Roman emperors, a remedy against bites, stings, and poisons; wrote *De Antidotis I* and *II,* which provided recipes for different antidotes, including mithridatum and panacea
Ibn Wahshiya	9th century	Famed Arab toxicologist; wrote toxicology treatise *Book on Poisons,* combining contemporary science, magic, and astrology
Moses Maimonides	1135–1204	Wrote *Treatise on Poisons and Their Antidotes*
Petrus Abbonus	1250–1315	Wrote *De Venenis*, major work on poisoning

Greek poet and physician who is considered to be one of the earliest toxicologists, experimented with animal poisons on condemned criminals.[142] Nicander's poems *Theriaca* and *Alexipharmaca* are considered to be the earliest extant Greek toxicologic texts, describing the presentations and treatment of poisonings from animal xenobiotics.[155] A notable fatality from the effects of an animal xenobiotic was Cleopatra (69–30 B.C.), who reportedly committed suicide by deliberately falling on an asp.[76]

Vegetable Poisons

Theophrastus (ca. 370–286 B.C.) described vegetable poisons in his treatise *De Historia Plantarum*.[77] Notorious poisonous plants included *Aconitum* species (monkshood, aconite), *Conium maculatum* (poison hemlock), *Hyoscyamus niger* (henbane), *Mandragora officinarum* (mandrake), *Papaver somniferum* (opium poppy), and *Veratrum album* (hellebore). Aconite was among the most frequently encountered poisonous plants and was described as the "queen mother of poisons."[155] Hemlock was the official poison used by the Greeks and was used in the execution of Socrates (ca. 470–399 B.C.) and many others.[144] Poisonous plants used in India at this time included *Cannabis indica* (marijuana), *Croton tiglium* (croton oil), and *Strychnos nux vomica* (poison nut, strychnine).[77]

Mineral Poisons

The mineral poisons of antiquity consisted of the metals antimony, arsenic, lead, and mercury. Undoubtedly, the most famous of these was lead. Lead was discovered as early as 3500 B.C. Although controversy continues about whether an epidemic of lead poisoning among the Roman aristocracy contributed to the fall of the Roman Empire, lead was certainly used extensively during this period.[55,118] In addition to its considerable use in plumbing,[44] lead was also used in the production of food and drink containers.[62] It was common practice to add lead directly to wine or to intentionally prepare the wine in a lead kettle to improve its taste. Not surprisingly, chronic lead poisoning became widespread. Nicander described the first case of lead poisoning in the 2nd century B.C.[159] Dioscorides, writing in the 1st century A.D., noted that fortified wine was "most hurtful to the nerves."[159] Lead-induced gout ("saturnine gout") may have also been widespread among the Roman elite.[118]

Gases

Although not animal, vegetable, or mineral in origin, the toxic effects of gases were also appreciated during antiquity. In the 3rd century B.C., Aristotle commented that "coal fumes lead to a heavy head and death,"[74] and Cicero (106–43 B.C.) referred to the use of coal fumes in suicides and executions.

Poisoners of Antiquity

Given the increasing awareness of the toxic properties of some naturally occurring xenobiotics and the lack of analytical detection techniques, homicidal poisoning was common during Roman times. During this period, members of the aristocracy commonly used "tasters" to shield themselves from potential poisoners, a practice also in vogue during the reign of Louis XIV in 17th-century France.[164]

One of the most infamous poisoners of ancient Rome was Locusta, who was known to experiment on slaves with poisons that included aconite, arsenic, belladonna, henbane, and poisonous fungi. In 54 A.D., Nero's mother, Agrippina, hired Locusta to poison Emperor Claudius (Agrippina's husband and Nero's stepfather) as part of a scheme to make Nero emperor. As a result of these activities, Claudius, who was a great lover of mushrooms, died from *Amanita phalloides* poisoning,[18] and in the next year, Britannicus (Nero's stepbrother) also became one of Locusta's victims. In this case, Locusta managed to fool the taster by preparing unusually hot soup that required additional cooling after the soup had been officially tasted. At the time of cooling, the poison was surreptitiously slipped into the soup. Almost immediately after drinking the soup, Britannicus collapsed and died. The exact poison remains in doubt, although some authorities suggest that it was a cyanogenic glycoside.[147]

Early Quests for the Universal Antidote

The recognition, classification, and use of poisons in ancient Greece and Rome were accompanied by an intensive search for a universal antidote. In fact, many of the physicians of this period devoted significant parts of their careers to this endeavor.[155] Mystery and superstition surrounded the origins and sources of these proposed antidotes. One of the earliest specific references to a protective therapy can be found in Homer's *Odyssey*, when Ulysses is advised to protect himself by taking the antidote "moli." Recent speculation suggests that moli referred to *Galanthus nivalis*, which contains a cholinesterase inhibitor. Moli could have been used as an antidote against poisonous plants such as *Datura stramonium* (jimsonweed) that contain the anticholinergic alkaloids scopolamine, atropine, and hyoscyamine.[127]

Theriacs and the Mithridatum

The Greeks referred to the universal antidote as the *alexipharmaca* or *theriac*.[79,155] The term *alexipharmaca* was derived from the words *alexipharmakos* ("which keeps off poison") and *antipharmakon* ("antidote"). Over the years, *alexipharmaca* was increasingly used to refer to a method of treatment, such as the induction of emesis by using a feather. Theriac, which originally had referred to poisonous reptiles or wild beasts, was later used to refer to the antidotes. Consumption of the early theriacs (ca. 200 B.C.) was reputed to make people "poison proof" against bites of all venomous animals except the asp. Their ingredients included aniseed, anmi, apoponax, fennel, meru, parsley, and wild thyme.[155]

The quest for the universal antidote was epitomized by the work of King Mithridates VI of Pontus (135–63 B.C.).[75] After repeatedly being subjected to poisoning attempts by his enemies during his youth, Mithridates sought protection by the development of universal antidotes. To find the best antidote, he performed acute toxicity experiments on criminals and slaves. The theriac he concocted, known as the "mithridatum," contained a minimum of 36 ingredients and was thought to be protective against aconite, scorpions, sea slugs, spiders, vipers, and all other poisonous substances. Mithridates took his concoction every day. Ironically, when an old man, Mithridates attempted suicide by poison but supposedly was unsuccessful because he had become poison proof. Having failed at self-poisoning, Mithridates was compelled to have a soldier kill him with a sword. Galen described Mithridates' experiences in a series of three books: *De Antidotis I*, *De Antidotis II*, and *De Theriaca ad Pisonem*.[75,160]

The Theriac of Andromachus, also known as the "Venice treacle" or "galene," is probably the most well-known theriac.[64] According to Galen, this preparation, formulated during the 1st century A.D., was considered an improvement over the mithridatum.[146] It was prepared by Andromachus (37–68 A.D.), physician to Emperor Nero. Andromachus added to the mithridatum ingredients such as the flesh of vipers, squills, and generous amounts of opium.[167] Other ingredients were removed. Altogether, 73 ingredients were required. It was advocated to "counteract all poisons and bites of venomous animals," as well as a host of other medical problems, such as colic, dropsy, and jaundice, and it was used both therapeutically and prophylactically.[155,160] As evidence of its efficacy, Galen demonstrated that fowl receiving poison followed by theriac had a higher survival rate than fowl receiving poison alone.[155] It is likely, however, that the scientific rigor and methodology used differed from current scientific practice.

By the Middle Ages, the Theriac of Andromachus contained more than 100 ingredients. Its synthesis was quite elaborate; the initial phase of production lasted months followed by an aging process that lasted years, somewhat similar to that of vintage wine.[98] The final product was often more solid than liquid in consistency.

Other theriac preparations were named after famous physicians (Damocrates, Nicolaus, Amando, Arnauld, and Abano) who contributed additional ingredients to the original formulation. Over the centuries, certain localities were celebrated for their own peculiar brand of theriac. Notable centers of theriac production included Bologna, Cairo, Florence, Genoa, Istanbul, and Venice. At times, theriac production was accompanied by great fanfare. For example, in Bologna, the mixing of the theriac could take place only under the direction of the medical professors at the university.[155]

Whether these preparations were of actual benefit is uncertain. Some suggest that the theriac had an antiseptic effect on the gastrointestinal (GI) tract, but others state that the sole benefit of the theriac derived from its formulation with opium.[98] Theriacs remained in vogue throughout the Middle Ages and Renaissance, and it was not until 1745 that their efficacy was finally questioned by William Heberden in *Antitheriaka: An Essay on Mithridatum and Theriaca*.[75] Nonetheless, pharmacopeias in France, Spain, and Germany continued to list these preparations until the last quarter of the 19th century, and theriac was still available in Italy and Turkey in the early 20th century.[19,98]

Sacred Earth

Beginning in the 5th century B.C., an adsorbent agent called *terra sigillata* was promoted as a universal antidote. This xenobiotic, also known as the "sacred sealed earth," consisted of red clay that could be found on only one particular hill on the Greek island of Lemnos. Perhaps somewhat akin to the 20th-century "universal antidote," it was advocated as effective in counteracting all poisons.[155] With great ceremony, once per year, the terra sigillata was retrieved from this hill and prepared for subsequent use. According to Dioscorides, this clay was formulated with goat's blood to make it into a paste. At one time, it was included as part of the Theriac of Andromachus. Demand for terra sigillata continued into the 15th century. Similar antidotal clays were found in Italy, Malta, Silesia, and England.[155]

Charms

Charms, such as toadstones, snakestones, unicorn horns, and bezoar stones, were also promoted as universal antidotes. Toadstones, found in the heads of old toads, were reputed to have the capability to extract poison from the site of a venomous bite or sting. In addition, the toadstone was supposedly able to detect the mere presence of poison by producing a sensation of heat upon contact with a poisonous substance.[155]

Similarly, snakestones extracted from the heads of cobras (known as *piedras della cobra de Capelos*) were also reported to have magical qualities.[14] The 17th-century Italian philosopher Athanasius Kircher (1602–1680) became an enthusiastic supporter of snakestone therapy for the treatment of snakebite after conducting experiments, demonstrating the antidotal attributes of these charms "in front of amazed spectators." Kircher attributed the efficacy of the snakestone to the theory of "attraction of like substances." Francesco Redi (1626–1698), a court physician and contemporary of Kircher, debunked this quixotic approach. A harbinger of future experimental toxicologists, Redi was unwilling to accept isolated case reports and field demonstrations as proof of the utility of the snakestone. Using a considerably more rigorous approach, *provando et riprovando* (by testing and retesting), Redi assessed the antidotal efficacy of snakestone on different animal species and different xenobiotics and failed to confirm any benefit.[14]

Much lore has surrounded the antidotal effects of the mythical unicorn horn. Ctesias, writing in 390 B.C., was the first to chronicle the wonders of the unicorn horn, claiming that drinking water or wine from the "horn of the unicorn" would protect against poison.[155] The horns were usually narwhal tusks or rhinoceros horns, and during the Middle Ages, the unicorn horn may have been worth as much as 10 times the price of gold. Similar to the toadstone, the unicorn horn was used both to detect poisons and to neutralize them. Supposedly, a cup made of unicorn horn would sweat if a poisonous substance was placed in it.[96] To give further credence to its use, a 1593 study on dogs poisoned by arsenic reportedly showed that the horn was protective.[96]

Bezoar stones, also touted as universal antidotes, consisted of stomach or intestinal calculi formed by the deposition of calcium phosphate around a hair, fruit pit, or gallstone. They were removed from wild goats, cows, and apes and administered orally to humans. The Persian name for the bezoar stone was *pad zahr* ("expeller of poisons"); the ancient Hebrews referred to the bezoar stone as *bel Zaard* ("every cure for poisons"). Over the years, regional variations of bezoar stones were popularized, including an Asian variety from wild goat of Persia, an Occidental variety from llamas of Peru, and a European variety from chamois of the Swiss mountains.[50,155]

OPIUM, COCA, CANNABIS, AND HALLUCINOGENS IN ANTIQUITY

Although it was not until the mid-19th century that the true perils of opioid addiction were first recognized, juice from the *Papaver somniferum* was known for its medicinal value in Egypt at least as early as the writing of the *Ebers Papyrus* in 1500 B.C. Egyptian pharmacologists of that time reportedly recommended opium poppy extract as a pacifier for children who exhibited incessant crying.[141] In Ancient Greece, Dioscorides and Galen were early advocates of opium as a therapeutic xenobiotic. During this time, it was also used as a means of suicide. Mithridates' lack of success in his own attempted suicide by poisoning may have been the result of an opium tolerance that had developed from previous repetitive use.[141] One of the earliest descriptions of the abuse potential of opium is attributed to Epistratos (304–257 B.C.), who criticized the use of opium for earache because it "dulled the sight and is a narcotic."[141]

Cocaine use dates back to at least 300 B.C., when South American Indians reportedly chewed coca leaves during religious ceremonies.[112] Chewing coca to increase work efficacy and to elevate mood has remained commonplace in some South American societies for thousands of years. An Egyptian mummy from about 950 B.C. revealed significant amounts of cocaine in the stomach and liver, suggesting oral use of cocaine occurred during this time period.[116] Large amounts of tetrahydrocannabinol (THC) were also found in the lung and muscle of the same mummy. Another investigation of 11 Egyptian (1079 B.C.–395 A.D.) and 72 Peruvian (200–1500 A.D.) mummies found cocaine, thought to be indigenous only to South America, and hashish, thought to be indigenous only to Asia, in both groups.[126]

Cannabis use in China dates back even further, to around 2700 B.C., when it was known as the "liberator of sin."[112] In India and Iran, cannabis was used as early as 1000 B.C. as an xenobiotic known as *bhang*.[115] Other currently abused xenobiotics that were known to the ancients include cannabis, hallucinogenic mushrooms, nutmeg, and peyote. As early as 1300 B.C., Peruvian Indian tribal ceremonies included the use of mescaline-containing San Pedro cacti.[112] The hallucinogenic mushroom, *Amanita muscaria*, known as "fly agaric," was used as a ritual drug and may have been known in India as "soma" around 2000 B.C.

EARLY ATTEMPTS AT GASTROINTESTINAL DECONTAMINATION

Nicander's *Alexipharmaca* (*Antidotes for Poisons*) recommended induction of emesis by one of several methods: (a) ingesting warm linseed oil, (b) tickling the hypopharynx with a feather, or (c) "emptying the gullet with a small twisted and curved paper."[98] Nicander also advocated the use of suction to limit envenomation.[156] The Romans referred to the feather as the "vomiting feather" or "pinna." Most commonly, the feather was used after a hearty feast to avoid the GI discomfort associated with overeating. At times, the pinna was dipped into a nauseating mixture to increase its efficacy.[101]

TOXICOLOGY DURING THE MEDIEVAL AND RENAISSANCE PERIODS

After Galen (ca. A.D. 129–200), there is relatively little documented attention to the subject of poisons until the works of Ibn Wahshiya in the 9th century. Citing Greek, Persian, and Indian texts, Wahshiya's work, titled *Book of Poisons*, combined contemporary science, magic, and astrology during his discussion of poison mechanisms (as they were understood at that time), symptomatology, antidotes (including his own recommendation for a universal antidote), and prophylaxis. He categorized poisons as lethal by sight, smell, touch, and sound, as well as by drinking and eating. For victims of an aconite-containing dart arrow, Ibn Wahshiya recommended excision followed by cauterization and topical treatment with onion and salt.[93]

Another significant medieval contribution to toxicology can be found in Moses Maimonides' (1135–1204) *Treatise on Poisons and Their Antidotes* (1198). In part one of this treatise, Maimonides discussed the bites of snakes and mad dogs and the stings of bees, wasps, spiders, and scorpions.[139] He also discussed the use of cupping glasses for bites (a progenitor of the modern suctioning device) and was one of the first to differentiate the hematotoxic

(hot) from the neurotoxic (cold) effects of poison. In part two, he discussed mineral and vegetable poisons and their antidotes. He described belladonna poisoning as causing a "redness and a sort of excitation."[139] He suggested that emesis should be induced by hot water, *Anethum graveolens* (dill), and oil, followed by fresh milk, butter, and honey. Although he rejected some of the popular treatments of the day, he advocated the use of the great theriac and the mithridatum as first- and second-line xenobiotics in the management of snakebite.[139]

On the subject of oleander poisoning, Petrus Abbonus (1250–1315) wrote that those who drink the juice, spines, or bark of oleander will develop anxiety, palpitations, and syncope.[22] He described the clinical presentation of opium overdose as someone who "will be dull, lazy, and sleepy, without feeling, and he will neither understand nor feel anything, and if he does not receive succor, he will die." Although this "succor" is not defined, he recommended that treatment of opium toxicity include drinking the strongest wine, rubbing the extremities with alkali and soap, and olfactory stimulation with pepper. To treat snakebite, Abbonus suggested the immediate application of a tourniquet, as well as oral suctioning of the bite wound, preferably performed by a servant. Interestingly, from a 21st-century perspective, Abbonus also suggested that St. John's wort had the magical power to free anything from poisons and attributed this virtue to the influence of the stars.[22]

The Scientists

Paracelsus' (1493–1541) study on the dose–response relationship is usually considered the beginning of the scientific approach to toxicology (Table 1–2). He was the first to emphasize the chemical nature of toxic xenobiotics.[123] Paracelsus stressed the need for proper observation and experimentation regarding the true response to xenobiotics. He underscored the need to differentiate between the therapeutic and toxic properties of chemicals when he stated in his *Third Defense*, "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."[43]

Although Paracelsus is the best known Renaissance toxicologist, Ambroise Pare (1510–1590) and William Piso (1611–1678) also contributed to the field. Pare argued against the use of the unicorn horn and bezoar stone.[100] He also wrote an early treatise on carbon monoxide poisoning. Piso is credited as one of the first to recognize the emetic properties of ipecacuanha.[136]

Medieval and Renaissance Poisoners

Along with these advances in toxicologic knowledge, the Renaissance is mainly remembered as the age of the poisoner, a time when the art of poisoning reached new heights (Table 1–3). In fact, poisoning was so rampant during this time that in 1531, King Henry VIII decreed that convicted poisoners should be boiled alive.[52] From the 15th to 17th centuries, schools of poisoning existed in Venice and Rome. In Venice, poisoning services were provided by a group called the Council of Ten, whose members were hired to perform murder by poison.[164]

Members of the infamous Borgia family were considered to be responsible for many poisonings during this period. They preferred to use a poison called "La Cantarella," a mixture of arsenic and phosphorus.[157] Rodrigo Borgia (1431–1503), who became Pope Alexander VI, and his son, Cesare Borgia, were reportedly responsible for the poisoning of cardinals and kings.

In the late 16th century, Catherine de Medici, wife of Henry II of France, introduced Italian poisoning techniques to France. She experimented on the poor, the sick, and the criminal. By analyzing the subsequent complaints of her victims, she is said to have learned the sites of action and times of onset, the clinical signs and symptoms, and the efficacies of poisons.[56] Murder by poison remained quite popular during the latter half of the 17th and the early part of the 18th centuries in Italy and France.

The Marchioness de Brinvilliers (1630–1676) tested her poison concoctions on hospitalized patients and on her servants and allegedly murdered her husband, father, and two siblings.[54,147] Among the favorite poisons of the Marchioness were arsenic, copper sulfate, corrosive sublimate (mercury bichloride), lead, and tartar emetic (antimony potassium tartrate).[157]

TABLE 1–2 Important People in the Later History of Toxicology

Person	*Date*	*Importance*
Paracelsus	1493–1541	Introduced the dose–response concept to toxicology
Ambroise Pare	1510–1590	Argued against unicorn horns and bezoars as antidotes
William Piso	1611–1678	First to study emetic qualities of ipecacuanha
Bernardino Ramazzini	1633–1714	Father of occupational medicine; wrote *De Morbis Artificum Diatriba*
Richard Mead	1673–1754	Wrote English-language book about poisoning
Percivall Pott	1714–1788	Wrote the first description of occupational cancer, relating the chimney sweep occupation to scrotal cancer
Felice Fontana	1730–1805	First scientific study of venomous snakes
Philip Physick	1767–1837	Early advocate of orogastric lavage to remove poisons
Baron Guillaume Dupuytren	1777–1835	Early advocate of orogastric lavage to remove poisons
Francois Magendie	1783–1855	Discovered emetine and studied the mechanisms of cyanide and strychnine
Bonaventure Orfila	1787–1853	Father of modern toxicology; wrote *Traite des Poisons;* first to isolate arsenic from human organs
James Marsh	1794–1846	Developed reduction test for arsenic
Robert Christison	1797–1882	Wrote *Treatise on Poisons,* one of the most influential texts of the early 19th century
Grand Marshall Bertrand	1813	Demonstrated the efficacy of charcoal in arsenic ingestion
Claude Bernard	1813–1878	Studied the mechanisms of toxicity of carbon monoxide and curare
Edward Jukes	1820	Self-experimented with orogastric lavage apparatus known as Jukes syringe
Theodore Wormley	1826–1897	Wrote *Micro-Chemistry of Poisons,* the first American book devoted exclusively to toxicology
Pierre Touery	1831	Demonstrated the efficacy of charcoal in strychnine ingestion
Hugo Reinsch	1842–1884	Developed qualitative tests for arsenic and mercury
Alfred Garrod	1846	Conducted the first systematic study of charcoal in an animal model
Max Gutzeit	1847–1915	Developed method to quantitate small amounts of arsenic
Benjamin Howard Rand	1848	Conducted the first study of the efficacy of charcoal in humans
O.H. Costill	1848	Wrote the first book on symptoms and treatment of poisoning
Louis Lewin	1850–1929	Studied many toxins, including methanol, chloroform, snake venom, carbon monoxide, lead, opioids, and hallucinogenic plants
Rudolf Kobert	1854–1918	Studied digitalis and ergot alkaloids
Albert Niemann	1860	Isolated cocaine alkaloids
Alice Hamilton	1869–1970	Conducted landmark investigations associating worksite chemical hazards with disease; led reform movement to improve worker safety

TABLE 1–3 Notable Poisoners from Antiquity to the Present

Poisoner	*Date*	*Victim(s)*	*Poison(s)*
Locusta	54–55 A.D.	Claudius and Britannicus	*Amanita phalloides*, cyanide
Cesare Borgia	1400s	Cardinals and kings	La Cantarella (arsenic and phosphorus)
Catherine de Medici	1519–1589	Poor, sick, criminals	Unknown
Hieronyma Spara	Died 1659	Taught women how to poison their husbands	Mana of St. Nicholas of Bari (arsenic trioxide)
Marchioness de Brinvilliers	Died 1676	Hospitalized patients, husband, father	Antimony, arsenic, copper, lead, mercury
Catherine Deshayes	Died 1680	>2,000 infants, many husbands	La poudre de succession (arsenic mixed with aconite, belladonna, and opium)
Madame Giulia Toffana	Died 1719	>600 people	Aqua toffana (arsenic trioxide)
Mary Blandy	1752	Father	Arsenic
Anna Maria Zwanizer	1807	Random people	Antimony, arsenic
Marie Lefarge	1839	Husband	Arsenic (first use of Marsh test)
John Tawell	1845	Mistress	Cyanide
William Palmer, MD	1855	Fellow gambler	Strychnine
Madeline Smith (acquitted)	1857	Lover	Arsenic
Edmond de la Pommerais, MD	1863	Patient and mistress	Digitalis
Edward William Pritchard, MD	1865	Wife and mother-in-law	Antimony
George Henry Lamson, MD	1881	Brother-in-law	Aconite
Adelaide Bartlett (acquitted)	1886	Husband	Chloroform
Florence Maybrick	1889	Husband	Arsenic
Thomas Neville Cream, MD	1891	Prostitutes	Strychnine
Johann Hoch	1892–1905	Serial wives	Arsenic
Cordelia Botkin	1898	Rival woman	Arsenic (in chocolate candy)
Roland Molineux	1898	Acquaintance	Cyanide of mercury
Hawley Harvey Crippen, MD	1910	Wife	Hyoscine
Frederick Henry Seddon	1911	Boarder	Arsenic (fly paper)
Henri Girard Landru	1912	Acquaintances	*Amanita phalloides*
Robert Armstrong	1921	Wife	Arsenic (weed killer)
Landru	1922	Many women	Cyanide
Suzanne Fazekas	1929	Supplied poison to 100 wives to kill husbands	Arsenic
Sadamichi Hirasawa	1948	Bank employees	Potassium cyanide
Christa Ambros Lehmann	1954	Friend, husband, father-in-law	E-605 (parathion)
Nannie Doss	1954	11 relatives, including five husbands	Arsenic
Carl Coppolino, MD	1965	Wife	Succinylcholine
Graham Frederick Young	1971	Stepmother, coworkers	Antimony, thallium
Judias V. Buenoano	1971	Husband, son	Arsenic
Ronald Clark O'Bryan	1974	Son and neighborhood children	Cyanide (in Halloween candy)
Governmental	1978	Georgi Markov, Bulgarian dissident	Ricin
Jim Jones	1978	>900 people in mass suicide	Cyanide
Harold Shipman, MD	1974–1998	>100 patients	Heroin
Unidentified	1982	Seven random people	Extra Strength Tylenol mixed with cyanide

(*Continued*)

TABLE 1–3 Notable Poisoners from Antiquity to the Present (*Continued*)

Poisoner	*Date*	*Victim(s)*	*Poison(s)*
Donald Harvey	1983–1987	Patients	Arsenic
George Trepal	1988	Neighbors	Thallium
Michael Swango, MD	1980s–1990s	Hospitalized patients	Arsenic, potassium chloride, succinylcholine
Charles Cullen, RN	1990s–2003	Hospitalized patients	Digoxin
State sponsored	2004	Viktor Yushchenko, Ukrainian presidential candidate	Dioxin
State sponsored	2006	Alexander Litvinenko	Polonium-210
State sponsored	2017	Kim Jong-nam	VX

Catherine Deshayes (1640–1680), a fortuneteller and sorceress, was one of the last "poisoners for hire" and was implicated in countless poisonings, including the killing of more than 2,000 infants.[56] Better known as "La Voisine," she reportedly sold poisons to women wishing to rid themselves of their husbands. Her particular brand of poison was a concoction of aconite, arsenic, belladonna, and opium known as "la poudre de succession."[157] Ultimately, de Brinvilliers was beheaded, and Deshayes was burned alive for her crimes. In an attempt to curtail these rampant poisonings, Louis XIV issued a decree in 1662 banning the sale of arsenic, mercury, and other poisons to customers not known to apothecaries and requiring buyers to sign a register declaring the purpose for their purchase.[147]

A major center for poison practitioners was Naples, the home of the notorious Madame Giulia Toffana. She reportedly poisoned more than 600 people, preferring a particular solution of white arsenic (arsenic trioxide), better known as "aqua toffana," and dispensed under the guise of a cosmetic. Eventually convicted of poisoning, Madame Toffana was executed in 1719.[21]

EIGHTEENTH- AND NINETEENTH-CENTURY DEVELOPMENTS IN TOXICOLOGY

The development of toxicology as a distinct specialty began during the 18th and 19th centuries (Table 1–2).[125] The mythological and magical mystique of poisoners began to be gradually replaced by an increasingly rational, scientific, and experimental approach to these xenobiotics. Much of the poison lore that had survived for almost 2,000 years was finally debunked and discarded. The 18th-century Italian Felice Fontana was one of the first to usher in the modern age. He was an early experimental toxicologist who studied the venom of the European viper and wrote the classic text *Traite sur le Venin de la Vipere* in 1781.[82] Through his exacting experimental study on the effects of venom, Fontana brought a scientific insight to toxicology previously lacking and demonstrated that clinical symptoms resulted from the poison (venom) acting on specific target organs. During the 18th and 19th centuries, attention focused on the detection of poisons and the study of toxic effects of xenobiotics in animals.[117] Issues relating to adverse effects of industrialization and unintentional poisoning in the workplace and home environment were raised. Also during this time, early experience and experimentation with methods of GI decontamination took place.

Development of Analytical Toxicology and the Study of Poisons

The French physician Bonaventure Orfila (1787–1853) is often called the father of modern toxicology.[117] He emphasized toxicology as a distinct, scientific discipline, separate from clinical medicine and pharmacology.[11] He was also an early medicolegal expert who championed the use of chemical analysis and autopsy material as evidence to prove that a poisoning had occurred. His treatise *Traite des Poisons* (1814)[122] evolved over five editions and was regarded as the foundation of experimental and forensic toxicology.[163] This text classified poisons into six groups: acrids, astringents, corrosives, narcoticoacrids, septics and putrefiants, and stupefacients and narcotics.

A number of other landmark works on poisoning also appeared during this period. In 1829, Robert Christison (1797–1882), a professor of medical jurisprudence and Orfila's student, wrote *A Treatise on Poisons*.[32] This work simplified Orfila's poison classification schema by categorizing poisons into three groups: irritants, narcotics, and narcoticoacrids. Less concerned with jurisprudence than with clinical toxicology, O.H. Costill's *A Practical Treatise on Poisons*, published in 1848, was the first modern clinically oriented text to emphasize the symptoms and treatment of poisoning.[36] In 1867, Theodore Wormley (1826–1897) published the first American book written exclusively on poisons titled the *Micro-Chemistry of Poisons*.[48,166]

During this time, important breakthroughs in the chemical analysis of poisons resulted from the search for a more reliable assay for arsenic.[66,162] Arsenic was widely available and was the suspected cause of a large number of deaths. In one study, arsenic was used in 31% of 679 homicidal poisonings.[157] A reliable means of detecting arsenic was much needed by the courts.

Until the 19th century, poisoning was mainly diagnosed by its resultant symptoms rather than by analytic tests. The first use of a chemical test as evidence in a poisoning trial occurred in the 1752 trial of Mary Blandy, who was accused of poisoning her father with arsenic.[104] Although Blandy was convicted and hanged publicly, the test used in this case was not very sensitive and depended in part on eliciting a garlic odor upon heating the gruel that the accused had fed to her father.

During the 19th century, James Marsh (1794–1846), Hugo Reinsch (1842–1884), and Max Gutzeit (1847–1915) each worked on this problem. Assays bearing their names are important contributions to the early history of analytic toxicology.[105,117] The "Marsh test" to detect arsenic was first used in a criminal case in 1839 during the trial of Marie Lefarge, who was accused of using arsenic to murder her husband.[147] Orfila's trial testimony that the victim's viscera contained minute amounts of arsenic helped to convict the defendant, although subsequent debate suggested that contamination of the forensic specimen may have also played a role.

In a further attempt to curtail criminal poisoning by arsenic, the British Parliament passed the Arsenic Act in 1851. This bill, which was one of the first modern laws to regulate the sale of poisons, required that the retail sale of arsenic be restricted to chemists, druggists, and apothecaries and that a poison book be maintained to record all arsenic sales.[15]

Homicidal poisonings remained common during the 19th century and early 20th century. Infamous poisoners of that time included William Palmer, Edward Pritchard, Harvey Crippen, and Frederick Seddon.[157] Many of these poisoners were physicians who used their knowledge of medicine and toxicology in an attempt to solve their domestic and financial difficulties by committing the "perfect" murder. Some of the poisons used were aconitine (by Lamson, who was a classmate of Christison), *Amanita phalloides* (by Girard), arsenic (by Maybrick, Seddon, and others), antimony (by Pritchard), cyanide (by Molineux and Tawell), digitalis (by Pommerais), hyoscine (by Crippen), and strychnine (by Palmer and Cream) (Table 1–3).[24,91,155,157]

In the early 20th century, forensic investigation into suspicious deaths, including poisonings, was significantly advanced with the development of

the medical examiner system replacing the much-flawed coroner system that was subject to widespread corruption. In 1918, the first centrally controlled medical examiner system was established in New York City. Alexander Gettler, considered the father of forensic toxicology in the United States, established a toxicology laboratory within the newly created New York City Medical Examiner's Office. Gettler pioneered new techniques for the detection of a variety of substances in biologic fluids, including carbon monoxide, chloroform, cyanide, and heavy metals.[49,117]

Systematic investigation into the underlying mechanisms of toxic substances also commenced during the 19th century. Francois Magendie (1783–1855) studied the mechanisms of toxicity and sites of action of cyanide, emetine, and strychnine.[47] Claude Bernard (1813–1878), a pioneering physiologist and a student of Magendie, made important contributions to the understanding of the toxicity of carbon monoxide and curare.[90] Rudolf Kobert (1854–1918) studied digitalis and ergot alkaloids and authored a textbook on toxicology for physicians and students.[87,120] Louis Lewin (1850–1929) was the first person to intensively study the differences between the pharmacologic and toxicologic actions of xenobiotics. Lewin studied chronic opium intoxication, as well as the toxicity of carbon monoxide, chloroform, lead, methanol, and snake venom. He also developed a classification system for psychoactive drugs, dividing them into euphorics, phantastics, inebriants, hypnotics, and excitants.[99]

The Origin of Occupational Toxicology

The origins of occupational toxicology can be traced to the early 18th century and to the contributions of Bernardino Ramazzini (1633–1714). Considered the father of occupational medicine, Ramazzini wrote *De Morbis Artificum Diatriba* (*Diseases of Workers*) in 1700, which was the first comprehensive text discussing the relationship between disease and workplace hazards.[53] Ramazzini's essential contribution to patient care is epitomized by the addition of a standard question to a patient's medical history: "What occupation does the patient follow?"[51] Altogether Ramazzini described diseases associated with 54 occupations, including hydrocarbon poisoning in painters, mercury poisoning in mirror makers, and pulmonary diseases in miners.

In 1775, Sir Percivall Pott proposed the first association between workplace exposure and cancer when he noticed a high incidence of scrotal cancer in English chimney sweeps. Pott's belief that the scrotal cancer was caused by prolonged exposure to tar and soot was confirmed by further investigation in the 1920s, indicating the carcinogenic nature of the polycyclic aromatic hydrocarbons contained in coal tar (including benzo[*a*]pyrene).[73]

Dr. Alice Hamilton (1869–1970) was another pioneer in occupational toxicology, whose rigorous scientific inquiry had a profound impact on linking chemical xenobiotics with human disease. A physician, scientist, humanitarian, and social reformer, Hamilton became the first female professor at Harvard University and conducted groundbreaking studies of many different occupational exposures and problems, including carbon monoxide poisoning in steelworkers, mercury poisoning in hatters, and wrist drop in lead workers. Hamilton's overriding concerns about these "dangerous trades" and her commitment to improving the health of workers led to extensive voluntary and regulatory reforms in the workplace.[60,65]

Advances in Gastrointestinal Decontamination

Using gastric lavage and charcoal to treat poisoned patients was introduced in the late 18th and early 19th century. A stomach pump was first designed by Munro Secundus in 1769 to administer neutralizing substances to sheep and cattle for the treatment of bloat.[25] The American surgeon Philip Physick (1768–1837) and the French surgeon Baron Guillaume Dupuytren (1777–1835) were two of the first physicians to advocate gastric lavage for the removal of poisons.[25] As early as 1805, Physick demonstrated the use of a "stomach tube" for this purpose. Using brandy and water as the irrigation fluid, he performed stomach washings in twins to wash out excessive doses of tincture of opium.[25] Dupuytren performed gastric emptying by first introducing warm water into the stomach via a large syringe attached to a long flexible sound and then withdrawing the "same water charged with poison."[25] Edward Jukes, a British surgeon, was another early advocate of poison removal by gastric lavage. Jukes first experimented on animals, performing gastric lavage after the oral administration of tincture of opium. Attempting to gain human experience, he experimented on himself, by first ingesting 10 drams (600 g) of tincture of opium and then performing gastric lavage using a 25-inch-long, 0.5-inch-diameter tube, which became known as Jukes syringe.[111] Other than some nausea and a 3-hour sleep, he suffered no ill effects, and the experiment was deemed a success.

The principle of using charcoal to adsorb xenobiotics was first described by Scheele (1773) and Lowitz (1785), but the medicinal use of charcoal dates to ancient times.[35] The earliest reference to the medicinal uses of charcoal is found in Egyptian papyrus from about 1500 B.C.[35] The charcoal used during Greek and Roman times, referred to as "wood charcoal," was used to treat those with anthrax, chlorosis, epilepsy, and vertigo. By the late 18th century, topical application of charcoal was recommended for gangrenous skin ulcers, and internal use of a charcoal–water suspension was recommended for use as a mouthwash and in the treatment of bilious conditions.[35]

The first hint that charcoal might have a role in the treatment of poisoning came from a series of courageous self-experiments in France during the early 19th century. In 1813, the French chemist Bertrand publicly demonstrated the antidotal properties of charcoal by surviving a 5-g ingestion of arsenic trioxide that had been mixed with charcoal.[69] Eighteen years later, before the French Academy of Medicine, the pharmacist Touery survived an ingestion consisting of 10 times the lethal dose of strychnine mixed with 15 g of charcoal.[69] One of the first reports of charcoal used in a poisoned patient was in 1834 by the American Hort, who successfully treated a mercury bichloride–poisoned patient with large amounts of powdered charcoal.[3]

In the 1840s, Garrod performed the first controlled study of charcoal when he examined its utility on a variety of poisons in animal models.[69] Garrod used dogs, cats, guinea pigs, and rabbits to demonstrate the potential benefits of charcoal in the management of strychnine poisoning. He also emphasized the importance of early use of charcoal and the proper ratio of charcoal to poison. Other toxic substances, such as aconite, hemlock, mercury bichloride, and morphine, were also studied during this period. The first charcoal efficacy studies in humans were performed by the American physician B. Rand in 1848.[69]

But it was not until the early 20th century that an activation process was added to the manufacture of charcoal to increase its effectiveness. In 1900, the Russian Ostrejko demonstrated that treating charcoal with superheated steam significantly enhanced its adsorbing power.[35] Despite this improvement and the favorable reports mentioned, charcoal was only occasionally used in GI decontamination until the early 1960s, when Holt and Holz repopularized its use.[63]

The Increasing Recognition of the Perils of Drug Abuse

Opioids

Although the medical use of opium was promoted by Paracelsus in the 16th century, its popularity was given a significant boost when the distinguished British physician Thomas Sydenham (1624–1689) formulated laudanum, which was a tincture of opium containing cinnamon, cloves, saffron, and sherry. Sydenham also formulated a different opium concoction known as "syrup of poppies."[86] A third opium preparation called Dover's powder was designed by Sydenham's protégé, Thomas Dover; this preparation contained ipecac, licorice, opium, salt-peter, and tartaric acid.

John Jones, the author of the 18th-century text *The Mysteries of Opium Reveal'd*, was another enthusiastic advocate of its "medicinal" uses.[86] A well-known opium user himself, Jones provided one of the earliest descriptions of opioid addiction. He insisted that opium offered many benefits if the dose was moderate but that discontinuation or a decrease in dose, particularly after "leaving off after long and lavish use," would result in such symptoms as sweating, itching, diarrhea, and melancholy. His recommendation for the treatment of these withdrawal symptoms included decreasing the dose of opium by 1% each day until the drug was totally withdrawn. During this period, a number of English writers became well-known opium

addicts including Elizabeth Barrett Browning, Samuel Taylor Coleridge, and Thomas De Quincey. De Quincey, author of *Confessions of an English Opium Eater*, was an early advocate of the recreational use of opioids. The famed Coleridge poem *Kubla Khan* referred to opium as the "milk of paradise," and De Quincey's *Confessions* suggested that opium held the "key to paradise." In many of these cases, the initiation of opium use for medical reasons led to recreational use, tolerance, and dependence.[86]

Although opium was first introduced to Asian societies by Arab physicians some time after the fall of the Roman Empire, the use of opium in Asian countries grew considerably during the 18th and 19th centuries. The growing dependence of China on opium was spurred on by the English desire to establish and profit from a flourishing drug trade.[141] Opium was grown in India and exported east. Despite Chinese protests and edicts against this practice, the importation of opium persisted throughout the 19th century, with the British going to war twice to maintain their right to sell opium. Not surprisingly, by the beginning of the 20th century, opium abuse in China was endemic.

In England, opium use continued to increase during the first half of the 19th century. During this period, opium was legal and freely available from the neighborhood grocer. To many, its use was considered no more problematic than alcohol use.[58] The Chinese usually self-administered opium by smoking, a custom that was brought to the United States by Chinese immigrants in the mid-19th century; the English use of opium was more often by ingestion, that is, "opium eating."

The liberal use of opioids as infant-soothing xenobiotics was one of the most unfortunate aspects of this period of unregulated opioid use.[87] Godfrey's Cordial, Mother's Friend, Mrs. Winslow's Soothing Syrup, and Quietness were among the most popular opioids for children.[94] They were advertised as producing a natural sleep and recommended for teething and bowel regulation, as well as for crying. Because of the wide availability of opioids during this period, the number of acute opioid overdoses in children was consequential and would remain problematic until these unsavory remedies were condemned and removed from the market.

With the discovery of morphine in 1805 and Alexander Wood's invention of the hypodermic syringe in 1853, parenteral administration of morphine became the preferred route of opioid administration for therapeutic use and abuse.[71] A legacy of the generous use of opium and morphine during the US Civil War was "soldiers' disease," referring to a rather large veteran population that returned from the war with a lingering opioid habit.[133] One hundred years later, opioid abuse and addiction would again become common among US military serving during the Vietnam War. Surveys indicated that as many as 20% of American soldiers in Vietnam were addicted to opioids during the war—in part because of their widespread availability and high purity there.[138]

Growing concerns about opioid abuse in England led to the passing of the Pharmacy Act of 1868, which restricted the sale of opium to registered chemists. But in 1898, the Bayer Pharmaceutical Company of Germany synthesized heroin from opium and also introduced aspirin in the late 1890s.[148] Although initially touted as a nonaddictive morphine substitute, problems with heroin use quickly became evident in the United States. Illicit heroin use reached epidemic proportions after World War II and again in the late 1960s.[72] Although heroin use appeared to have leveled off by the end of the 20th century, an epidemic of prescription opioid abuse followed by a resurgence in heroin use occurred during the first years of the 21st century.[85]

Cocaine

Ironically, during the later part of the 19th century, Sigmund Freud and Robert Christison, among others, promoted cocaine as a treatment for opioid addiction. After Albert Niemann's isolation of cocaine alkaloid from coca leaf in 1860, growing enthusiasm for cocaine as a panacea ensued.[80] Some of the most important medical figures of the time, including William Halsted, the famed Johns Hopkins surgeon, also extolled the virtues of cocaine use. Halsted championed the anesthetic properties of this drug, although his own use of cocaine and subsequent morphine use in an attempt to overcome his cocaine dependency would later take a considerable toll.[121] In 1884, Freud wrote *Uber Cocaine*,[27] advocating cocaine as a cure for opium and morphine addiction and as a treatment for fatigue and hysteria.

During the last third of the 19th century, cocaine was added to many popular nonprescription tonics. In 1863, Angelo Mariani, a Frenchman, introduced a new wine, "Vin Mariani," that consisted of a mixture of cocaine and wine (6 mg of cocaine alkaloid per ounce) and was sold as a digestive aid and restorative.[112] In direct competition with the French tonic was the American-made Coca-Cola, developed by J.S. Pemberton. It was originally formulated with coca and caffeine and marketed as a headache remedy and invigorator. With the public demand for cocaine increasing, patent medication manufacturers were adding cocaine to thousands of products. One such asthma remedy was "Dr. Tucker's Asthma Specific," which contained 420 mg of cocaine per ounce and was applied directly to the nasal mucosa.[80] By the end of the 19th century, the first American cocaine epidemic was underway.[114]

Similar to the medical and societal adversities associated with opioid use, the increasing use of cocaine led to a growing concern about comparable adverse effects. In 1886, the first reports of cocaine-related cardiac arrest and stroke were published.[134] Reports of cocaine habituation occurring in patients using cocaine to treat their underlying opioid addiction also began to appear. In 1902, a popular book, *Eight Years in Cocaine Hell*, described some of these problems. *Century Magazine* called cocaine "the most harmful of all habit-forming drugs," and a report in *The New York Times* stated that cocaine was destroying "its victims more swiftly and surely than opium."[42] In 1910, President William Taft proclaimed cocaine to be "public enemy number 1."

In an attempt to curb the increasing problems associated with drug abuse and addiction, the 1914 Harrison Narcotics Act mandated stringent control over the sale and distribution of narcotics (defined as opium, opium derivatives, and cocaine).[42] It was the first federal law in the United States to criminalize the nonmedical use of drugs. The bill required doctors, pharmacists, and others who prescribed narcotics to register and to pay a tax. A similar law, the Dangerous Drugs Act, was passed in the United Kingdom in 1920.[58] To help enforce these drug laws in the United States, the Narcotics Division of the Prohibition Unit of the Internal Revenue Service (a progenitor of the Drug Enforcement Agency) was established in 1920. In 1924, the Harrison Act was further strengthened with the passage of new legislation that banned the importation of opium for the purpose of manufacturing heroin, essentially outlawing the medicinal uses of heroin. With the legal venues to purchase these drugs now eliminated, users were forced to buy from illegal street dealers, creating a burgeoning black market that still exists today.

Sedative–Hypnotics

The introduction to medical practice of the anesthetics nitrous oxide, ether, and chloroform during the 19th century was accompanied by the recreational use of these anesthetics and the first reports of volatile substance abuse. Chloroform "jags," ether "frolics," and nitrous parties became a new type of entertainment. Humphry Davy was an early self-experimenter with the exhilarating effects associated with nitrous oxide inhalation. In certain Irish towns, especially where the temperance movement was strong, ether drinking became quite popular.[107] Horace Wells, the American dentist who introduced chloroform as an anesthetic, became dependent on this volatile solvent and later committed suicide.

Until the last half of the 19th century aconite, alcohol, hemlock, opium, and prussic acid (cyanide) were the primary xenobiotics used for sedation.[33] During the 1860s, new, more specific sedative–hypnotics, such as chloral hydrate and potassium bromide, were introduced into medical practice. In particular, chloral hydrate was hailed as a wonder drug that was relatively safe compared with opium and was recommended for insomnia, anxiety, and delirium tremens, as well as for scarlet fever, asthma, and cancer. But within a few years, problems with acute toxicity of chloral hydrate, as well as its potential to produce tolerance and physical dependence, became apparent.[33] Mixing chloral hydrate with ethanol, both of which inhibit each other's metabolism by competing with alcohol dehydrogenase, was noted to produce a rather powerful "knockout" combination that would become known as a "Mickey Finn," allegedly named after a Chicago saloon proprietor.[16] Abuse of chloral

hydrate, as well as other new sedatives such as potassium bromide, would prove to be a harbinger of 20th-century sedative–hypnotic abuse.

Absinthe, an ethanol-containing beverage that was manufactured with an extract from wormwood (*Artemisia absinthium*), was very popular during the last half of the 19th century.[89] This emerald-colored, very bitter drink was memorialized in the paintings of Degas, Toulouse-Lautrec, and Van Gogh and was a staple of French society during this period.[12] α-Thujone, a psychoactive component of wormwood and a noncompetitive γ-aminobutyric acid type A ($GABA_A$ antagonist), is thought to be responsible for the pleasant feelings, hyperexcitability, and significant neurotoxicity associated with this drink.[68] Van Gogh's debilitating episodes of psychosis were likely exacerbated by absinthe drinking.[152] Because of the medical problems associated with its use, absinthe was banned throughout most of Europe by the early 20th century.

Hallucinogens

Native Americans used peyote in religious ceremonies since at least the 17th century. Hallucinogenic mushrooms, particularly *Psilocybe* mushrooms, were also used in the religious life of Native Americans. These were called "teonanacatl," which means "God's sacred mushrooms" or "God's flesh."[128] Interest in the recreational use of cannabis also accelerated during the 19th century after Napoleon's troops brought the drug back from Egypt, where its use among the lower classes was widespread. In 1843, several French Romantics, including Balzac, Baudelaire, Gautier, and Hugo, formed a hashish club called "Le Club des Hachichins" in the Parisian apartment of a young French painter. Fitz Hugh Ludlow's *The Hasheesh Eater*, published in 1857, was an early American text espousing the virtues of marijuana.[97]

A more recent event that had significant impact on modern-day hallucinogen use was the synthesis of lysergic acid diethylamide (LSD) by Albert Hofmann in 1938.[67] Working for Sandoz Pharmaceutical Company, Hofmann synthesized LSD while investigating the pharmacologic properties of ergot alkaloids. Subsequent self-experimentation by Hofmann led to the first description of its hallucinogenic effects and stimulated research into the therapeutic use of LSD. Hofmann is also credited with isolating psilocybin as the active ingredient in *Psilocybe mexicana* mushrooms in 1958.[112]

TWENTIETH- AND TWENTY-FIRST-CENTURY EVENTS

Early Regulatory Initiatives

The development of medical toxicology as a medical subspecialty and the important role of poison control centers began shortly after World War II. Before then, serious attention to the problem of household poisonings in the United States was limited to a few federal legislative antipoisoning initiatives (Table 1–4). The 1906 Pure Food and Drug Act was the first federal legislation that sought to protect the public from problematic and potentially unsafe drugs and food. The driving force behind this reform was Harvey Wiley, the chief chemist at the Department of Agriculture. Beginning in the 1880s, Wiley investigated the problems of contaminated food. In 1902, he organized the "poison squad," which consisted of a group of volunteers who did self-experiments with food preservatives.[4] Revelations from the "poison squad," as well as the publication of Upton Sinclair's muckraking novel *The Jungle*[146] in 1906, exposed unhygienic practices of the meatpacking industry and led to growing support for legislative intervention. Samuel Hopkins Adams' reports about the patent medicine industry revealed that some drug manufacturers added opioids to soothing syrups for infants and led to the call for reform.[135] Although the 1906 regulations were mostly concerned with protecting the public from adulterated food, regulations protecting against misbranded patent medications were also included.

The Federal Caustic Poison Act of 1927 was the first federal legislation to specifically address household poisoning. As early as 1859, bottles clearly demarcated "poison" were manufactured in response to a rash of unfortunate dispensing errors that occurred when oxalic acid was unintentionally substituted for a similarly appearing Epsom salts solution.[28] Before 1927, however, "poison" warning labels were not required on chemical containers, regardless of toxicity or availability. The 1927 Caustic Act was spearheaded by the efforts of Chevalier Jackson, an otolaryngologist, who showed that unintentional exposures to household caustics were an increasingly frequent cause of severe oropharyngeal and GI burns. Under this statute, for the first time, alkali- and acid-containing products had to clearly display a "poison" warning label.[78,154]

The most pivotal regulatory initiative in the United States before World War II—and perhaps the most significant American toxicologic regulation of the 20th century—was the Federal Food, Drug, and Cosmetic Act of 1938. Although the Food and Drug Administration (FDA) had been established in 1930 and legislation to strengthen the 1906 Pure Food and Drug Act was considered by Congress in 1933, the proposed revisions still had not been passed by 1938. Then the elixir of sulfanilamide tragedy in 1938 (Chap. 2) claimed the lives of 105 people who had ingested a prescribed liquid preparation of the antibiotic sulfanilamide inappropriately dissolved in diethylene glycol. This event finally provided the catalyst for legislative intervention.[109,161] Before the elixir disaster, proposed legislation called only for the banning of false and misleading drug labeling and for the outlawing of dangerous drugs without mandatory drug safety testing. After the tragedy, the proposal was strengthened to require assessment of drug safety before marketing, and the legislation was ultimately passed.

The Development of Poison Control Centers

World War II led to the rapid proliferation of new xenobiotics in the marketplace and in the household.[39] At the same time, suicide was recognized as a leading cause of death from these xenobiotics.[9] Both of these factors led the medical community to develop a response to the serious problems of unintentional and intentional poisonings. In Europe during the late 1940s, special toxicology wards were organized in Copenhagen and Budapest,[59] and a poison information service was begun in the Netherlands (Table 1–5).[158] A 1952 American Academy of Pediatrics study revealed that more than 50% of childhood "accidents" in the United States were the result of unintentional poisonings.[61] This study led Edward Press to open the first US poison control center in Chicago in 1953.[129] Press believed that it was extremely difficult for individual physicians to keep abreast of product information, toxicity, and treatment for the rapidly increasing number of potentially poisonous household products. His initial center was organized as a cooperative effort among the departments of pediatrics at several Chicago medical schools, with the goal of collecting and disseminating product information to inquiring physicians, mainly pediatricians.[132]

By 1957, 17 poison control centers were operating in the United States.[39] With the Chicago center serving as a model, these early centers responded to physician callers by providing ingredient and toxicity information about drug and household products and making treatment recommendations. Records were kept of the calls, and preventive strategies were introduced into the community. As more poison control centers opened, a second important function, providing information to calls from the general public, became increasingly common. The physician pioneers in poison prevention and poison treatment were predominantly pediatricians who focused on unintentional childhood ingestions.[137]

During these early years in the development of poison control centers, each center had to collect its own product information, which was a laborious and often redundant task.[38] In an effort to coordinate its operations and to avoid unnecessary duplication, Surgeon General James Goddard responded to the recommendation of the American Public Health Service and established the National Clearinghouse for Poison Control Centers in 1957.[106] This organization, placed under the Bureau of Product Safety of the Food and Drug Administration, disseminated 5-inch by 8-inch index cards containing poison information to each center to help standardize poison control center information resources. The Clearinghouse also collected and tabulated poison data from each of the centers.

Between 1953 and 1972, a rapid, uncoordinated proliferation of poison control centers occurred in the United States.[103] In 1962, there were 462 poison control centers. By 1970, this number had risen to 590,[95] and by 1978, there were 661 poison control centers in the United States, including 100 centers

TABLE 1–4 Protecting Our Health: Important US Regulatory Initiatives Pertaining to Xenobiotics

Date	*Federal Legislation*	*Intent*
1906	Pure Food and Drug Act	Early regulatory initiative; prohibits interstate commerce of misbranded and adulterated foods and drugs.
1914	Harrison Narcotics Act	First federal law to criminalize the nonmedical use of drugs. Taxed and regulated distribution and sale of narcotics (opium, opium derivatives, and cocaine).
1927	Federal Caustic Poison Act	Mandated labeling of concentrated caustics.
1930	Food and Drug Administration (FDA)	Established successor to the Bureau of Chemistry; promulgation of food and drug regulations.
1937	Marijuana Tax Act	Applied controls to marijuana similar to those applied to narcotics.
1938	Federal Food, Drug, and Cosmetic Act	Required toxicity testing of pharmaceuticals before marketing.
1948	Federal Insecticide, Fungicide, and Rodenticide Act	Provided federal control for pesticide sale, distribution, and use.
1951	Durham-Humphrey Amendment	Restricted many therapeutic drugs to sale by prescription only.
1960	Federal Hazardous Substances Labeling Act	Mandated prominent labeling warnings on hazardous household chemical products.
1962	Kefauver-Harris Drug Amendments	Required drug manufacturers to demonstrate efficacy before marketing.
1963	Clean Air Act	Regulated air emissions by setting maximum pollutant standards.
1966	Child Protection Act	Banned hazardous toys when adequate label warnings could not be written.
1970	Comprehensive Drug Abuse and Control Act	Replaced and updated all previous laws concerning narcotics and other dangerous drugs.
1970	Environmental Protection Agency (EPA)	Established and enforced environmental protection standards.
1970	Occupational Safety and Health Act (OSHA)	Enacted to improve worker and workplace safety. Created National Institute for Occupational Safety and Health (NIOSH) as research institution for OSHA.
1970	Poison Prevention Packaging Act	Mandated child-resistant safety caps on certain pharmaceutical preparations to decrease unintentional childhood poisoning.
1972	Clean Water Act	Regulated discharge of pollutants into US waters.
1972	Consumer Product Safety Act	Established Consumer Product Safety Commission (CPSC) to reduce injuries and deaths from consumer products.
1972	Hazardous Material Transportation Act	Authorized the Department of Transportation to develop, promulgate, and enforce regulations for the safe transportation of hazardous materials.
1973	Drug Enforcement Administration (DEA)	Successor to the Bureau of Narcotics and Dangerous Drugs; charged with enforcing federal drug laws.
1973	Lead-based Paint Poison Prevention Act	Regulated the use of lead in residential paint. Lead in some paints was banned by Congress in 1978.
1974	Safe Drinking Water Act	Set safe standards for water purity.
1976	Resource Conservation and Recovery Act (RCRA)	Authorized EPA to control hazardous waste from the "cradle to grave," including the generation, transportation, treatment, storage, and disposal of hazardous waste.
1976	Toxic Substances Control Act	Emphasis on law enforcement. Authorized EPA to track 75,000 industrial chemicals produced or imported into the United States. Required testing of chemicals that pose environmental or human health risk.
1980	Comprehensive Environmental Response Compensation and Liability act (CERCLA)	Set controls for hazardous waste sites. Established trust fund (Superfund) to provide cleanup for these sites. Agency for Toxic Substances and Disease Registry (ATSDR) created.
1983	Federal Anti-Tampering Act	Response to cyanide laced Tylenol deaths. Outlawed tampering with packaged consumer products.
1986	Controlled Substance Analogue Enforcement Act	Instituted legal controls on analog (designer) drugs with chemical structures similar to controlled substances.
1986	Drug-Free Federal Workplace Program	Executive order mandating drug testing of federal employees in sensitive positions.
1986	Superfund Amendments and Reauthorization Act (SARA)	Amendment to CERCLA. Increased funding for the research and cleanup of hazardous waste (SARA) sites.
1988	Labeling of Hazardous Art Materials Act	Required review of all art materials to determine hazard potential and mandated warning labels for hazardous materials.
1994	Dietary Supplement Health and Education Act	Permitted dietary supplements including many herbal preparations to bypass FDA scrutiny.
1997	FDA Modernization Act	Accelerated FDA reviews, regulated advertising of unapproved uses of approved drugs.
2002	The Public Health Security and Bioterrorism Preparedness and Response Act	Tightened control on biologic agents and toxins; increased safety of the US food and drug supply and drinking water; and strengthened the Strategic National Stockpile.
2005	Combat Methamphetamine Epidemic Act	Part of the Patriot Act, this legislation restricted nonprescription sale of the methamphetamine precursor drugs ephedrine and pseudoephedrine used in the home production of methamphetamine.
2009	Family Smoking Prevention and Tobacco Control Act	Empowered FDA to set standards for tobacco products.
2016	Comprehensive Addiction and Recovery Act (CARA)	Federal response to prescription opioid and heroin epidemic providing for expansion of medication-assisted treatment with buprenorphine and methadone and expanded use of naloxone by first responders and community members.

TABLE 1–5 Milestones in the Development of Medical Toxicology in the United States

Year	*Milestone*
1952	American Academy of Pediatrics study shows that 51% of children's "accidents" are the result of the ingestion of potential poisons
1953	First US poison control center opens in Chicago
1957	National Clearinghouse for Poison Control Centers established
1958	American Association of Poison Control Centers (AAPCC) founded
1961	First Poison Prevention Week
1963	Initial call for development of regional Poison Control Centers (PCCs)
1964	Creation of European Association for PCCs
1968	American Academy of Clinical Toxicology (AACT) established
1972	Introduction of microfiche technology to poison information
1974	American Board of Medical Toxicology (ABMT) established
1978	AAPCC introduces standards of regional designation
1983	First examination given for Specialist in Poison Information (SPI)
1985	American Board of Applied Toxicology (ABAT) established
1992	Medical Toxicology recognized by American Board of Medical Specialties (ABMS)
1993	American College of Medical Toxicology established
1994	First ABMS examination in Medical Toxicology
2000	Accreditation Council for Graduate Medical Education (ACGME) approval of residency training programs in Medical Toxicology
2000	Poison Control Center Enhancement and Awareness Act
2004	Institute of Medicine (IOM) report on the future of poison control centers is released, calling for a greater integration between public health sector and poison control services

in the state of Illinois alone.[143] The nature of calls to centers changed as lay public–generated calls began to outnumber physician-generated calls. Recognizing the public relations value and strong popular support associated with poison control centers, some hospitals started poison control centers without adequately recognizing or providing for the associated responsibilities. Unfortunately, many of these centers offered no more than a part-time telephone service located in the back of the emergency department or pharmacy, staffed by poorly trained personnel.[143]

Despite the "growing pains" of these poison services during this period, many significant achievements were made. A dedicated group of physicians and other health care professionals began devoting an increasing proportion of their time to poison related matters. In 1958, the American Association of Poison Control Centers (AAPCC) was founded to promote closer cooperation between poison control centers, to establish uniform standards, and to develop educational programs for the general public and health care professionals.[61] Annual research meetings were held, and important legislative initiatives were stimulated by the organization.[106] Examples of such legislation include the Federal Hazardous Substances Labeling Act of 1960, which improved product labeling; the Child Protection Act of 1966, which extended labeling statutes to pesticides and other hazardous xenobiotics; and the Poison Prevention Packaging Act of 1970, which mandated safety packaging. In 1961, in an attempt to heighten public awareness of the dangers of unintentional poisoning, the third week of March was designated as the Annual National Poison Prevention Week.

Another organization that would become important, the American Academy of Clinical Toxicology (AACT), was founded in 1968 by a diverse group of toxicologists.[34] This group was "interested in applying principles of rational toxicology to patient treatment" and in improving the standards of care on a national basis.[140] The first modern textbooks of clinical toxicology began to appear in the mid-1950s with the publication of Dreisbach's *Handbook of Poisoning* (1955);[45] Gleason, Gosselin, and Hodge's *Clinical Toxicology of Commercial Products* (1957);[57] and Arena's *Poisoning* (1963).[10] Major advancements in the storage and retrieval of poison information were also instituted during these years. Information as noted earlier on consumer products initially appeared on index cards distributed regularly to poison control centers by the National Clearinghouse, and by 1978, more than 16,000 individual product cards had been issued.[143] The introduction of microfiche technology in 1972 enabled the storage of much larger amounts of data in much smaller spaces at the individual poison control centers. Toxifile and POISINDEX, two large drug and poison databases using microfiche technology, were introduced and gradually replaced the much more limited index card system.[143] During the 1980s, POISINDEX, which had become the standard database, was made more accessible by using CD-ROM technology. Sophisticated information about the most obscure xenobiotics was now instantaneously available by computer at every poison control center.

In 1978, the poison control center movement entered an important new stage in its development when the AAPCC introduced standards for regional poison control center designation.[103] By defining strict criteria, the AAPCC sought to improve poison control center operations significantly and to offer a national standard of service. These criteria included using poison specialists dedicated exclusively to operating the poison control center 24 hours per day and serving a catchment area of between 1 and 10 million people. Not surprisingly, this professionalization of the poison control center movement led to a rapid consolidation of services. An AAPCC credentialing examination for poison information specialists was inaugurated in 1983 to help ensure the quality and standards of poison control center staff.[7]

In 2000, the Poison Control Center Enhancement and Awareness Act was passed by Congress and signed into law by President Clinton. For the first time, federal funding became available to provide assistance for poison prevention and to stabilize the funding of regional poison control centers. This federal assistance permitted the establishment of a single nationwide toll-free phone number (800-222-1222) to access poison control centers. At present, 55 centers contribute data to a National Poison Database System (NPDS), which from 1983 to 2006 was known as Toxic Exposure Surveillance System (TESS). The Centers for Disease Control and Prevention (CDC) collaborates with the AAPCC to conduct real-time surveillance of these data to help facilitate the early detection of chemical exposures of public health importance.[165]

A poison control center movement has also grown and evolved in Europe over the past 35 years, but unlike the movement in the United States, it focused from the beginning on establishing strong centralized toxicology treatment centers.[131] In the late 1950s, Gaultier in Paris developed an inpatient unit dedicated to the care of poisoned patients.[59] In the United Kingdom, the National Poison Information Service developed at Guys Hospital in 1963 under Roy Goulding. Henry Matthew initiated a regional poisoning treatment center in Edinburgh about the same time.[131] In 1964, the European Association for Poison Control Centers was formed at Tours, France.[59]

The Rise of Environmental Toxicology and Further Regulatory Protection from Toxic Substances

The rise of the environmental movement during the 1960s can be traced, in part, to the publication of Rachel Carson's *Silent Spring* in 1962, which revealed the perils of an increasingly toxic environment.[29] The movement also benefited from the new awareness by those involved with the poison movement of the growing menace of xenobiotics in the home environment.[26] Battery casing fume poisoning, resulting from the burning of discarded lead battery cases, and acrodynia, resulting from exposure to a variety of mercury-containing products,[41] both demonstrated that young children are

particularly vulnerable to low-dose exposures from certain xenobiotics. Worries about the persistence of pesticides in the ecosystem and the increasing number of chemicals introduced into the environment added to concerns of the environment as a potential source of illness, heralding a drive for additional regulatory protection.

Starting with the Clean Air Act in 1963, laws were passed to help reduce the toxic burden on our environment (Table 1–4). The establishment of the Environmental Protection Agency (EPA) in 1970 spearheaded this attempt at protecting our environment, and during the next 10 years, numerous protective regulations were introduced. Among the most important initiatives was the Occupational Safety and Health Act of 1970, which established the Occupational Safety and Health Administration (OSHA). This act mandates that employers provide safe work conditions for their employees. Specific exposure limits to toxic chemicals in the workplace were promulgated. The Consumer Product Safety Commission was created in 1972 to protect the public from consumer products that posed an unreasonable risk of illness or injury. Cancer-producing xenobiotics, such as asbestos, benzene, and vinyl chloride, were banned from consumer products as a result of these new regulations. Toxic waste disasters such as those at Love Canal, New York, and Times Beach, Missouri, led to the passing of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA, also known as the Superfund) in 1980. This fund is designed to help pay for cleanup of hazardous substance releases posing a potential threat to public health. The Superfund legislation also led to the creation of the Agency for Toxic Substances and Disease Registry (ATSDR), a federal public health agency charged with determining the nature and extent of health problems at Superfund sites and advising the US EPA and state health and environmental agencies on the need for cleanup and other actions to protect the public's health. In 2003, the ATSDR became part of the National Center for Environmental Health of the CDC.

Medical Toxicology Comes of Age

Over the past 50 years, the primary specialties of medical toxicologists have changed. The development of emergency medicine and preventive medicine as medical specialties led to the training of more physicians with a dedicated interest in toxicology. By the early 1990s, emergency physicians accounted for more than half the number of practicing medical toxicologists. The increased diversity of medical toxicologists with primary training in emergency medicine, pediatrics, preventive medicine, or internal medicine has helped broaden the goals of poison control centers and medical toxicologists beyond the treatment of acute unintentional childhood ingestions. The scope of medical toxicology now includes a much wider array of toxic exposures, including acute and chronic, adult and pediatric, unintentional and intentional, and occupational and environmental exposures.

The development of medical toxicology as a medical subspecialty began in 1974, when the AACT created the American Board of Medical Toxicology (ABMT) to recognize physician practitioners of medical toxicology.[5] From 1974 to 1992, 209 physicians obtained board certification, and formal subspecialty recognition of medical toxicology by the American Board of Medical Specialties (ABMS) was granted in 1992. In that year, a conjoint subboard with representatives from the American Board of Emergency Medicine, American Board of Pediatrics, and American Board of Preventive Medicine was established, and the first ABMS-sanctioned examination in medical toxicology was offered in 1994. By 2016, a total of more than 600 physicians were board certified in medical toxicology. The American College of Medical Toxicology (ACMT) was founded in 1994 as a physician-based organization designed to advance clinical, educational, and research goals in medical toxicology. In 1999, the Accreditation Council of Graduate Medical Education (ACGME) in the United States formally recognized postgraduate education in medical toxicology, and by 2018, 27 fellowship training programs were approved. During the 1990s in the United States, some medical toxicologists began to work on establishing regional toxicology treatment centers. Adapting the European model, such toxicology treatment centers could serve as referral centers for patients requiring advanced toxicologic evaluation and treatment. Goals of such inpatient regional centers included enhancing care of poisoned patients, strengthening toxicology training, and facilitating research. The evaluation of the clinical efficacy and fiscal viability of such programs is ongoing. More recently, an increasing number of medical toxicologists have expanded their practice into addiction medicine responding to the prescription opioid crisis.[88]

The professional maturation of advanced practice pharmacists and nurses with primary interests in clinical toxicology occurred over the past two decades. In 1985, the AACT established the American Board of Applied Toxicology (ABAT) to administer certifying examinations for nonphysician practitioners of medical toxicology who meet their rigorous standards.[4] By 2017, more than 115 toxicologists, who mostly held either a PharmD or a PhD in pharmacology or toxicology, were certified by this board.

Recent Poisonings and Poisoners

Although accounting for just a tiny fraction of all homicidal deaths (0.16% in the United States), notorious lethal poisonings continued throughout the 20th and 21st centuries (Table 1–3).[1]

In England, Graham Frederick Young developed a macabre fascination with poisons.[30] In 1971, at age 14 years, he killed his stepmother and other family members with arsenic and antimony. Sent away to a psychiatric hospital, he was released at age 24 years, when he was no longer considered to be a threat to society. Within months of his release, he again engaged in lethal poisonings, killing several of his coworkers with thallium. Ultimately, he died in prison in 1990.

In 1978, Georgi Markov, a Bulgarian defector living in London, developed multisystem failure and died 4 days after having been stabbed by an umbrella carried by an unknown assailant. The postmortem examination revealed a pinhead-sized metal sphere embedded in his thigh where he had been stabbed. Investigators hypothesized that this sphere had most likely carried a lethal dose of ricin into the victim.[37] This theory was greatly supported when ricin was isolated from the pellet of a second victim who was stabbed under similar circumstances.

In 1982, deliberate tampering with nonprescription Tylenol preparations with potassium cyanide caused seven deaths in Chicago.[46] Because of this tragedy, packaging of nonprescription medications was changed to decrease the possibility of future product tampering.[113] The perpetrator(s) were never apprehended, and other deaths from nonprescription product tampering were reported in 1991.[31]

In 1998, Judias Buenoano, known as the "black widow," was executed for murdering her husband with arsenic in 1971 to collect insurance money. She was the first woman executed in Florida in 150 years. The fatal poisoning had remained undetected until 1983, when Buenoano was accused of trying to murder her fiancé with arsenic and by car bombing. Exhumation of the husband's body, 12 years after he died, revealed substantial amounts of arsenic in the remains.[2]

Health care providers continue to be implicated in several poisoning homicides as well. An epidemic of mysterious cardiopulmonary arrests at the Ann Arbor Veterans Administration Hospital in Michigan in July and August 1975 was attributed to the homicidal use of pancuronium by two nurses.[153] Intentional digoxin poisoning by hospital personnel may have explained some of the increased number of deaths on a cardiology ward of a Toronto pediatric hospital in 1981, but the cause of the high mortality rate remained unclear.[23] In 2000, an English general practitioner Harold Shipman was convicted of murdering 15 female patients with heroin and may have murdered as many as 297 patients during his 24 year career. These recent revelations prompted calls for strengthening the death certification process, improving preservation of case records, and developing better procedures to monitor controlled drugs.[70]

Also in 2000, Michael Swango, an American physician, pleaded guilty to the charge of poisoning a number of patients under his care during his residency training. Succinylcholine, potassium chloride, and arsenic were used to kill his patients.[151] Attention to more careful physician credentialing and to maintenance of a national physician database arose from this case because the poisonings occurred at multiple hospitals across the country. Continuing concerns about health care providers acting as serial killers is

highlighted by a recent case in New Jersey in which a nurse, Charles Cullen, was found responsible for killing patients with digoxin.[17]

By the end of the 20th century, 24 centuries after Socrates was executed by poison hemlock, the means of implementing capital punishment had come full circle. Government-sanctioned execution in the United States again favored the use of a "state" poison—this time, employing single drug and multiple drug protocols using sodium thiopental, pentobarbital, midazolam, hydromorphone, pancuronium, and potassium chloride.[81]

The use of a poison to achieve political ends has again resurfaced in several incidents from the former Soviet Union and its allies. In December 2004, it was announced that the Ukrainian presidential candidate Viktor Yushchenko was poisoned with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a potent dioxin.[149] The dramatic development of chloracne over the face of this public person during the previous several months suggested dioxin as a possibly culprit. Given the paucity of reports of acute dioxin poisoning, however, it was not until laboratory tests confirmed that Yushchenko's dioxin concentrations were more than 6,000 times normal that this diagnosis was confirmed. In another case, a former KGB agent and Russian dissident Alexander Litvinenko was murdered with polonium-210. Initially thought to be a possible case of heavy metal poisoning, Litvinenko developed acute radiation syndrome manifested by GI symptoms followed by alopecia and pancytopenia before he died.[108] In February 2017, the nerve agent VX was believed responsible for the death of the North Korean leader's elder brother Kim Jong-nam.[124]

Other Developments

Medical Errors

Beginning in the 1980s, several highly publicized medication errors received considerable public attention and provided a stimulus for the initiation of change in policies and systems. Ironically, all of the cases occurred at nationally preeminent university teaching hospitals. In 1984, 18-year-old Libby Zion died from severe hyperthermia soon after hospital admission. Although the cause of her death was likely multifactorial, drug–drug interactions and the failure to recognize and appropriately treat her agitated delirium also contributed to her death.[13] State and national guidelines for closer house staff supervision, improved working conditions, and a heightened awareness of consequential drug–drug interactions resulted from the medical, legislative, and legal issues of this case. In 1994, a prominent health journalist for the *Boston Globe*, Betsy Lehman, was the unfortunate victim of another preventable dosing error when she inadvertently received four times the dose of the chemotherapeutic cyclophosphamide as part of an experimental protocol.[83] Despite treatment at a world-renowned cancer center, multiple physicians, nurses, and pharmacists failed to notice this erroneous medication order. An overhaul of the medication-ordering system was implemented at that institution after this tragic event.

Another highly publicized death occurred in 1999, when 18-year-old Jesse Gelsinger died after enrolling in an experimental gene-therapy study. Gelsinger, who had ornithine transcarbamylase deficiency, died from multiorgan failure 4 days after receiving, by hepatic infusion, the first dose of an engineered adenovirus containing the normal gene. Although this unexpected death was not the direct result of a dosing or drug–drug interaction error, the FDA review concluded that major research violations had occurred, including failure to report adverse effects with this therapy in animals and earlier clinical trials and to properly obtain informed consent.[145] In 2001, Ellen Roche, a 24-year-old healthy volunteer in an asthma study at John Hopkins University, developed a progressive pulmonary illness and died 1 month after receiving 1 g of hexamethonium by inhalation as part of the study protocol.[150] Hexamethonium, a ganglionic blocker, was once used to treat hypertension but was removed from the market in 1972. The investigators were cited for failing to indicate on the consent form that hexamethonium was experimental and not FDA approved. Calls for additional safeguards to protect patients in research studies resulted from these cases.

In late 1999, the problems of medical errors finally received the high visibility and deserved attention in the United States with the publication and subsequent reaction to an Institute of Medicine (IOM) report suggesting that 44,000 to 98,000 fatalities each year were the result of medical errors.[84] Many of these errors were attributed to preventable medication errors. The IOM report focused on its findings that errors usually resulted from system faults and not solely from the carelessness of individuals.

Toxicology in the Twenty-First Century

As new challenges and opportunities arise in the 21st century, new toxicologic disciplines have emerged such as toxicogenomics, precision medicine, and nanotoxicology.[40,92,119] These nascent fields constitute the toxicologic responses to rapid advances in genetics and material sciences. Toxicogenomics combines toxicology with genomics dealing with how genes and proteins respond to toxic substances. The study of toxicogenomics attempts to better decipher the molecular events underlying toxicologic mechanisms, develop predictors of toxicity through the establishment of better molecular biomarkers, and better understand genetic susceptibilities that pertain to toxic substances such as unanticipated idiosyncratic drug reactions. Applying the principles of toxicogenomics has given birth to the field of precision medicine, also known as personalized medicine. Using such an approach drug therapy may be able to be individually tailored improving the prediction of drug efficacy and safety by accounting for genomic and metabolomics factors.[110]

Nanotoxicology refers to the toxicology of engineered tiny particles, usually smaller than 100 nm. Given the extremely small size of nanoparticles, typical barriers at portals of entry may not prevent absorption or may themselves be adversely affected by the nanoparticles. Ongoing studies focus on the translocation of these particles to sensitive target sites such as the central nervous system or bone marrow (Chap. 125).[119,168]

SUMMARY

- Since the dawn of recorded history, toxicology has impacted greatly on human events and our ecosystem.
- Over the millennia, although the important poisons of the day have changed to some degree, toxic xenobiotics continue to challenge our safety.
- The era of poisoners for hire may have long ago reached its pinnacle, but problems with drug abuse, intentional self-poisoning, and exposure to environmental chemicals continue to challenge us.
- Knowledge acquired by one generation is often forgotten or discarded inappropriately by the next generation, leading to a cyclical historic course.

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2 TOXICOLOGIC MISFORTUNES AND CATASTROPHES IN HISTORY

Paul M. Wax

Throughout history, mass poisonings have caused suffering and misfortune. From the ergot epidemics of the Middle Ages to contemporary industrial disasters, these mass events have had great political, economic, social, and environmental ramifications. Particularly within the past 100 years, as the number of toxins and potential toxins has risen dramatically, toxic disasters have become increasingly common events. The sites of some of these events—Bhopal (India), Chernobyl (Ukraine), Jonestown (Guyana), Love Canal (New York), Minamata Bay (Japan), Seveso (Italy), West Bengal (India)—have come to symbolize our increasing potential for environmental toxicity. Globalization has led to the proliferation and rapid distribution of toxic chemicals throughout the world. Many factories that store large amounts of potentially lethal chemicals are not secure. Given the increasing attention to terrorism preparedness, an appreciation of chemicals as agents of opportunity for terrorists has suddenly assumed great importance. This chapter provides an overview of some of the most consequential and historically important toxin-associated mass poisonings that represent human and environmental disasters.

GAS DISASTERS

Inhalation of toxic gases and oral ingestions resulting in food poisoning tend to subject the greatest number of people to adverse consequences of a toxic exposure. Toxic gas exposures may be the result of a natural disaster (volcanic eruption), industrial mishap (fire, chemical release), chemical warfare, or an intentional homicidal or genocidal endeavor (concentration camp gas chamber). Depending on the toxin, the clinical presentation may be acute, with a rapid onset of toxicity (cyanide), or subacute or chronic, with a gradual onset of toxicity (air pollution).

One of the earliest recorded toxic gas disasters resulted from the eruption of Mount Vesuvius near Pompeii, Italy, in 79 A.D. (Table 2–1). Poisonous gases generated from the volcanic activity reportedly killed thousands of people.[35] A more recent natural disaster occurred in 1986 in Cameroon, when excessive amounts of carbon dioxide spontaneously erupted from Lake Nyos, a volcanic crater lake.[19] Approximately 1,700 human and countless animal fatalities resulted from exposure to this asphyxiant.

A toxic gas leak at the Union Carbide pesticide plant in Bhopal, India, in 1984 resulted in one of the greatest civilian toxic disasters in modern history.[144] An unintended exothermic reaction at this carbaryl-producing plant caused the release of more than 24,000 kg of methyl isocyanate. This gas was quickly dispersed through the air over the densely populated area surrounding the factory where many of the workers lived, resulting in at least 2,500 deaths and 200,000 injuries.[88] The initial response to this disaster was greatly limited by a lack of pertinent information about the toxicity of this chemical as well as the poverty of the residents. A follow-up study 10 years later showed persistence of small-airway obstructive disease among survivors as well as chronic ophthalmic problems.[31] Calls for improvement in disaster preparedness and strengthened "right-to-know" laws regarding potential toxic exposures resulted from this tragedy.[50,144]

The release into the atmosphere of 26 tons of hydrofluoric acid at a petrochemical plant in Texas in October 1987 resulted in 939 people seeking medical attention at nearby hospitals. Ninety-four people were hospitalized, but there were no deaths.[154]

More than any other single toxin, carbon monoxide is involved in the largest number of toxic disasters. Catastrophic fires, such as the Cocoanut Grove Nightclub fire in 1943, have caused hundreds of deaths at a time, many of them from carbon monoxide poisoning.[37] A 1990 fire deliberately started at the Happy Land Social Club in the Bronx, New York, claimed 87 victims, including a large number of nonburn deaths,[78] and the 2003 fire at the Station nightclub in West Warwick, Rhode Island, killed 98 people.[128] Carbon monoxide poisoning was a major determinant in many of these deaths, although hydrogen cyanide gas and simple asphyxiation may have also contributed to the overall mortality.

Another notable toxic gas disaster involving a fire occurred at the Cleveland Clinic in Cleveland, Ohio, in 1929, where a fire in the radiology department resulted in 125 deaths.[34] The burning of nitrocellulose radiographs produced nitrogen dioxide, cyanide, and carbon monoxide gases held responsible for many of the fatalities. In 2003, at least 243 people died and 10,000 became ill after a drilling well exploded in Xiaoyang, China, releasing hydrogen sulfide and natural gas into the air.[159] A toxic gas cloud covered 25 square kilometers. Ninety percent of the villagers who lived in the village adjoining the gas well died.

The release of a dioxin-containing chemical cloud into the atmosphere from an explosion at a hexachlorophene production factory in Seveso, Italy

TABLE 2–1 Gas Disasters

Xenobiotic	*Location*	*Date*	*Significance*
Poisonous volcanic gases	Pompeii, Italy	79 A.D.	>2,000 deaths from eruption of Mt. Vesuvius
Smog (SO_2)	London, England	1873	268 deaths from bronchitis
NO_2, CO, CN	Cleveland Clinic, Cleveland, OH	1929	Fire in radiology department; 125 deaths
Smog (SO_2)	Meuse Valley, Belgium	1930	64 deaths
CO, CN	Cocoanut Grove Lounge, Boston, Mass	1942	498 deaths from fire
CO	Salerno, Italy	1944	>500 deaths on a train stalled in a tunnel
Smog (SO_2)	Donora, PA	1948	20 deaths; thousands ill
Smog (SO_2)	London, England	1952	4,000 deaths attributed to the fog and smog
Dioxin	Seveso, Italy	1976	Unintentional industrial release of dioxin into environment; chloracne
Methyl isocyanate	Bhopal, India	1984	>2,500 deaths; 200,000 injuries
Carbon dioxide	Cameroon, Africa	1986	>1,700 deaths from release of gas from Lake Nyos
Hydrofluoric acid	Texas City, TX	1987	Atmospheric release; 94 hospitalized
CO, CN	Happy Land Social Club, Bronx, NY	1990	87 deaths in fire from toxic smoke
Hydrogen sulfide	Xiaoyang, China	2003	243 deaths and 10,000 became ill from gas poisoning after a gas well exploded
CO, CN	West Warwick, RI	2003	98 deaths in fire

in 1976, resulted in one of the most serious exposures to dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin {TCDD}).[49] The lethality of this xenobiotic in animals has caused considerable concern for acute and latent injury from human exposure. Although chloracne was the only significant clinical finding related to the dioxin exposure at 5-year follow-up[9] more recent data after 30 years suggest a positive correlation between TCDD serum concentration and cancer incidence.[147]

Air pollution is another source of toxic gases that causes significant disease and death. Complaints about smoky air date back to at least 1272, when King Edward I banned the burning of mineral coal.[142] By the 19th century, the era of rapid industrialization in England, winter "fogs" became increasingly problematic. An 1873 London fog was responsible for 268 deaths from bronchitis. Excessive smog (a portmanteau of smoke and fog) in the Meuse Valley of Belgium in 1930 and in Donora, Pennsylvania, in 1948, was also blamed for excess morbidity and mortality. In 1952, another dense sulfur dioxide–laden smog in London was responsible for 4,000 deaths.[74] Both the initiation of long-overdue air pollution reform in England and the passing of the 1956 Clean Air Act by Parliament resulted from this latter "fog."

WARFARE AND TERRORISM

Exposure to xenobiotics with the deliberate intent to inflict harm claimed an extraordinary number of victims during the 20th century (Table 2–2). During World War I, chlorine, phosgene, and the liquid vesicant mustard were used as battlefield weapons, with mustard causing approximately 80% of the chemical casualties.[130] Reportedly, 100,000 deaths and 1.2 million casualties were attributable to these chemical attacks.[37] The toxic exposures resulted in severe airway irritation, acute respiratory distress syndrome, hemorrhagic pneumonitis, skin blistering, and ophthalmic damage. Mustard was used again in the 1980s during the war between Iran and Iraq.

The Nazis used poisonous gases during World War II to commit genocide. Initially, the Nazis used carbon monoxide to kill. To expedite the killing process, Nazi scientists developed Zyklon-B gas (hydrogen cyanide gas). As many as 10,000 people per day were killed by the rapidly acting cyanide, and millions of deaths were attributable to the use of these gases.

Agent Orange was widely used as a defoliant during the Vietnam War. This herbicide consisted of a mixture of 2,4,5-trichlorophenoxy-acetic acid (2,4,5-T) and 2,4-dichlorophenoxyacetic acid (2,4-D), as well as small amounts of a contaminant, TCDD. Over the years, a large number of adverse health effects have been attributed to Agent Orange exposure. Although a 2002 Institute of Medicine study concluded that among Vietnam veterans, there was sufficient evidence to demonstrate an association between this herbicide exposure and chronic lymphocytic leukemia, soft tissue sarcomas, non-Hodgkin lymphomas, Hodgkin disease, and chloracne,[55] a 2015 critical review concluded that causation has yet to be established.[123]

Mass exposure to the very potent organic phosphorus compound sarin occurred in March 1995, when terrorists released this chemical weapon in three separate Tokyo subway lines.[104] Eleven people were killed, and 5,510 people sought emergency medical evaluation at more than 200 hospitals and clinics in the area.[131] This calamity introduced the spectra of terrorism to the modern emergency medical services system, resulting in a greater emphasis on hospital preparedness, including planning for the psychological consequences of such events. Sarin exposure also resulted in several deaths and hundreds of casualties in Matsumoto, Japan, in June 1994.[93,101] During the Syrian Civil War, sarin and chlorine were used on multiple occasions.[75]

After the terrorist attacks on New York City in September 11, 2001, that resulted in the collapse of World Trade Center, persistent cough and increased bronchial responsiveness were noted among 8% of New York City Fire Department workers who were exposed to large amounts of dust and other particulates during the clean-up.[110,111] This condition, known as World Trade Center cough syndrome, is characterized by upper airway (chronic rhinosinusitis) and lower airway findings (bronchitis, asthma, or both) as well as, at times, gastroesophageal reflux dysfunction. The risk of development of hyperreactivity and reactive airways dysfunction was clearly associated with the intensity of exposure.[16] A World Trade Center health registry was established to investigate and care for those exposed workers who may be at increased risk for development of cancer and other chronic diseases.[72,98] Registry data suggest that some workers appear to be at an increased risk for development of sarcoidosis[58] and persistent lower respiratory tract symptoms.[57]

The Russian military used a mysterious "gas" to incapacitate Chechen rebels at a Moscow theatre in 2002, resulting in the deaths of more than 120 hostages. One report suggested that the gas contained a mixture of the highly potent aerosolized fentanyl derivatives carfentanil and remifentanil.[115] Better preparation of the rescuers with suitable amounts of naloxone might have helped prevent some of these seemingly unanticipated casualties.[148]

Ricin was found in several government buildings, including a mail processing plant in Greenville, South Carolina, in 2003 and the Dirksen Senate Office Building in Washington, DC, in 2004. Although no cases of ricin-associated illness ensued, increased concern was generated because the method of delivery was thought to be the mail, and irradiation procedures designed to kill microbials such as anthrax would not inactivate chemical toxins such as ricin.[14,124]

TABLE 2–2 Warfare and Terrorism Disasters

Toxin	*Location*	*Date*	*Significance*
Chlorine, mustard gas, phosgene	Ypres, Belgium	1915–1918	100,000 dead and 1.2 million casualties from chemicals during World War I
Cyanide, Carbon Monoxide	Europe	1939–1945	Millions murdered by Zyklon-B (HCN) gas
Agent Orange	Vietnam	1960s	Contained dioxin; excess skin cancer
Mustard gas	Iraq–Iran	1982	New cycle of war gas casualties
Yet to be determined	Persian Gulf	1991	Gulf War syndrome
Sarin	Matsumoto, Japan	1994	First terrorist attack in Japan using sarin
Sarin	Tokyo, Japan	1995	Subway exposure; 5,510 people sought medical attention
Dust and other particulates	New York, NY	2001	World Trade Center collapse from terrorist air strike
Carfentanil & Remifentanil	Moscow, Russia	2002	Used by the Russian military to subdue terrorists in Moscow theater
Ricin	Washington, DC	2004	Detected in Dirksen Senate Office Building; no illness reported
Chlorine	Iraq	2007	Used against US troops and Iraqi civilians
Sarin	Syria	2013, 2017	Used against Syrian civilians

FOOD DISASTERS

Unintentional contamination of food and drink has led to numerous toxic disasters (Table 2–3). Ergot, produced by the fungus *Claviceps purpurea*, caused epidemic ergotism as the result of eating breads and cereals made from rye contaminated by *C. purpurea*. In some epidemics, convulsive manifestations predominated, and in others, gangrenous manifestations predominated.[90] Ergot-induced severe vasospasm was thought to be responsible for both presentations.[89,90] In 994 A.D., 40,000 people died in Aquitania, France, in one such epidemic.[70] Convulsive ergotism was initially described as a "fire which twisted the people," and the term "St. Anthony's fire" (*ignis sacer*) was used to refer to the excruciating burning pain experienced in the extremities that is an early manifestation of gangrenous ergotism. The events surrounding the Salem, Massachusetts, witchcraft trials have also been attributed to the ingestion of contaminated rye. The bizarre neuropsychiatric manifestations exhibited by some of the individuals associated with this event may have been caused by the hallucinogenic properties of ergotamine, a lysergic acid diethylamide (LSD) precursor.[23,84]

During the last half of the 20th century, unintentional mass poisoning from food and drink contaminated with toxic chemicals became all too common. One of the more unusual poisonings occurred in Turkey in 1956 when wheat seed intended for planting was treated with the fungicide hexachlorobenzene and then inadvertently used for human consumption. Approximately 4,000 cases of porphyria cutanea tarda were attributed to the ingestion of this toxic wheat seed.[125]

Another example of chemical food poisoning took place in Epping, England, in 1965. In this incident, a sack of flour became contaminated with methylenedianiline when the chemical unintentionally spilled onto the flour during transport to a bakery. Subsequent ingestion of bread baked with the contaminated flour produced hepatitis in 84 people. This outbreak of toxic hepatitis became known as Epping jaundice.[63]

The manufacture of polybrominated biphenyls (PBBs) in a factory that also produced food supplements for livestock resulted in the unintentional contamination of a large amount of livestock feed in Michigan in 1973.[24] Significant morbidity and mortality among the livestock population resulted, and increased human tissue concentrations of PBBs were reported,[155] although human toxicity seemed limited to vague constitutional symptoms and abnormal liver function test results.

The chemical contamination of rice oil in Japan in 1968 caused a syndrome called Yusho ("rice oil disease"). This occurred when heat-exchange fluid containing polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs) leaked from a heating pipe into the rice oil. More than 1,600 people developed chloracne, hyperpigmentation, an increased incidence of liver cancer, or adverse reproductive effects. In 1979 in Taiwan, 2,000 people developed similar clinical manifestations after ingesting another batch of PCB-contaminated rice oil. This latter epidemic was referred to as Yu-Cheng ("oil disease").[56] These polychlorinated chemicals are very biopersistent, with follow-up testing 40 years later demonstrating blood half-lives approaching infinity in some patients.[85]

In another oil contamination epidemic, consumption of illegally marketed cooking oil in Spain in 1981 was responsible for a mysterious poisoning epidemic that affected more than 19,000 people and resulted in at least 340 deaths. Exposed patients developed a multisystem disorder referred to as

TABLE 2–3 Food Disasters

Xenobiotic	*Location*	*Date*	*Significance*
Ergot	Aquitania, France	994 A.D.	40,000 died in the epidemic
Ergot	Salem, MA	1692	Neuropsychiatric symptoms may be attributable to ergot
Lead	Devonshire, England	1700s	Colic from cider contaminated during production
Lead	Canada	1846	134 men died during the Franklin expedition, possibly because of contamination of food stored in lead cans
Cadmium	Japan	1939–1954	Itai-Itai ("ouch-ouch") disease
Hexachlorobenzene	Turkey	1956	4,000 cases of porphyria cutanea tarda
Methyl mercury	Minamata Bay, Japan	1950s	Consumption of organic mercury poisoned fish
Triorthocresyl phosphate	Meknes, Morocco	1959	Cooking oil adulterated with turbojet lubricant
Methylenedianiline	Epping, England	1965	Jaundice
Polychlorinated biphenyls	Japan	1968	Yusho ("rice oil disease")
Methyl mercury	Iraq	1971	>400 deaths from contaminated grain
Polybrominated biphenyls	Michigan	1973	97% of Michigan residents contaminated through food chain
Polychlorinated biphenyls	Taiwan	1979	Yu-Cheng ("oil disease")
Rapeseed oil (denatured)	Spain	1981	Toxic oil syndrome affected 19,000 people
Arsenic	Buenos Aires	1987	Malicious contamination of meat; 61 people underwent chelation
Arsenic	Bangladesh and West Bengal, India	1990s–present	Contaminated ground water; millions exposed; 100,000s with symptoms; greatest mass poisoning in history
Tetramine	China	2002	Snacks deliberately contaminated, resulting in 42 deaths and 300 people with symptoms
Arsenic	Maine	2003	Intentional contamination of coffee; one death and 16 cases of illness
Nicotine	Michigan	2003	Deliberate contamination of ground beef; 92 people became ill
Melamine	China	2008	50,000 hospitalized from tainted infant formula

toxic oil syndrome (or toxic epidemic syndrome), characterized by pneumonitis, eosinophilia, pulmonary hypertension, scleroderma-like features, and neuromuscular changes. Although this syndrome was associated with the consumption of rapeseed oil denatured with 2% aniline, the exact etiology was not definitively identified at the time. Subsequent investigations suggest that the fatty acid oleyl anilide may have been the putative xenobiotic.[59,60,108]

In 1999, an outbreak of health complaints related to consuming Coca-Cola occurred in Belgium, when 943 people, mostly children, complained of gastrointestinal (GI) symptoms, malaise, headaches, and palpitations after drinking Coca-Cola.[102] Many of those affected complained of an "off taste" or bad odor to the soft drink. In some of the Coca-Cola bottles, the carbon dioxide was contaminated with small amounts of carbonyl sulfide, which hydrolyzes to hydrogen sulfide, and may have been responsible for odor-triggered reactions. Mass psychogenic illness may have contributed to the large number of medical complaints because the concentrations of the carbonyl sulfide and hydrogen sulfide were very low and unlikely to cause systemic toxicity.[39]

Epidemics of heavy metal poisoning from contaminated food and drink have also occurred throughout history. Epidemic lead poisoning is associated with many different vehicles of transmission, including leaden bowls, kettles, and pipes. A famous 18th-century epidemic was known as the Devonshire colic. Although the exact etiology of this disorder was unknown for many years, later evidence suggested that the ingestion of lead-contaminated cider was responsible.[145]

Intentional chemical contamination of food may also occur. Multiple cases of metal poisoning occurred in Buenos Aires in 1987, when vandals broke into a butcher's shop and poured an unknown amount of a 45% sodium arsenite solution over 200 kg of partly minced meat.[117] The contaminated meat was purchased by 718 people. Of 307 meat purchasers who submitted to urine sampling, 49 had urine arsenic concentrations of 76 to 500 mcg/dL, and 12 had urine arsenic concentrations above 500 mcg/dL (normal urine arsenic concentration is <50–100 mcg/dL).

Cases of deliberate mass poisoning have heightened concerns about food safety and security. In China in 2002, a jealous food vendor adulterated fried dough sticks, sesame cakes, and rice prepared in a rival's snack bar by surreptitiously putting a large amount of tetramine (tetramethylene disulfotetramine) into the raw pastry material. More than 300 people who consumed these adulterated snacks became ill, and 42 died.[30] In Maine in 2003, a disillusioned parishioner contaminated the communal coffee pot at a church bake sale with arsenic. One victim died within 12 hours, and five others developed hypotension.[156] In 2003 in Michigan, 92 people became ill after ingesting contaminated ground beef deliberately contaminated with a nicotine pesticide by a supermarket employee.[6]

At the end of the 20th century and beginning of the 21st century, what may be the greatest mass poisoning in history occurred in Bangladesh and India's West Bengal State[33,95,112,135] (Chap. 86). In Bangladesh alone, 60 million people routinely drank arsenic-contaminated ground water, and at least 220,000 inhabitants of India's West Bengal were diagnosed with arsenic poisoning.[94] Symptoms reported include melanosis, depigmentation, hyperkeratosis, hepatomegaly, splenomegaly, squamous cell carcinoma, intraepidermal carcinoma, and gangrene.[33] In a country long plagued by dysentery, attempts to purify the water supply led to the drilling of millions of wells into the superficial water table. Unknown to the engineers, this water was naturally contaminated with arsenic, creating several thousand tube wells with extremely high concentrations of arsenic—up to 40 times the acceptable concentration. Although toxicity from arsenic-contaminated groundwater was previously reported from other areas of the world, including Argentina, China, Mexico, Taiwan (black foot disease), and Thailand, the number of people at risk in Bangladesh and West Bengal is by far the largest. A 2016 report suggests that 40 million people in Bangladesh may still be exposed to unsafe concentrations of arsenic in the water with tens of thousands of deaths per year attributed to arsenic exposure.[73]

Methyl mercury is responsible for several poisoning epidemics in the past half century. During the 1950s, a Japanese chemical factory that manufactured vinyl chloride and acetaldehyde routinely discharged mercury into Minamata Bay, resulting in contamination of the aquatic food chain. An epidemic of methyl mercury poisoning ensued as the local people ate the poisoned fish.[109,141] Chronic brain damage, tunnel vision, deafness, and severe congenital defects were associated with this mass poisoning.[109] Another mass epidemic of methyl mercury poisoning occurred in Iraq in 1971, when the local population consumed homemade bread prepared from wheat seed treated with a methyl mercury fungicide.[15] Six thousand hospital admissions and more than 400 deaths were associated with this mass poisoning. As was the case of the hexachlorobenzene exposure in Turkey 15 years previously, the treated grain, intended for use as seed, was instead utilized as food.

From 1939 to 1954, contamination of the local water supply with the wastewater runoff from a zinc–lead–cadmium mine in Japan was believed responsible for causing Itai-Itai ("ouch-ouch") disease, an unusual chronic syndrome manifested by extreme bone pain and osteomalacia. The local water was used for drinking and irrigation of the rice fields. Approximately 200 people who lived along the banks of the Jintsu River developed these peculiar symptoms, which were thought most likely to be caused by the cadmium.[2]

More than 50,000 infants were hospitalized in China in 2008 from the ill effects of melamine-contaminated powdered infant formulae.[54] Melamine (1,3,5-triazine–2,4,6-triamine) is a component in many adhesives, glues, plastics, and laminated products (eg, plywood, cleaners, cement, cleansers, fire-retardant paint). More than 20 Chinese companies produced the tainted formula. Analysis of these formulas found melamine concentrations as high as 2,500 ppm. Clinically, exposure to high doses of melamine has been associated with the development of nephrolithiasis, obstructive uropathy, and in some cases acute kidney failure.[146] Melamine contamination of pet food resulting in deaths in dogs and cats was previously reported.[22] The melamine disaster also demonstrates that globalization and international agribusiness may facilitate worldwide distribution of contaminated foodstuffs. After the initial reports of melamine contamination in China, investigation in the United States revealed that certain brands of cookies, biscuits, candies, and milk sold in this country were also tainted with melamine, some of which was traced to an origin in China.[54]

MEDICINAL DRUG DISASTERS

Illness and death as a consequence of therapeutic drug use occur as sporadic events, usually affecting individual patients, or as mass poisoning, affecting multiple (sometimes hundreds or thousands) patients. Sporadic single-patient medication-induced tragedies usually result from errors (Chaps. 1 and 135) or unforeseen idiosyncratic reactions. Mass therapeutic drug disasters have generally occurred secondary to poor safety testing, a lack of understanding of diluents and excipients, drug contamination, or problems with unanticipated drug–drug interactions or drug toxicity (Table 2–4).

In September and October 1937, more than 105 deaths were associated with the use of one of the early sulfa preparations—elixir of sulfanilamide-Massengill—that contained 72% diethylene glycol as the vehicle for drug delivery. Little was known about diethylene glycol toxicity at the time, and many cases of acute kidney failure and death occurred.[41] To avoid similar tragedies in the future, animal drug testing was mandated by the Food, Drug, and Cosmetic Act of 1938.[149] Unfortunately, diethylene glycol continues to be sporadically used in other countries as a medicinal diluent, resulting in deaths in South Africa (1969), India (1986), Nigeria (1990), Bangladesh (1990–1992), and Haiti (1995–1996).[150] In 1996 in Haiti, at least 88 Haitian children died (case fatality rate of 98% for those who remained in Haiti) after ingesting an acetaminophen (APAP) elixir formulated with diethylene glycol–contaminated glycerin.[103,122] In Panama in 2006, glycerin contaminated with diethylene glycol found in prescription liquid cough syrup resulted in at least 121 cases of poisoning and 78 deaths (case fatality rate, 65.5%).[18,114] Investigators of this last outbreak discovered that the contaminated glycerin was imported to Panama from China via a European broker, demonstrating that improprieties in pharmaceutical manufacturing may have worldwide implications. In Nigeria in 2009, a tainted teething formula was responsible for 84 deaths in children.[7] The pharmaceutical manufacturers intended to

TABLE 2–4 Medicinal Disasters

Xenobiotic	*Location*	*Date*	*Significance*
Thallium	United States	1920s–1930s	Treatment of ringworm; 31 deaths
Diethylene glycol	United States	1937	Elixir of sulfanilamide; kidney failure
Thorotrast	United States	1930s–1950s	Hepatic angiosarcoma
Phenobarbital	United States	1940–1941	Contaminated sulfathiazole: 82 deaths
Diethylstilbestrol	United States, Europe	1940s–1970s	Vaginal adenocarcinomas in patients' daughters and urogenital abnormalities in sons
Stalinon	France	1954	Severe neurotoxicity from triethyltin
Clioquinol	Japan	1955–1970	Subacute myelooptic neuropathy; 10,000 symptomatic
Thalidomide	Europe	1960s	5,000 cases of phocomelia
Isoproterenol 30%	Great Britain	1961–1967	3,000 excess asthma deaths
Pentachlorophenol	United States	1967	Used in hospital laundry; nine neonates ill, two deaths
Benzyl alcohol	United States	1981	Neonatal gasping syndrome
Tylenol–cyanide	Chicago	1982	Tampering incident resulted in seven homicides
L-Tryptophan	United States	1989	Eosinophilia myalgia syndrome
Diethylene glycol	Haiti	1996	Contaminated acetaminophen elixir; kidney failure; >88 pediatric deaths
Diethylene glycol	Panama	2006	Contaminated cough preparation, causing 78 deaths
Diethylene glycol	Nigeria	2009	Contaminated teething formula, causing 84 deaths

purchase propylene glycol, a component of the teething formula, but had bought the diluent in a jerrycan instead of the original container, and the chemical contained diethylene glycol (Special Considerations: SC9).

A lesser known drug manufacturing event, also involving an early sulfa antimicrobial, occurred in 1940 to 1941, when at least 82 people died from the therapeutic use of sulfathiazole that was contaminated with phenobarbital (Luminal).[136] The responsible pharmaceutical company, Winthrop Chemical, produced both sulfathiazole and phenobarbital, and the contamination likely occurred during the tableting process because the tableting machines for the two medications were adjacent to each other and were used interchangeably. Each contaminated sulfathiazole tablet contained about 350 mg of phenobarbital (and no sulfathiazole), and the typical sulfathiazole dosing regimen was several tablets within the first few hours of therapy. Twenty-nine percent of the production lot was contaminated. Food and Drug Administration (FDA) intervention was required to assist with the recovery of the tablets, although 22,000 contaminated tablets were never found.[136]

In the early 1960s, one of the worst drug-related modern-day events occurred with the release of thalidomide as an antiemetic and sedative–hypnotic.[32] Its use as a sedative–hypnotic by pregnant women caused about 5,000 babies to be born with severe congenital limb anomalies.[90] This tragedy was largely confined to Europe, Australia, and Canada, where the drug was initially marketed. The United States was spared because of the length of time required for review and the rigorous scrutiny of new drug applications by the FDA.[86]

A major therapeutic drug event that did occur in the United States involved the recommended and subsequent widespread use of diethylstilbestrol (DES) for the treatment of threatened and habitual abortions. Despite the lack of convincing efficacy data, as many as 10 million Americans received DES during pregnancy or in utero during a 30-year period, until the drug was prohibited for use during pregnancy in 1971. Adverse health effects associated with DES use include increased risk for breast cancer in "DES mothers" and increased risk of a rare form of vaginal cancer, reproductive tract anomalies, and premature births in "DES daughters."[43,48]

Thorotrast (thorium dioxide 25%) is an intravenous radiologic contrast medium that was widely used between 1928 and 1955. Its use was associated with the delayed development of hepatic angiosarcomas, as well as skeletal sarcomas, leukemia, and "thorotrastomas" (malignancies at the site of extravasated thorotrast).[134,151]

The use of thallium to treat ringworm infections in the 1920s and 1930s also led to needless morbidity and mortality.[44] Understanding that thallium caused alopecia, dermatologists and other physicians prescribed thallium acetate, both as pills and as a topical ointment (Koremlu), to remove the infected hair. A 1934 study found 692 cases of thallium toxicity after oral and topical application and 31 deaths after oral use.[97] "Medicinal" thallium was subsequently removed from the market.

The "Stalinon affair" in France in 1954 involved the unintentional contamination of a proprietary oral medication that was marketed for the treatment of staphylococcal skin infections, osteomyelitis, and anthrax. Although it was supposed to contain diethyltin diiodide and linoleic acid, triethyltin, a potent neurotoxin and the most toxic of organotin compounds, and trimethyltin were present as impurities. Of the approximately 1,000 people who received this medication, 217 patients developed symptoms, and 102 patients died.[10,17]

An unusual syndrome, featuring a constellation of abdominal symptoms (pain and diarrhea) followed by neurologic symptoms (peripheral neuropathy and visual disturbances, including blindness) was experienced by approximately 10,000 Japanese people between 1955 and 1970, resulting in several hundred deaths.[66] This presentation, subsequently labeled subacute myelooptic neuropathy (SMON), was associated with the use of the GI disinfectant clioquinol, known in the West as Entero-Vioform and most often used for the prevention of travelers' diarrhea.[100] In Japan, this drug was referred to as "sei-cho-zai" ("active in normalizing intestinal function"). It was incorporated into more than 100 nonprescription medications and was used by millions of people, often for weeks or months. The exact mechanism of toxicity has not been determined, but recent investigators theorize that clioquinol may enhance the cellular uptake of certain metals, particularly zinc, and that the clioquinol–zinc chelate may act as a mitochondrial toxin, causing this syndrome.[13] New cases declined rapidly when clioquinol was banned in Japan.

In 1981, a number of premature neonates died with a "gasping syndrome," manifested by severe metabolic acidosis, respiratory depression with

gasping, and encephalopathy.[42] Before the development of these findings, the infants had all received multiple injections of heparinized bacteriostatic sodium chloride solution (to flush their indwelling catheters) and bacteriostatic water (to mix medications), both of which contained 0.9% benzyl alcohol. Accumulation of large amounts of benzyl alcohol and its metabolite benzoic acid in the blood was thought to be responsible for this syndrome.[42]

In 1989 and 1990, eosinophilia-myalgia syndrome, a debilitating syndrome somewhat similar to toxic oil syndrome, developed in more than 1,500 people who had used the dietary supplement L-tryptophan.[143] These patients presented with disabling myalgias and eosinophilia, often accompanied by extremity edema, dyspnea, and arthralgias. Skin changes, neuropathy, and weight loss sometimes developed. Intensive investigation revealed that all affected patients had ingested L-tryptophan produced by a single manufacturer that had recently introduced a new process involving genetically altered bacteria to improve L-tryptophan production. A contaminant produced by this process probably was responsible for this syndrome.[20] The banning of L-tryptophan by the FDA set in motion the passage of the Dietary Supplement Health and Education Act of 1994. This legislation, which attempted to regulate an uncontrolled industry, facilitated industry marketing of dietary supplements bypassing FDA scrutiny. In 2001, the FDA loosened the restrictions on the marketing of tryptophan, which is now sold through some compounding pharmacies.

A number of pharmaceuticals previously approved by the FDA have been withdrawn from the market because of concerns about health risks.[158] Many more drugs have been given "black box warnings" by the FDA because of their propensity to cause serious or life-threatening adverse effects.[83] Some of the withdrawn drugs were responsible for causing serious drug–drug interactions (astemizole, cisapride, mibefradil, terfenadine).[96] Other drugs were withdrawn because of a propensity to cause hepatotoxicity (troglitazone), anaphylaxis (bromfenac sodium), valvular heart disease (fenfluramine, dexfenfluramine), rhabdomyolysis (cerivastatin), hemorrhagic stroke (phenylpropanolamine), and other adverse cardiac and neurologic effects (ephedra, rofecoxib). One of the more disconcerting drug problems to arise was the development of cardiac valvulopathy and pulmonary hypertension in patients taking the weight-loss drug combination fenfluramine and phentermine (fen-phen) or dexfenfluramine.[28,129] The histopathologic features observed with this condition were similar to the valvular lesions associated with ergotamine and carcinoid syndrome. Interestingly, appetite suppressant medications, as well as ergotamine and the carcinoid syndrome, all increase available serotonin.

ALCOHOL AND ILLICIT DRUG DISASTERS

Unintended toxic disasters have also involved the use of alcohol and other drugs of abuse (Table 2–5). Arsenical neuropathy developed in an estimated 40,000 people in France in 1828, when wine and bread were unintentionally contaminated by arsenious acid.[82] The use of arsenic-contaminated sugar in the production of beer in England in 1900 resulted in at least 6,000 cases of peripheral neuropathy and 70 deaths (Staffordshire beer epidemic).[5]

TABLE 2–5 Alcohol and Illicit Drug Disasters

Xenobiotic	*Location*	*Date*	*Significance*
Arsenious acid	France	1828	40,000 cases of polyneuropathy from contaminated wine and bread
Arsenic	Staffordshire, England	1900	Contaminated sugar used in beer production
Triorthocresyl phosphate	United States	1930–1931	Ginger Jake paralysis
Methanol	Atlanta, GA	1951	Epidemic from ingesting bootleg whiskey
Cobalt	Quebec City, Canada and others	1960s	Beer cardiomyopathy
Methanol	Jackson, MI	1979	Occurred in a prison
MPTP	San Jose, CA	1982	Illicit meperidine manufacturing resulting in drug-induced parkinsonism
Heroin heated on aluminum foil	Netherlands	1982	Spongiform leukoencephalopathy
3-Methyl fentanyl	Pittsburgh, PA	1988	"China-white" epidemic
Methanol	Baroda, India	1989	Moonshine contamination; 100 deaths
Fentanyl	New York City	1990	"Tango and Cash" epidemic
Methanol	New Delhi, India	1991	Antidiarrheal medication contaminated with methanol; >200 deaths
Methanol	Cuttack, India	1992	Methanol-tainted liquor; 162 deaths
Scopolamine	US East Coast	1995–1996	325 cases of anticholinergic poisoning in heroin users
Methanol	Cambodia	1998	>60 deaths
Opioids	United States	1999–present	Epidemic of opioid fatalities from prescription opioids and heroin with >42,420 opioid deaths in 2016
Methanol	Nicaragua	2006	800 ill, 15 blind, 45 deaths
Methanol	India	2011	>143 deaths
Methanol	Czech Republic	2012	121 ill; 41 deaths
Methanol	Libya	2013	1066 ill; 101 deaths
Methanol	Kenya	2014	Two outbreaks: 341 ill and 100 deaths; 126 ill and 26 deaths
Fentanyl and analogs	United States	2015–present	Dramatic increase in opioid deaths from fentanyl and analogs such as carfentanil

MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

During the early 20th century, particularly during Prohibition, the ethanolic extract of Jamaican ginger (sold as "the Jake") was a popular ethanol substitute in the southern and Midwestern United States.[91] It was sold legally because it was considered a medical supplement to treat headaches and aid digestion and was not subject to Prohibition. For years, the Jake was sold adulterated with castor oil, but in 1930, as the price of castor oil rose, the Jake was reformulated with an alternative adulterant, triorthocresyl phosphate (TOCP). Little was previously known about the toxicity of this compound, and TOCP proved to be a potent neurotoxin. From 1930 to 1931, at least 50,000 people who drank the Jake developed TOCP poisoning, manifested by upper and lower extremity weakness ("ginger Jake paralysis") and gait impairment ("Jake walk" or "Jake leg").[91] A quarter century later, in Morocco, the dilution of cooking oil with a turbojet lubricant containing TOCP caused an additional 10,000 cases of TOCP-induced paralysis.[132]

In the 1960s, cobalt was added to several brands of beer as a foam stabilizer. Certain local breweries in Quebec City, Canada; Minneapolis, Minnesota; Omaha, Nebraska; and Louvain, Belgium, added 0.5 to 5.5 ppm of cobalt to their beer. This resulted in epidemics of fulminant heart failure among heavy beer drinkers (named cobalt-beer cardiomyopathy).[1,92]

Epidemic methanol poisoning among those seeking ethanol and other inebriants is well described. In one such incident in Atlanta, Georgia, in 1951, the ingestion of methanol-contaminated bootleg whiskey caused 323 cases of methanol poisoning, including 41 deaths.[21] In another epidemic in 1979, 46 prisoners became ill after ingesting a methanol-containing diluent used in copy machines.[137]

In recent years, major mass methanol poisonings have continued to occur in developing countries, where store-bought alcohol is often prohibitively expensive. In Baroda, India, in 1989, at least 100 people died, and another 200 became ill after drinking a homemade liquor that was contaminated with methanol.[4] In New Delhi, India, in 1991, an inexpensive antidiarrheal medicine, advertised to contain large amounts of ethanol, was instead contaminated with methanol, causing more than 200 deaths.[27] The following year, in Cuttack, India, 162 people died, and an additional 448 were hospitalized after drinking methanol-tainted liquor.[11] A major epidemic of methanol poisoning occurred in 1998 in Cambodia, when rice wine was contaminated with methanol.[3] At least 60 deaths and 400 cases of illness were attributed to the methanol. In 2011 in Sangrampur, India, more than 143 died from drinking methanol-tainted bootleg alcohol.[77] A mass methanol poisoning in the Czech Republic in 2012 in 121 people resulted in a fatality rate of 34%.[160] Most recently in 2013 in Libya, more than 1,000 people were poisoned with methanol with a fatality rate of 10%, and in 2014 in Kenya, two outbreaks of methanol poisoning occurred among 341 and 126 people with fatality rates of 29% and 21% respectively.[118]

So-called designer drugs are responsible for several toxicologic disasters. In 1982, several injection drug users living in San Jose, California, who were attempting to use a meperidine analog, MPPP (1-methyl-4-phenyl-4-propionoxy-piperidine), developed a peculiar, irreversible neurologic disease closely resembling Parkinson disease.[68] Investigation revealed that these patients had unknowingly injected trace amounts of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), which was present as an inadvertent product of the clandestine MPPP synthesis. The subsequent metabolism of MPTP to MPP^+ resulted in a toxic compound that selectively destroyed cells in the substantia nigra, depleting dopamine stores or products and causing severe and irreversible parkinsonism. The vigorous pursuit of the cause of this disaster led to a better understanding of the pathophysiology of parkinsonism.

Another example of a "designer drug" poisoning occurred in the New York City metropolitan area in 1991, when a sudden epidemic of opioid overdoses occurred among heroin users who bought envelopes labeled "Tango and Cash."[38] Expecting to receive a new brand of heroin, the drug users instead purchased the much more potent fentanyl. Increased and unpredictable toxicity resulted from the inability of the dealer to adjust ("cut") the fentanyl dose properly. Some purchasers presumably received little or no fentanyl, but others received potentially lethal doses. A similar epidemic involving 3-methylfentanyl occurred in 1988 in Pittsburgh, Pennsylvania.[80]

At least 325 cases of anticholinergic poisoning occurred among heroin users in New York City; Newark, New Jersey; Philadelphia, Pennsylvania; and Baltimore, Maryland, from 1995 to 1996.[8] The "street drug" used in these cases was adulterated with scopolamine. Whereas naloxone treatment was associated with increased agitation and hallucinations, physostigmine administration resulted in resolution of symptoms. Why the heroin was adulterated was unknown, although the use of an opiate–scopolamine mixture was reminiscent of the morphine–scopolamine combination therapy known as "twilight sleep" that was extensively used in obstetric anesthesia during the early 20th century.[106] Another unexpected complication of heroin use was observed in the Netherlands in the 1980s, when 47 heroin users developed mutism and spastic quadriparesis that was pathologically demonstrated to be spongiform leukoencephalopathy.[157] In these and subsequent cases in Europe and the United States, the users inhaled heroin vapors after the heroin powder had been heated on aluminum foil, a drug administration technique known as "chasing the dragon."[64,157] The exact toxic mechanism has not been elucidated.

Since 1999, an epidemic of opioid deaths has occurred in the United States. Described by the Centers for Disease Control and Prevention (CDC) as the worst drug overdose epidemic in US history,[62] from 1999 to 2014, the number of drug overdose deaths nearly tripled in the United States.[119] Drug overdose deaths now surpass the number of fatalities from motor vehicle collisions and are similar in number to the annual mortality at the height of the HIV/AIDS epidemic in the US. According to the CDC, in 2016, of the 63,632 drug overdose deaths in the United States, opioids were implicated in approximately 42,420 (66.4%) deaths.[119] This opioid overdose epidemic was fueled by an exponential increase in prescription opioid consumption, including a 500% increase in oxycodone consumption. Accompanying this epidemic has been a 900% increase in individuals seeking treatment for opioid use disorders.[62] What began as an epidemic of prescription opioid overdose deaths has now been associated with an epidemic of heroin overdose deaths as prescription opioid abusers switched to easier-to-obtain heroin as their opioid of choice. In 2015 and 2016, an increase in designer opioid overdose deaths emerged, including deaths attributed to fentanyl and fentanyl analogs such as carfentanil.[121,133]

OCCUPATION-RELATED CHEMICAL DISASTERS

Unfortunately, occupation-related toxic epidemics have become increasingly common (Table 2–6). Such poisoning syndromes tend to have an insidious onset and may not be recognized clinically until years after the exposure. A specific xenobiotic may cause myriad problems, among the most worrisome being the carcinogenic and mutagenic potentials.

Although the 18th-century observations of Ramazzini and Pott introduced the concept of certain diseases as a direct result of toxic exposures in the workplace, it was not until the height of the 19th-century industrial revolution that the problems associated with the increasingly hazardous workplace became apparent.[53] During the 1860s, a peculiar disorder, attributed to the effects of inhaling mercury vapor, was described among manufacturers of felt hats in New Jersey.[152] Mercury nitrate was used as an essential part of the felting process at the time. "Hatter's shakes" refers to the tremor that developed in an estimated 10% to 60% of hatters surveyed.[152] Extreme shyness, another manifestation of mercurialism, also developed in many hatters in later studies. Five percent of hatters during this period died from renal failure.

Other notable 19th-century and early 20th-century occupational tragedies included an increased incidence of mandibular necrosis (phossy jaw) among workers in the matchmaking industry who were exposed to white phosphorus,[51] an increased incidence of bladder tumors among synthetic dye makers who used β–naphthylamine,[45] and an increased incidence of aplastic anemia among artificial leather manufacturers who used benzene.[127] The epidemic of phossy jaw among matchmakers had a latency period of 5 years and a mortality rate of 20% and has been called the "greatest tragedy

TABLE 2–6 Occupational Disasters

Xenobiotic	*Location*	*Date*	*Significance*
Polycyclic aromatic hydrocarbons	England	1700s	Scrotal cancer among chimney sweeps; first description of hydrocarbons occupational cancer
Mercury	New Jersey	Mid to late 1800s	Outbreak of mercurialism in hatters
White phosphorus	Europe	Mid to late 1800s	Phossy jaw in matchmakers
β-Naphthylamine	Worldwide	Early 1900s	Bladder cancer in dye makers
Benzene	Newark, NJ	1916–1928	Aplastic anemia among artificial leather manufacturers
Asbestos	Worldwide	20th century	Millions at risk for asbestos-related disease
Vinyl chloride	Louisville, KY	1960s–1970s	Hepatic angiosarcoma among plastics workers
Chlordecone	James River, VA	1973–1975	Neurologic abnormalities among insecticide workers
1,2-Dibromochloropropane	California	1974	Infertility among pesticide makers
Lead	Zamfara, Nigeria	2010	400 deaths in children exposed to lead from artisanal mining operation

in the whole story of occupational disease."[25] The problem continued in the United States until Congress passed the White Phosphorus Match Act in 1912, which established a prohibitive tax on white phosphorus matches.

Since antiquity, occupational lead poisoning has been a constant threat. Workplace exposure to lead was particularly problematic during the 19th century and early 20th century because of the large number of industries that relied heavily on lead. One of the most notorious of the "lead trades" was the actual production of white lead and lead oxides. Palsies, encephalopathy, and deaths from severe poisoning were reported.[47] Other occupations that resulted in dangerous lead exposures included pottery glazing, rubber manufacturing, pigment manufacturing, painting, printing, and plumbing.[79] Given the increasing awareness of harm suffered in the workplace, the British Factory and Workshop Act of 1895 required governmental notification of occupational diseases caused by lead, mercury, and phosphorus poisoning, as well as of occupational diseases caused by anthrax.[69]

In 2010, an outbreak of fatal lead poisoning in children who were environmentally exposed to lead from an artisanal gold mining operation in Zamfara, Nigeria, was reported.[46] Approximately 400 deaths from lead poisoning occurred over a 3-month period. As a result of this mass lead poisoning outbreak, 1,156 children underwent chelation therapy. Of 3,180 treatment courses administered, 36% commenced with venous blood lead concentrations greater than 80 mcg/dL, and 6% had concentrations greater than 120 mcg/dL.[140]

Exposures to asbestos during the 20th century have resulted in continuing extremely consequential occupational and environmental disasters.[29,99] Even though the first case of asbestosis was reported in 1907, asbestos was heavily used in the shipbuilding industries in the 1940s as an insulating and fireproofing material. Since the early 1940s, 8 to 11 million individuals were occupationally exposed to asbestos,[71] including 4.5 million individuals who worked in the shipyards. Asbestos-related diseases include mesothelioma, lung cancer, and pulmonary fibrosis (asbestosis). A threefold excess of cancer deaths, primarily of excess lung cancer deaths, has been observed in asbestos-exposed insulation workers.[126]

The manufacture and use of a variety of newly synthesized chemicals has also resulted in mass occupational poisonings. In Louisville, Kentucky, in 1974, an increased incidence of angiosarcoma of the liver was first noticed among polyvinyl chloride polymerization workers who were exposed to vinyl chloride monomer.[36] In 1975, chemical factory workers exposed to the organochlorine insecticide chlordecone (Kepone) experienced a high incidence of neurologic abnormalities, including tremor and chaotic eye movements.[138] An increased incidence of infertility among male Californian pesticide workers exposed to 1,2-dibromochloropropane (DBCP) was noted in 1977.[153]

RADIATION DISASTERS

A discussion of mass poisonings is incomplete without mention of the large number of radiation disasters that have characterized the 20th century (Table 2–7). The first significant mass exposure to radiation occurred among several thousand teenage girls and young women employed in the dial-painting industry.[26] These workers painted luminous numbers on watch and instrument dials with paint that contained radium. Exposure occurred by licking the paint brushes and inhaling radium-laden dust. Studies showed an increase in bone-related cancers, as well as aplastic anemia and leukemia, in exposed workers.[81,107]

At the time of the "watch" disaster, radium was also being sold as a nostrum touted to cure all sorts of ailments, including rheumatism, syphilis, multiple sclerosis, and sexual dysfunction. Referred to as "mild radium therapy" to differentiate it from the higher dose radium that was used in the treatment of cancer at that time, such particle-emitting isotopes were hailed as powerful natural elixirs that acted as metabolic catalysts to deliver direct energy transfusions.[76]

During the 1920s, dozens of patent medications containing small doses of radium were sold as radioactive tablets, liniments, or liquids. One of the most infamous preparations was Radithor. Each half-ounce bottle contained slightly more than one curie of radium (^{228}Ra and ^{226}Ra). This radioactive

TABLE 2–7 Radiation Disasters

Xenobiotic	*Location*	*Date*	*Significance*
Radium	Orange, NJ	1910s–1920s	Increase in bone cancer in dial-painting workers
Radium	United States	1920s	"Radithor" (radioactive water) sold as radium-containing patent medication
Radiation	Hiroshima and Nagasaki, Japan	1945	First atomic bombs dropped at the end of World War II; clinical effects still evident today
Radiation	Chernobyl, Ukraine	1986	Unintentional radioactive release; acute radiation sickness
Cesium	Goiania, Brazil	1987	Acute radiation sickness and radiation burns
Cesium, iodine	Fukushima, Japan	2011	Unintentional radioactive release after earthquake and tsunami

water was sold all over the world "as harmless in every respect" and was heavily promoted as a sexual stimulant and aphrodisiac, taking on the glamour of a recreational drug for the wealthy.[76] More than 400,000 bottles were sold. The 1932 death of Eben Byers a Radithor connoisseur, from chronic radiation poisoning drew increased public and governmental scrutiny to this unregulated radium industry and helped end the era of radioactive patent medications.[76]

Concerns about the health effects of radiation have continued to escalate since the dawn of the nuclear age in 1945. Long-term follow-up studies 50 years after the atomic bombings at Hiroshima and Nagasaki demonstrate an increased incidence of leukemia, other cancers, radiation cataracts, hyperparathyroidism, delayed growth and development, and chromosomal anomalies in exposed individuals.[61]

The unintentional nuclear disaster at Chernobyl, Ukraine, in April 1986 again forced the world to confront the medical consequences of 20th-century scientific advances that created the atomic age.[40] The release of radioactive material resulted in 31 deaths and the hospitalization of more than 200 people for acute radiation sickness. By 2003, the predominant long-term effects of the event appeared to be childhood thyroid cancer and psychological consequences.[113] In some areas of heavy contamination, the increase in childhood thyroid cancer has increased 100-fold.[120]

Another serious radiation event occurred in Goiania, Brazil, in 1987 when an abandoned radiotherapy unit was opened in a junkyard and 244 people were exposed to cesium (^{137}Cs). Of those exposed, 104 showed evidence of internal contamination, 28 had local radiation injuries, and 8 developed acute radiation syndrome. There were at least 4 deaths.[105,116]

In September 1999, a nuclear event at a uranium-processing plant in Japan set off an uncontrolled chain reaction, exposing 49 people to radiation.[65] Radiation measured outside the facility reached 4,000 times the normal ambient level. Two workers died from the effects of the radiation.

A 9.0 magnitude earthquake and tsunami in Japan in March 2011 caused equipment failure at the Fukushima Daiichi nuclear plant resulted in a release of radioactive material into the atmosphere and seawater. Nearby foodstuff and drinking water was contaminated with cesium (^{137}Cs) and iodine (^{131}I).[139] Although there were no cases of acute radiation syndrome, significant psychological and social effects resulted from this incident.[87]

MASS SUICIDE BY POISON

Mass poisonings have also manifested themselves as events of mass suicide. In 1978 in Jonestown, Guyana, 911 members of the Peoples Temple died after drinking a beverage containing cyanide.[12] In 1997, phenobarbital and ethanol (sometimes assisted by physical asphyxiation) was the suicidal method favored by 39 members of the Heavens Gate cult in Rancho Santa Fe, California, a means of suicide recommended in the book *Final Exit*.[52] Apparently, the cult members committed suicide to shed their bodies in hopes of hopping aboard an alien spaceship they believed was in the wake of the Hale-Bopp comet.[67]

SUMMARY

- There are significant lessons to be learned from mass poisonings.
- An understanding of the pathogenesis of these mass poisonings pertaining to drug, food, and occupational safety is critically important to prevent future disasters.
- Such events make us aware that many of the toxic xenobiotics involved are potential agents of opportunity for terrorists and nonterrorists who seek to harm others.
- Given the practical and ethical limitations in studying the effects of many specific xenobiotics in humans, lessons from these unfortunate tragedies must be fully mastered and retained for future generations.

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CASE STUDY 1

History Police were called to a public area where a young man was shirtless and acting bizarrely. It was a hot summer day with a temperature of 92°F (33°C) and a dew point of 75°F (24°C). The man, who appeared confused, was pacing and gesturing as if he was hallucinating. When the police approached him, he began to run away, but after a struggle, he was subdued. The paramedics were called because of his behavior. When they arrived, they found an agitated and confused man whose arms and legs were restrained and in a full-body bag. He was diaphoretic with 6 to 7 mm pupils, and he was breathing rapidly and had a pulse of 180 beats/min. Because of the restraints, no other vital signs were obtained, and the patient was transported to the emergency department (ED).

Physical Examination On arrival to the ED, a team of physicians, nurses, and hospital security personnel removed the patient from the body bag, restrained him, and transfered him to a hospital stretcher. An arm was held in place, and an intravenous (IV) line was administered. Blood was obtained for analysis, and midazolam (10 mg IV) was given. Within a few moments, the patient became calmer, and the following vital signs were obtained: blood pressure, 198/122 mm Hg; pulse, 188 beats/min; respiratory rate, 38 breaths/min; tympanic temperature, 104.6°F (40.3°C); oxygen saturation, 98% on room air; and glucose, 187 mg/dL. Physical examination revealed a diaphoretic young man who was mumbling incoherently and was hot to the touch. There were no signs of trauma, and his pupils were 7 mm and reactive to light. His chest was clear, and his heart rate was regular and tachycardic without extra sounds. His abdomen was soft and nontender with normal bowel sounds. A complete neurologic assessment could not be performed, as he was disoriented, distracted, and unable to follow commands. His pupils were reactive, and oculocephalic reflexes were present. Muscle tone was increased symmetrically, and reflexes were brisk, with three to four beats of clonus noted at both ankles. His toes were downgoing.

What Is the Toxicologic Differential Diagnosis? This patient presents with agitation, tachycardia, hypertension, hyperthermia, diaphoresis, mydriasis, and disorientation. Although this presentation is fairly characteristic of a sympathomimetic toxic syndrome (Chaps. 3, 73, and 75) additional considerations must include alcohol and sedative–hypnotic withdrawal (Chaps. 14 and 77), hallucinogens (Chap. 79), and phencyclidine (Chap. 83). These and other etiologies for the hyperthermia are listed in Table CS1–1.

Initial Management A rectal probe was inserted, and the patient's core temperature was noted to be 109.2°F (42.9°C). This single vital sign abnormality takes precedence over the others and requires emergent intervention, regardless of the etiology. An additional 5 mg of IV midazolam was administered (Antidotes in Depth: A26) to further control the agitation, and the patient was placed in an ice-water bath (Chap. 29). While in the bath, another 5 mg of midazolam was needed to control his behavior. One liter of 0.9 sodium chloride was infused through the peripheral IV line, and a Foley catheter was inserted, which drained a scant amount of dark yellow urine.

Within 15 minutes, the patient's core temperature fell to 101.4°F (38.6°C); he was removed from the ice bath, dried, and placed on a clean, dry stretcher. At that time, the following vital signs were obtained: blood pressure, 148/94 mm Hg; pulse, 120 beats/min; respiratory rate, 24 breaths/min; core temperature, 99.2°F (37.3°C); oxygen saturation, 96% on room air; and end-tidal carbon dioxide, 46 mm Hg.

What Clinical and Laboratory Analyses Can Help Exclude Life-Threatening Consequences of This Patient's Presentation? The consequences of hyperthermia include injury to many organ systems as outlined in Table CS1–2. An electrocardiogram (ECG) should be obtained because it can rapidly detect critical myocardial injury and life-threatening electrolyte abnormalities. A rapid assessment of electrolytes, kidney and liver function, coagulation status, acid–base balance, creatine kinase, troponin, and a urinalysis are all indicated. Severe abnormalities should be addressed as detected. In this case, although the urine dipstick showed the large presence of blood, no red blood cells were seen or microscopic analysis leading to a clinical suspicion of rhabdomyolysis. The patient was started on fluids at twice his maintenance requirement as well as a bicarbonate infusion (Antidotes in Depth: A5).

Further Diagnosis and Treatment The patient remained calm and began to answer questions a few hours later. The ECG showed sinus tachycardia with normal intervals and no pattern of injury. However, the laboratory results were remarkable for a creatinine of 3.4 mg/dL, a bicarbonate of 12 mEq/L, an anion gap of 30 mEq/L, and a creatine kinase of greater than 100,000 IU/L, compatible with an acute kidney injury to rhabdomyolysis. Although repeat electrolytes showed a rapid correction of the bicarbonate and anion gap, the creatinine continued to rise, and the creatine kinase remained greater than 100,000 IU/L. A nephrology consult was obtained because of the potential need for hemodialysis, but the patient continued to have an adequate urine output, and urine electrolytes demonstrated a retained ability to concentrate the urine.

The patient regained a normal mental status and related that the last thing he remembered was smoking crack cocaine. Over the course of one week, the creatine kinase fell, and the serum creatinine stabilized at 1.7 mg/dL. Referrals were made to an outpatient detoxification center and a primary physician, and the patient was discharged.

TABLE CS1–1 Xenobiotics, Potentiators and Interactions Associated with Life-Threatening Hyperthermia

- Alcohol withdrawal
- Anticholinergics (atropine, antihistamines)
- Malignant hyperthermia
- Monoamine oxidase inhibitor overdose
- Neuroleptic malignant syndrome
- Oxidative phosphorylation uncouplers (dinitrophenol, salicylates)
- Phencyclidine
- Sedative–hypnotic withdrawal
- Serotonin toxicity
- Sympathomimetics (cocaine, amphetamines)
- Thyrotoxicosis factitia

TABLE CS1–2 Major Organ System Complications of Hyperthermia

Organ System	Complication
Brain	Cerebral edema
Lungs	Acute respiratory distress syndrome
Heart	Myocardial stunning, myocardial infarction, dysrhythmias
Gastrointestinal	Hepatic injury
Kidneys	Acute kidney injury
Hematological	Coagulopathy
Muscle	Rhabdomyolysis

3 INITIAL EVALUATION OF THE PATIENT: VITAL SIGNS AND TOXIC SYNDROMES

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For more than 200 years, American health care providers have attempted to standardize their approach to the assessment of patients. At the New York Hospital in 1865, pulse rate, respiratory rate, and temperature were incorporated into the bedside chart and called "vital signs."[9] It was not until the early part of the 20th century, however, that blood pressure determination also became routine. Additional components of the present standard emergency assessment, such as oxygen saturation by pulse oximetry, capillary blood glucose, and pain severity, are sometimes considered vital signs. Although they are essential components of the clinical evaluation and are important considerations throughout this text, they are not discussed in this chapter. Similarly, invasive and noninvasive modalities for the bedside assessment of organ function, such as capnometry, focused ultrasonography, arterial Doppler analysis, arterial catheterization, and tissue oxygen saturation, are not discussed here but appear in relevant sections of this textbook.[1]

In the practice of medical toxicology, vital signs play an important role beyond assessing and monitoring the overall status of a patient, because they frequently provide valuable physiologic clues to the toxicologic etiology and severity of an illness. The vital signs also are a valuable parameter used to assess and monitor a patient's response to treatment and antidotal therapy.

Table 3–1 presents the normal vital signs for various age groups. However, this broad range of values considered normal should serve merely as a guide. Only a complete assessment of a patient can determine whether or not a particular vital sign is truly clinically normal in the particular clinical setting. This table of normal vital signs is useful in assessing children because normal values for children vary considerably with age, and knowing the range of normal variation is essential. Normal rectal temperature in adults is defined as 96.8° to 100.4°F (35°–38°C), and, although less reliable, a normal oral temperature is considered 95.0° to 99.6°F (36.4°–37.5°C).

The difficulty in defining what constitutes "normal" vital signs in an emergency setting is inadequately addressed and may prove to be an impossible undertaking. Published normal values likely have little relevance for an acutely ill or anxious patient in the emergency setting, yet that is precisely the environment in which abnormal vital signs must be identified and addressed. Even in nonemergent situations, "normalcy" of vital signs depends on the clinical condition of the patient. A sleeping or comatose patient may have physiologic bradycardia, although a slow heart rate is often appropriate for this low energy requiring state. For these reasons, descriptions of vital signs as "normal" or "stable" are too nonspecific to be meaningful and therefore should never be accepted as defining normalcy in an individual patient. Conversely, no patient should be considered too agitated, too young, or too gravely ill for the practitioner to obtain a complete set of vital signs; indeed, these patients urgently need a thorough evaluation that includes all of the vital signs. Also, the vital signs must be recorded as accurately as possible, first in the prehospital setting, again, with precision and accuracy, as soon as a patient arrives in the emergency department (ED), and continuously thereafter as clinically indicated to identify trends.

Many xenobiotics affect the autonomic nervous system, which in turn affects the vital signs via the sympathetic pathway, the parasympathetic pathway, or both. Meticulous attention to both the initial and repeated determinations of vital signs is of extreme importance in identifying a pattern of changes suggesting a particular xenobiotic or group of xenobiotics. The value of serial monitoring of the vital signs is demonstrated by the patient who presents with anticholinergic toxicity and receives the antidote, physostigmine. In this situation, it is important to recognize when tachycardia becomes bradycardia (eg, anticholinergic syndrome followed by physostigmine excess). Meticulous attention to these changes ensures that the therapeutic interventions should be modified or adjusted accordingly.

Similarly, a patient who has opioid-induced bradypnea (a decreased rate of breathing) will either normalize or develop tachypnea (an increased rate of breathing) after the administration of the opioid antagonist naloxone. The analysis becomes exceedingly complicated when that patient is potentially exposed to two or more xenobiotics, such as an opioid combined with cocaine. In this situation, the effects of cocaine become "unmasked" by the naloxone used to counteract the opioid, and the clinician must then differentiate naloxone-induced opioid withdrawal from cocaine toxicity. The assessment starts by analyzing diverse information, including vital signs, history, and physical examination.

Table 3–2 describes the most typical toxic syndromes. This table includes only vital signs that are thought to be characteristically abnormal or pathognomonic and directly related to the toxicologic effect of the xenobiotic. The primary purpose of the table, however, is to include many findings, in addition to the vital signs, that together constitute a toxic syndrome. Mofenson and Greensher[8] coined the term *toxidromes* from the words *toxic syndromes* to describe the groups of signs and symptoms that consistently result from particular toxins. These syndromes are usually best described by a combination of the vital signs and clinically apparent end-organ manifestations. The signs that prove most clinically useful are those involving the central nervous system (CNS; mental status), ophthalmic system (pupil size), gastrointestinal system (peristalsis), dermatologic system (skin dryness versus diaphoresis), mucous membranes (moistness versus dryness), and genitourinary system (urinary retention versus incontinence).

Table 3–2 includes some of the most important signs and symptoms and the xenobiotics most commonly responsible for these manifestations.

TABLE 3–1 Normal Vital Signs by Age[a]

Age	*Systolic BP (mm Hg)*	*Diastolic BP (mm Hg)*	*Pulse (beats/min)*	*Respirations (breaths/min)[b]*
Adult	120	80	50–90	16–24
16 years	≤120	<80	80	16–30
12 years	119	76	85	16–30
10 years	115	74	90	16–30
6 years	107	69	100	20–30
4 years	104	65	110	20–30
4 months	90	50	145	30–35
2 months	85	50	145	30–35
Newborn	65	50	145	35–40

[a]The normal rectal temperature is defined as 96.8°F to 100.4°F (35°–38°C) for all ages. For children 1 year of age or younger, these values are the mean values for the 50th percentile. For older children, these values represent the 90th percentile at a specific age for the 50th percentile of weight in that age group.

These respiration values were determined in the emergency department and may be environment and situation dependent.

BP = blood pressure.

TABLE 3–2 Toxic Syndromes

	Vital Signs								
Group	*BP*	*P*	*R*	*T*	*Mental Status*	*Pupil Size*	*Peristalsis*	*Diaphoresis*	*Other*
Anticholinergics	–/↑	↑	±	↑	Delirium	↑	↓	↓	Dry mucous membranes, flush, urinary retention
Cholinergics	±	±	±	–	Normal to depressed	±	↑	↑	Salivation, lacrimation, urination, diarrhea, bronchorrhea, fasciculations, paralysis
Ethanol or sedative–hypnotics	↓	↓	↓	–/↓	Depressed, agitated	±	↓	–	Hyporeflexia, ataxia
Opioids	↓	↓	↓	↓	Depressed	↓	↓	–	Hyporeflexia
Serotonin toxicity	↑	↑	–/↑	–/↑	Normal to agitated delirium	–/↑	↑	↑	Clonus, tremor, seizures
Sympathomimetics	↑	↑	↑	↑	Agitated	↑	–/↑	↑	Tremor, seizures diaphoresis
Withdrawal from ethanol or sedative–hypnotics	↑	↑	↑	↑	Agitated, disoriented hallucinations	↑	↑	↑	Tremor, seizures diaphoresis
Withdrawal from opioids	↑	↑	–	–	Normal, anxious	↑	↑	↑	Vomiting, rhinorrhea, piloerection, diarrhea, yawning

↑ = increases; ↓ = decreases; ± = variable; – = change unlikely; BP = blood pressure; P = pulse; R = respirations; T = temperature.

A detailed analysis of each sign, symptom, and toxic syndrome can be found in the pertinent chapters throughout the text. In this chapter, the most typical toxic syndromes are considered to enable the appropriate assessment and differential diagnosis of a poisoned patient.

In considering a toxic syndrome, the reader should always remember that the actual clinical manifestations of a poisoning are far more variable than the syndromes described in Table 3–2. The concept of the toxic syndrome is most useful when thinking about a clinical presentation and formulating a framework for assessment. Although some patients present in a "classic" fashion, others manifest partial toxic syndromes or formes frustes. These incomplete syndromes still provide at least a clue to the correct diagnosis. It is important to understand that incomplete or atypical presentations (particularly in the presence of multiple xenobiotics) do not necessarily imply less severe disease and, therefore, are comparably important to appreciate.

In some instances, an unexpected combination of findings is particularly helpful in identifying a xenobiotic or a combination of xenobiotics. For example, a dissociation between such typically paired changes as an increase in pulse with a decrease in blood pressure (cyclic antidepressants or phenothiazines) or the presentation of a decrease in pulse with an increase in blood pressure (ergot alkaloids) may be extremely helpful in diagnosing a toxic etiology. The use of these unexpected or atypical clinical findings is demonstrated in Chap. 16.

BLOOD PRESSURE

Xenobiotics cause hypotension by four major mechanisms: decreased peripheral vascular resistance, decreased myocardial contractility, dysrhythmias, and depletion of intravascular volume. Many xenobiotics initially cause orthostatic hypotension without marked supine hypotension, and any xenobiotic that affects autonomic control of the heart or peripheral capacitance vessels may lead to orthostatic hypotension (Table 3–3). Hypertension from xenobiotics is caused by CNS sympathetic overactivity, increased myocardial contractility, increased peripheral vascular resistance, or a combination thereof.

Blood pressure and pulse rate may vary significantly as a result of changes in receptor responsiveness, degree of physical fitness, and degree of vascular elasticity. Changing patterns of blood pressure often assist in the diagnostic evaluation: overdose with a monoamine oxidase inhibitor characteristically causes an initial normal blood pressure followed by hypertension, which in turn is followed abruptly by severe hypotension (Chap. 71).

PULSE RATE

Extremely useful clinical information can be obtained by evaluating the pulse rate (Table 3–4 and Chap. 16). Although the carotid artery is usually easily palpable, for reasons of both safety and reliability, the brachial artery is preferred in infants and the radial artery in adults older than 60 years. The normal heart rate for adults was defined by consensus studies suggesting that 95% of the population has bradycardia and tachycardia thresholds of 50 beats/min and 90 beats/min, making absolute definitions unrealistic, particularly in the ED.

TABLE 3–3 Common Xenobiotics That Affect the Blood Pressure[a]

Hypotension	*Hypertension*
α_1-Adrenergic antagonists	α_1-Adrenergic agonists
α_2-Adrenergic agonists (central)	α_2-Adrenergic agonists (central) (early)
β-Adrenergic antagonists	α_2-Adrenergic antagonists
β_2-Adrenergic agonists	Ergot alkaloids
Angiotensin-converting enzyme inhibitors	Ethanol and sedative-hypnotic withdrawal
Angiotensin receptor blockers	Lead (chronic)
Antidysrhythmics	Monoamine oxidase inhibitors (overdose early and drug–food interaction)
Calcium channel blockers	Nicotine (early)
Cyanide	Phencyclidine
Cyclic antidepressants	Sympathomimetics
Ethanol and other alcohols	
Iron	
Methylxanthines	
Nitrates and nitrites	
Nitroprusside	
Opioids	
Phenothiazines	
Phosphodiesterase-5 inhibitors	
Sedative–hypnotics	

[a]Chapter 16 lists additional xenobiotics that affect hemodynamic function.

TABLE 3–4 Common Xenobiotics That Affect the Pulse Rate[a]

Bradycardia	*Tachycardia*
α_2-Adrenergic agonists (central)	α_1-Adrenergic antagonists
β-Adrenergic antagonists	Anticholinergics
Baclofen	Antipsychotics
Calcium channel blockers (nondihydropyridine)	β-Adrenergic agonists
Carbamates	Cyclic antidepressants
Cardioactive steroids	Disulfiram–ethanol interaction
Ciguatoxin	Ethanol and sedative–hypnotic withdrawal
Ergot alkaloids	Iron
γ-Hydroxybutyric acid	Methylxanthines
Opioids	Phencyclidine
Organic phosphorus compounds	Sympathomimetics
Synthetic cannabinoids	Thyroid hormone
	Thiamine deficiency
	Yohimbine

[a]Chapter 16 lists additional xenobiotics that affect the heart rate.

Because pulse rate is the net result of a balance between sympathetic (adrenergic) and parasympathetic (muscarinic and nicotinic) tone, many xenobiotics that exert therapeutic or toxic effects or cause pain syndromes, hyperthermia, or volume depletion also affect the pulse rate. Whereas hypotension, such as that related to vasodilation or hypovolemia, generally leads to a reflex tachycardia, abrupt hypertension occasionally causes reflex bradycardia. Additionally, there is a direct correlation between pulse rate and temperature in that pulse rate increases approximately 8 beats/min for each 1.8°F (1°C) elevation in temperature.[7]

The inability to differentiate easily between sympathomimetic and anticholinergic xenobiotic effects by vital signs alone illustrates the principle that no single vital sign abnormality can definitively establish a toxicologic diagnosis. In trying to differentiate between a sympathomimetic and anticholinergic toxic syndrome, it should be understood that although tachycardia commonly results from both sympathomimetic and anticholinergic xenobiotics, when tachycardia is accompanied by diaphoresis or increased bowel sounds, sympathomimetic toxicity is suggested, but when tachycardia is accompanied by decreased sweating, absent bowel sounds, and urinary retention, anticholinergic toxicity is likely.

RESPIRATORY RATE

Establishment of an airway and evaluation of respiratory status are the initial priorities in patient stabilization. Although respirations are typically assessed initially for rate alone, careful observation of the depth and pattern is essential (Table 3–5) for establishing the etiology of a systemic illness or toxicity.[3] Unfortunately, very few investigators have actually measured the respiratory rate in large populations of normal people, let alone in ED patients. Two papers investigating respiratory rates in ED patients differ substantially in their determinations of normal ranges from the remainder of the literature.[4,5] The combined results of these investigations suggest "normal" respiratory rates are 16 to 24 breaths/min in adults with more rapid rates that are inversely related to age in children.

TABLE 3–5 Common Xenobiotics That Affect Respiration[a]

Bradypnea	*Tachypnea*
α_2-Adrenergic agonists (central)	Cyanide
Botulinum toxin	Dinitrophenol and congeners
Carbamates	Epinephrine
Elapidae venom	Ethylene glycol
Ethanol and other alcohols	Hydrogen sulfide
γ-Hydroxybutyric acid	Methanol
Magnesium	Methemoglobin producers
Neuromuscular blockers	Methylxanthines
Opioids	Nicotine (early)
Organic phosphorus compounds	Pulmonary irritants
Sedative–hypnotics	Salicylates
Tetanospasmin	Sympathomimetics
Tetrodotoxin	

[a]Chapter 28 lists additional xenobiotics affecting respiratory rate.

Hyperventilation means an increase in minute ventilation above normal and it may result from tachypnea, hyperpnea or both. Tachypnea can also produce hypoventilation. When hyperventilation results solely or predominantly from hyperpnea, clinicians may miss this important finding entirely, instead erroneously describing such a hyperventilating patient as normally ventilating or even *hypoventilating* if bradypnea is also present. The ventilatory status of the patient must be viewed in the context of the patient's physiologic condition. Even in patients admitted to an intensive care unit and therefore with a high likeliness of illness, the sensitivity of clinical assessment on the ability to predict severe respiratory dysfunction was only 70%.[11]

Hyperventilation results from the direct effect of a CNS stimulant, such as salicylates, on the brainstem. However, salicylate poisoning characteristically produces hyperventilation by tachypnea, but it also produces hyperpnea with or without tachypnea. Metabolic acidosis, whether of a toxicologic etiology or not, typically results in an attempt by the patient to normalize her or his blood pH through hyperventilation. Pulmonary injury from any source, including aspiration of gastric contents, may lead to hypoxemia with a resultant tachypnea. Later, tachypnea may change to bradypnea, hypopnea (shallow breathing), or both. Bradypnea may occur when a CNS depressant acts on the brainstem. A progression from fast to slow breathing may also occur in a patient exposed to increasing concentrations of cyanide or carbon monoxide.

TEMPERATURE

Temperature evaluation and control are critical, yet our ability to recognize abnormal temperatures by clinical examination is limited.[6] However, temperature assessment can be done only if safe and reliable equipment is used. The risks of inaccuracy are substantial when an oral temperature is taken in a tachypneic patient, an axillary temperature or a temporal artery temperature is taken in any patient (especially those found outdoors), or a tympanic temperature is taken in a patient with cerumen impaction.[10] Obtaining rectal temperatures using a nonglass probe is essential for safe and accurate temperature determinations in agitated individuals and is considered the standard method of temperature determination in this textbook. Although concerns for infection control have limited the use of rectal temperatures, screening by other routes is acceptable, but rectal temperature assessments remain the most accurate.[10] Rectal temperatures should be obtained when the temperature obtained by another route is not consistent with the expected clinical findings.

The core temperature or deep internal temperature (T) is relatively stable (98.6° ± 1.08°F; 37° ± 0.6°C) under normal physiologic circumstances. Hypothermia (T <95.0°F; <35°C) and hyperthermia (T >100.4°F; >38°C) are common manifestations of toxicity. Severe or significant hypothermia and hyperthermia, unless immediately recognized and managed appropriately, may result in grave complications and inappropriate or inadequate resuscitative efforts. Life-threatening hyperthermia (T >106°F; >41.1°C) from any cause may lead to extensive rhabdomyolysis, myoglobinuric kidney failure, and direct liver and brain injury and must therefore be identified and corrected immediately.

Hyperthermia often results from a distinct neurologic response to a signal demanding thermal "upregulation." This signal can be from internal generation of heat beyond the capacity of the body to dissipate heat, such as occurs in association with agitation or mitochondrial uncoupling, or from an externally imposed physical or environmental factor, such as the environmental conditions causing heat stroke or the excessive swaddling in clothing causing hyperthermia in infants. Fever, or pyrexia, is hyperthermia caused by an elevation in the hypothalamic thermoregulatory setpoint.[2]

Regardless of etiology, core temperatures higher than 106°F (41.1°C) are extremely rare unless normal feedback mechanisms are overwhelmed.