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Editors

Critical Care Toxicology

Diagnosis and Management of the Critically Poisoned Patient

Second Edition

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With 675 Figures and 487 Tables

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Foreword

Critical Care Toxicology belongs in every critical care unit, emergency department, poison center, library, emergency response center, and on the most easily reached shelf for anyone interested in or who comes in contact with medical toxicology. This masterful compilation of information has many attributes, among which are:

- Evidence based well-referenced information
- Editors and authors who are experts in their fields
- Concise and clear presentation
- Tables that convey critical data
- Figures and diagrams that are clinically relevant
- Paragraph headers that allow focused access to information
- Calculations and formulas that are fully explained
- Lists of treatment materials to obtain in advance with contact information of unusual items
- Therapeutic dosages that are detailed enough to be utilized without additional references

In most cases, diagnostic and therapeutic information can be obtained in a few minutes given the book's careful organization. For those patients presenting with complicated or multiple exposures, the structure provides a straightforward method of rapidly developing and working through a differential diagnosis.

The quality of this book should come as no surprise after looking at the impressive listing of authors. The editors, each of whom I have known, worked with, and respected for many years, have selected an international group of experts whose credibility is unmatched. They represent the best of our profession of medical toxicology and have written a large percentage of the most important and groundbreaking publications in our field. The editors and authors are the most sought-after educators in our annual toxicology meetings around the world and provide clinical expertise as well as leadership and training for all of us who work in this wide and varied area.

In the preface to the first edition of *Critical Care Toxicology*, the word "passion" occurs in the very first sentence. For all of us who have ever written a scientific monograph, paper, chapter, book, or prepared a teaching session, the word passion certainly defines a major requirement for preparation of materials

that will communicate the knowledge that is intended. It takes time and effort to write something that will stand the test of time, and when written with passion it means that the author has not skipped over anything and left nothing of importance unaddressed. It requires thorough knowledge of the subject, real world experience, fully researched literature, and draft after draft until communication is assured. When reading this book, it is apparent that the editors and authors have achieved their goal.

Before writing this foreword, the editors provided me with some chapters from the second edition. In reviewing four of them – "Acid-base," "Hypotension and Shock," "Seizures," and "Acute Respiratory Distress Syndrome" – it was readily apparent that this second edition is an improvement on an already excellent book. More current materials are included as expected, but using these chapters as examples the authors have dramatically improved this book. Acid-base in the critical care setting is a complicated and often difficult issue. To address that the authors have doubled the length of this chapter and substantially added information which will be valuable to all who utilize it. The chapters on hypotension and shock and acute respiratory distress syndrome have been broken out of their previous locations and addressed comprehensively to reflect their importance. The chapter on seizures has also been doubled in length and contains a considerable amount of new information that is clearly presented.

The authors have also added speed of access to this book through the use of a table of contents at the beginning of each chapter. This further enhances the ability of the reader to get to an answer under emergent circumstances.

The book also has another purpose than just providing critical information in a clinical setting. It provides a very readable and understandable educational experience for all those who are studying this area. This must include addressing controversial areas with which the reader may be familiar and if not familiar ought to be familiar, and this book engages all of this.

Even those of us who have been in this field for a long time stand to learn something from this book. The discussion of the strong anion gap in the acid-base chapter coupled with the very practical explanations of the other factors in this important area is the clearest I have ever read. An area in which I have little knowledge is malignant hyperthermia, and this chapter provides a clear explanation along with even a phone number and website to get additional updated information in what is apparently a rapidly evolving issue. The editors clearly want readers to get the right answers to their questions.

Critical Care Toxicology covers all of the areas in medical toxicology in a series of well-written chapters following the excellent chapters that provide an approach to the critically poisoned patient and an understanding of toxic syndromes. Images of various aspects of toxicological encounters provide visual reinforcement of the written materials.

The index is very well done and comprehensive. Unlike the 7th edition in 1959 of Nelson's pediatric text where the editor's daughter, who hated having to produce the index, entered under B "Birds, for the" and listed the entire book, the index of *Critical Care Toxicology* was obviously prepared by someone who had a passion for helping readers get to answers.

Critical Care Toxicology provides a very valuable contribution to all aspects of medical toxicology from education to, as the title states, critical care. It should be readily accessible to everyone who may face this issue from forming a differential diagnosis to rendering care.

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Preface to the Second Edition

Those readers who are familiar with the first edition of *Critical Care Toxicology* (CCT) know that it was about passion – our collective passion for caring for patients with the group of fascinating physiological derangements caused by exogenous chemical exposures. While our passion for the field of clinical toxicology remains unabated, an additional theme that characterizes the second edition of *Critical Care Toxicology* is scientific evidence.

In the 10 years since the publication of the first edition, a considerable body of new scientific evidence has emerged, new antidotes have become available, and systematic reviews and meta-analyses have become more commonplace in the field of clinical toxicology. Seizing upon the opportunity to provide a compendium of this accumulated evidence-based knowledge, we have worked with our chapter authors to assure that they have stayed true to the existing body of empirical data and, in the many places, where data gaps exist identify them so that the user of this book will understand the basis for the treatment recommendations we provide. In order for the user of CCT to quickly discern the veracity of the evidence supporting the treatment recommendations provided, we have adopted the US Public Health Service's rating of scientific evidence. These gradings allow the reader to instantly know the level of scientific support for various treatment recommendations and thus to be able to rely most heavily on well-supported therapeutic modalities.

We are highly cognizant of the reality that there are many areas where the evidence base relating to treatment decisions is insufficient. Nevertheless, the clinician treating the critically poisoned patient still requires guidance. Given that so many of our chapter authors represent the world's authority on their topic, we have also strongly encouraged them to give their highly informed opinions on how to proceed in the many areas where there are clear knowledge gaps. Where they have supplied these opinions they have been identified as such, and we have worked with them to also explain their thought processes underlying these opinions.

We are very proud of the group of chapter authors that have been brought together in CCT. Where possible we have endeavored to recruit a group of international experts in their respective subject matter who are also experienced clinicians, proficient in the intensive care of patients poisoned by the toxins and toxicants they have addressed. This quest for such a uniquely qualified group of chapter authors has required us to seek out scholars from many areas of the world. Being such highly respected individuals, our chapter

authors are for the most part very busy with their various academic and clinical pursuits. We are greatly indebted to them for the generous donation of the time they gave us to not only produce their excellent chapters but also to put up with our compulsively detailed editing and challenges to them for justification of the information contained in their chapters. In most instances, they have done so because they were dedicated to the idea of working with us to achieve the goals enumerated above.

Critical Care Toxicology is not a static textbook in the traditional sense. The online version is a living dynamic document that can, and will, be updated as needed and new chapters will be provided beyond the date of the original publication of the current edition. In this way, we will feel confident that you, the reader of CCT, will have the most up-to-date information available to you in your care of your critically poisoned patients.

Jeffrey Brent
Keith Burkhart
Paul Dargan
Benjamin Hatten
Bruno Megarbane
Robert Palmer
Julian White

Preface to the First Edition

To us, this book is about passion. It is the result of the passion we share for the clinical challenges we face every day in caring for critically poisoned patients and in understanding their unique and enchanting pathophysiology and its therapeutic implications. This is a passion we hope to elicit in all who venture into the world of clinical toxicology as they read this book. To the medical toxicologist, the care of the seriously poisoned patients merges the diverse worlds of critical care, emergency medicine, pharmacology, altered drug pharmacokinetics (hence the term "toxicokinetics"), diagnostic challenges, multisystem involvement in often otherwise healthy patients, and the use of specific and often esoteric treatment strategies and antidotes.

Before embarking on the extraordinarily labor-intensive activity of generating a book of this depth and complexity, we queried the importance of producing another clinical toxicology textbook. We are aware of several excellent general clinical toxicology textbooks on the market and appreciate their attempts to achieve a far greater breadth than the present work. However, toxicology is such a broad field that general textbooks encompassing all of clinical toxicology necessarily must limit the extent of their coverage of the intensive care unit management of major poisonings. Thus, the intensivist, and critically poisoned patients, deserve a reference that specifically addresses their needs. This need is made all the more important by the life-threatening nature of many of these poisonings. Stark evidence of the complexity of just these issues is that to cover them adequately required 160 chapters and 1633 pages.

Our goal was to have the most knowledgeable and experienced medical toxicologists author relevant chapters. In order to achieve this goal we drafted our colleagues with unique experience and expertise worldwide. As witnessed by our contributor list, all continents, except Antarctica, are represented. We proudly boast that our collective chapter authors represent a significant proportion of the most experienced critical care toxicologists in the world. Medical toxicologists interested in acute care tend to be domiciled at the bedside, in poison centers, or both. Because of the highly clinical nature of this book, we selected authors with a predominantly bedside care orientation.

With the ready access to facts and data via the Internet, the very nature of hard copy books has changed dramatically. No longer is it necessary for books to be compendia of facts. However, electronic databases cannot convey the reasoned clinical approaches and the synthesis of pathophysiology with

clinical effects and treatment that characterizes the pages that follow. Certainly, important physiologic and monitoring parameters as well as drug dosages are amply provided. The degree to which they are included represents our view of the best balance between those that are important to know and the desire to dedicate as much space as necessary to an elucidation of relevant concepts and a critical discussion of therapeutic controversies. We have embraced rather than glossed over controversies. The reader will find that this is not simply a "how to" handbook. Our aim is to provide the practitioner with the data needed to care for his or her individual patients. As an aid to those who choose to delve more deeply into the concepts, approaches, and controversies in this book, chapters are well referenced with primary source citations.

It is our hope and expectation that this book will evoke the same passion in the reader that the subject does for us.

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About the Editors

Jeffrey Brent holds the rank of Distinguished Clinical Professor of Medicine, in the Division of Clinical Pharmacology and Toxicology, at the University of Colorado, School of Medicine. He holds secondary appointments in the Departments of Emergency Medicine and Pediatrics and in the Colorado School of Public Health.

Dr. Brent has received numerous awards and honors during his professional career. Among these are multiple career achievement awards, including the Louis Roche Award by the European Association of Poisons Centres and Clinical Toxicologists, the Career Achievement Award by the American Academy of Clinical Toxicology, the Ellenhorn Award by the American College of Medical Toxicology, and the Clinical Translational Toxicology Career Achievement Award by the Society of Toxicology.

A former President of the American Academy of Clinical Toxicology, Dr. Brent has also served on the board of directors of the American College of Medical Toxicology.

Dr. Brent has served as a consultant to the World Health Organization and to several US government agencies, including the Department of Health and Human Services, and the National Vaccine Program. Currently, he is an active consultant with the US Food and Drug Administration.

Dr. Brent is Director of a large National Institutes of Health and Food and Drug Administration supported multicenter research group in clinical toxicology known as the Toxicology Investigators Consortium.

Keith K. Burkhart Dr. Burkhart is the Senior Advisor for Medical Toxicology and Lead Medical Officer for the Biomedical Informatics Team in the Division of Applied Regulatory Science in the Office of Clinical Pharmacology within the Office of Translational Science in the Center for Drug Evaluation and Research at the FDA. He is board certified in Emergency Medicine and Medical Toxicology. He is a Clinical Professor of Emergency Medicine at the Penn State University. He practices critical care toxicology at the PinnacleHealth Hospital System. He is the former Medical Director of the Penn State Poison Center. Dr. Burkhart received his medical toxicology training at the Rocky Mountain Poison Center in Denver. He received his emergency medicine training at the University of Cincinnati. He is a graduate of the former Medical College of Pennsylvania, now Drexel University. He is a past President of the American College of Medical Toxicology. His FDA work focuses upon using bioinformatics and cheminformatics tools to data mine the FDA Adverse Event Reporting System to learn mechanistic insights into drug safety issues.

Paul Dargan Professor Paul I Dargan is a Consultant Physician and Clinical Toxicologist and Clinical Director at Guy's and St Thomas' NHS Foundation Trust, London, UK. He is also a Professor of Clinical Toxicology at King's College London. He has an active research program with a focus on recreational drug toxicity, new psychoactive substances, prescription medicine misuse, self-poisoning (in particular, paracetamol/acetaminophen), and heavy

metal toxicity (in particular, lead). He has published over 250 peer-reviewed papers and numerous book chapters. He is active in postgraduate training in clinical toxicology and in undergraduate education of medical students at King's College London Medical School. He is a board member of the European Association of Poisons Control Centres and Clinical Toxicologists, and the Asia Pacific Association of Clinical Toxicology. He sits on the UK Advisory Council on the Misuse of Drugs (ACMD) and the Scientific Committee of the European Monitoring Centre for Drugs and Drugs Addiction (EMCDDA). He is an expert adviser to a number of other bodies, including the US Food and Drug Administration (FDA) and the World Health Organization (WHO).

Benjamin Hatten Dr. Hatten received his M.D. in 2006 at the University of Texas – Southwestern Medical Center in Dallas, TX. After completion of this degree, he entered residency in emergency medicine at Denver Health Medical Center in Denver, CO. Subsequently, he entered the medical toxicology fellowship training at Oregon Health and Science University in Portland, OR. During his fellowship, he simultaneously obtained a Masters in Public Health in epidemiology and biostatistics. Upon completion of his fellowship and M.P.H. degree, he returned to Denver in 2013 and joined the faculty at the University of Colorado School of Medicine, the Rocky Mountain Poison and Drug Center, and Toxicology Associates. He is currently an Assistant Professor at the University of Colorado School of Medicine with a primary appointment in the Section of Medical Toxicology, Department of Emergency Medicine. In addition, he is an attending physician at the Rocky Mountain Poison and Drug Center as well as a member of Toxicology Associates, Prof. LLC – a hospital based, single specialty medical group dedicated solely to medical toxicology. Dr. Hatten is board certified in both emergency medicine and medical toxicology.

Bruno Mégarbane is Professor of Critical Care Medicine at Paris Diderot University and directs a research team at INSERM UMRS-1144. He is the Head of the Department of Medical and Toxicological Critical Care at Lariboisière Hospital, Assistance Publique – Hôpitaux de Paris, in Paris, France. He is the current President of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT). He conducted several clinical and experimental studies in clinical toxicology, mainly regarding mechanisms of opioid-related respiratory toxicity, prognostic factors of life-threatening poisonings, and management of refractory cardiotoxicant poisonings using ECMO. He is a member of the EXTRIP group and an Associate Editor for *Clinical Toxicology*.

Robert Palmer Clinical Assistant Professor, Medical Toxicology, Emergency Medicine, School of Medicine, University of Colorado, Aurora, CO, USA. Attending Toxicologist and Faculty, Medical Toxicology Fellowship Program, Rocky Mountain Poison and Drug Center, Denver Health and Hospitals Authority, Denver, CO, USA.

Dr. Robert Palmer received his undergraduate degree in chemistry from the University of Idaho. His M.S. and Ph.D. degrees were obtained in organic-medicinal chemistry from the University of Washington in Seattle. He completed a postdoctoral appointment at the University of Washington Health Sciences Center, followed by joining the faculty at the University of New Mexico in Albuquerque. Dr. Palmer then relocated to Colorado and completed a fellowship in clinical toxicology at the Rocky Mountain Poison and Drug Center (RMPDC) in Denver, CO. He is board certified in clinical toxicology

and an elected Fellow of the American Academy of Clinical Toxicology. Dr. Palmer maintains a faculty position at RMPDC teaching in the medical toxicology fellowship program, as well as serving as an attending toxicologist on the medical toxicology clinical service. He is a member of multiple medical and scientific associations and lectures locally, nationally, and internationally. He has authored over 50 scientific papers and more than 30 book chapters. Among his clinical and research interests are postmortem toxicology and opioid abuse.

Julian White is Professor and Head of Toxinology at the Women's and Children's Hospital, Adelaide, Australia. He has been treating cases of envenoming since he graduated from the University of Adelaide Medical School over 40 years ago and in 1990 was invited to found the Toxinology Dept., WCH. Author of hundreds of papers, monographs, book chapters, and books, mostly on aspects of toxinology, he is internationally known for his work as a clinical toxinologist and has presented at many international meetings, mostly by invitation. In 1997, he co-founded the Clinical Toxinology Short Course, through the University of Adelaide, and this internationally recognized course, the only one of its type, is run every 2 years, plus mini-versions at selected medical meetings, and attracts both an international expert faculty and doctors attending from many nations. Julian has been involved in aspects of venom research and clinical research throughout most of his career. Since 1994, he has been the national consultant on envenoming for the sole Australian antivenom producer, CSL Ltd (now Seqirus), via his hospital (WCH; he is not paid by CSL/Seqirus). He has been an occasional consultant on clinical toxinology to WHO since about 1988 and to Australian Poisons Information Centres since the 1990s. A current focus of his activity is the Myanmar Snakebite Project, a large foreign aid project, funded by the Australian Government, aiming to improve outcomes for snakebite patients in that country. He is also developing a higher-level training program for clinical toxinology at the international level, through his role as Chair of the Board of Clinical Toxinology of the International Society on Toxinology

(IST); he is also Secretary of IST and is on the editorial board of *Toxicon*. He founded the Clinical Toxinology Resources Website (www.toxinology.com) in 2002. In 2015, he was presented with an award for "Outstanding Contribution to Medicine" by the Australian Medical Association and in 2016 was made a Member of the Order of Australia (AM) for his work in clinical toxinology. Julian is married, has two adult children, and lives with his wife in the Adelaide Hills, when not traveling overseas to meetings.

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Part I

General Management of the Critically Poisoned Patient

The Critically Poisoned Patient

1

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Medical toxicology is a medical subspecialty focusing on the diagnosis, management, and prevention of poisoning and other adverse health effects due to medications, drug overdose, acute drug abuse problems, chemical exposures, occupational and environmental toxins, biological agents, and envenomations. Critical care is the specialized care of patients whose conditions are life-threatening and who require comprehensive care and constant monitoring, usually in intensive care units. The disciplines of critical care medicine and medical toxicology have been intertwined throughout medical history. Texts combining the principles of these closely related specialties may be traced to medieval times; Maimonides wrote his *Treatise on Poison and Their Antidotes* in 1198 [1]. In his *Treatise*, Maimonides outlined the classification, diagnosis, and antidotal therapy of poisonings and described some resuscitation methods of the age. He also, in undoubtedly what was among the first attempts to evaluate therapies critically, refuted many of the then-popular treatments. The need to continually reevaluate – and commonly refute – generally accepted therapies continues to this day. This book continues this tradition in the spirit

established by Maimonides, except, of course, with a more data-driven approach.

Descriptions of the use of specific antidotal therapy dates back to Homer's *Odyssey*, in which Ulysses was advised to use "moly," likely a natural cholinesterase inhibitor, to treat poisoning from anticholinergic plants such as *Datura stramonium* [2]. Other publications from ancient times addressing the use of poisoning therapies include Nicander's *Alexipharmaca*, or "that which keeps off poisons"; Dioscordes' *Materia Medica*; and Galen's *DeAntidotis* and *De Theriaca ad Pisonem* [3, 4].

The identification, diagnosis, and therapy of poisons began in Greek and Roman times, with classifications by Dioscordes of poisonings by source and speed of action [3]. The Greek Nicander and King Mithridates of Pontus described the use of "theriacs" and "alexipharmacas" as universal antidotes and red clay ingestion or induction of emesis with feathers or oil to prevent toxin absorption [3]. In addition to his general description of poisons, Maimonides suggested emesis by ingesting oil, water, and honey [1]. Antimony salt, also known as tartar emetic, was widely used to induce stomach emptying and functioned as a sedative and cathartic in the nineteenth century, but it was replaced in the early twentieth century by saltwater emetics, mustard powder, mechanical throat stimulation, copper sulfate, and apomorphine [5, 6]. Ipecac syrup was first employed to induce emesis in the seventeenth century and became the emetic of choice in the twentieth century. Gastric lavage was first advocated by Munro in 1769 and supported by the physicians Physik of Philadelphia, Jukes of Britain, Dupuytren of France, and Bryce of Edinburgh [7]. In the sixteenth century, Paracelcus emphasized the fundamental importance – and to this day, the often overlooked – dose relationship of chemicals and drugs and the need for scientific study of toxins. Charcoal to adsorb toxins was described in the eighteenth century and employed in self-experiments by Bertrand and Touery, who publicly ingested toxins followed by a dose of charcoal [8]. The "universal antidote" of magnesium oxide, tannic acid, and activated charcoal was touted as the definitive adsorbent of toxins throughout the twentieth century, until it was recognized to be inferior to activated charcoal alone [5]. Activated charcoal ultimately replaced other means of gastric decontamination beginning in the 1970s [8].

Textbooks establishing medical toxicology as a unique scientific specialty began to appear in the nineteenth century, with the publication of Orfila's *Traite des Poisons* in Paris in 1814, which emphasized experimental and forensic toxicology, followed by his student Christison's writing the first of several editions from Edinburgh of *Treatise on Poisons* in 1829 [9]. Christison reportedly first highlighted the lifesaving properties of artificial respiration in opium poisoning, showing the close relationship between medical toxicology and critical care medicine [7] (Fig. 1). Other texts of that era were Costill's *A Practical Treatise on Poisons* and Taylor's *On Poisons*, both published in 1848. Early texts of the twentieth century on clinical toxicology include Leschke's *Clinical Toxicology*; Driesbach's *Handbook of Poisoning*; Gleason, Gosselin, and Hodge's *Clinical Toxicology of Commercial Products*; and Jay Arena's *Poisoning*. Historical toxicology reference texts are listed in Table 1.

More specific therapies and antidotes to treat poisonings also date back in history. Beginning with Maimonides, some examples include the use of natural anticholinesterase inhibitors to treat anticholinergic poisoning, *Strychnos nuxvomica* (strychnine) as an arousal and emetic agent, and in the 1800s the use of rabbit brain to protect against *Amanita phalloides* mushroom poisoning [1, 6]. Physostigmine, an anticholinesterase inhibitor from the Calabar bean, reportedly was advocated for atropine poisoning by Christison's successor to the Chair of Medical Jurisprudence in Edinburgh, Thomas Fraser [7]. Arousal of the patient affected by opiate or sedative toxicity was popularized in the nineteenth and twentieth centuries, first by mechanical stimulation and later by the use of analeptics [7]. The latter included natural agents, such as caffeine, strychnine, cocaine, camphor, picrotoxin, and lobeline, and later synthetic agents, such as pentylenetetrazol, nikethamide, methylphenidate, and bemegride [10]. The use of analeptics eventually was

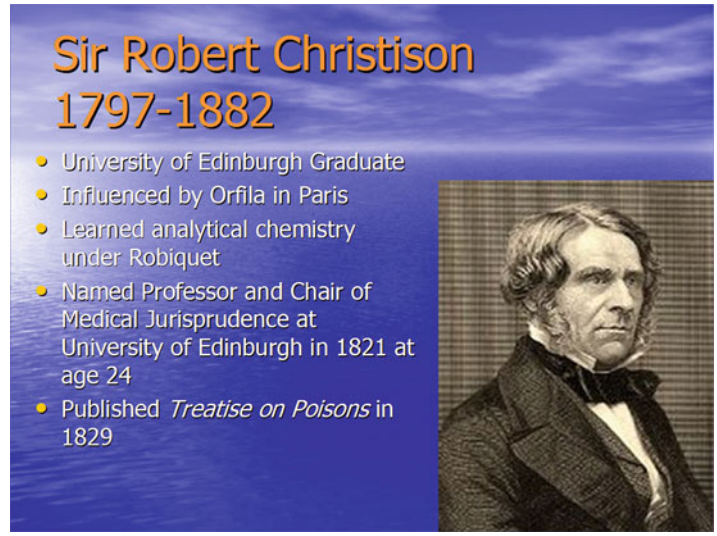

Fig. 1 Sir Robert Christison (Picture from Wikipedia under the Creative Commons license)

Table 1 Historical toxicology reference texts

Text	Author	Date	City
A Treatise on Poisons	M.C. Cooke	1770	London
Traite des Toxicologie	H.J.B. Orfila	1813	Paris
A Treatise on Poisons	Robert Christison	1829	Edinburgh
On Poisons	Alfred Taylor	1848	London
A Practical Treatise on Poisons	O.H. Costill	1848	Philadelphia
Micro-Chemistry of Poisons	Theodore Wormley	1869	New York
What to Do in Cases of Poisoning	William Murrell	1884	New York
A Manual of Medical Jurisprudence, General Toxicology	M.D. Ewell	1887	Boston
A Manual of Medical Jurisprudence and Toxicology	Henry Chapman	1896	Philadelphia
Handbuch der Toxicologie	A.K. Kunkel	1899	Jena
Manual of Toxicology	R.A. Witthaus	1911	New York
Handbook of Poisoning	R.H. Driesbach	1955	Los Altos, CA
Clinical Toxicology	C.H. Thienes	1955	Philadelphia, PA
Clinical Toxicology of Commercial Products	Gleason, Gosselin & Hodge	1957	Baltimore
Poisoning	J.M. Arena	1963	Springfield, IL
Medical Toxicology	Ellenhorn & Barceloux	1988	New York, NY

recognized to cause serious complications, such as hyperthermia, seizures, delirium, and increased mortality [10]. One of the most important advances in medical toxicology occurred in Scandinavia in the 1940s, when intensive supportive care with mechanical ventilation and cardiovascular support instead of analeptics was shown to reduce mortality from barbiturate poisoning from 20% to 2% [9, 10]. The overlap of critical care medicine and medical toxicology again was reinforced. This overlap further included the advocacy for poisoned patients of close observation and monitoring; airway protection; frequent pulmonary toilet; and careful attention to fluid and electrolyte balance, cardiovascular status, and position changes.

Later advances in toxicology in the twentieth century included the discovery of the opiate antagonists/agonists nalorphine and levallorphan and the pure antagonist naloxone, the

development of highly specific and sensitive assays for drugs and chemicals, greater understanding of pharmacokinetic principles, refinement of the principles of urinary pH manipulation to enhance drug excretion, and implementation of extracorporeal removal techniques. In the twenty-first century, progress has been made in the application of immunotherapies as antidotes, the development of additional antidotes to reverse specific drug effects, the use of lipid infusion and hyperinsulinemia-euglycemia therapies, the wide availability of toxicology information via computer software and the Internet, and the early use of toxicogenetics to determine individual variations in responses to toxins and treatments. The most important advance has been the increasing number of medical toxicologists providing bedside care.

Epidemiology

Incidence

Poisonings has become an epidemic worldwide, and since 2008 has been the leading cause of injury death in the United States, exceeding those from motor vehicle deaths and falls (Figs. 1 and 2) [11].

Since 2000, the rate of deaths from drug overdoses has increased by 137%, including a 200% increase in the rate of deaths involving opioids [12]. In 1999, poisoning deaths numbered 12,986, increasing to 20,950 in 2004, 38,851 in 2013, and to an astonishing 47,055 in 2014 [11–13] (Table 2). This represents an incidence of poisoning deaths of 4.4 per 100,000 population in 1999, to 7.1 in 2004, and to 14.7 in 2014. Of the 47,055 drug overdose deaths in 2014, 28,647 (61%) involved some type of opioid, including heroin (Fig. 3) [12]. Most drug poisoning deaths occur in those between the ages of 25–64, with the highest rate in the 45–54 age group (Fig. 4) [14]. In the United Kingdom, there is a reported incidence of 310 poisonings per 100,000 population, or 170,000 annual hospital visits, much lower than the US rate [14, 15]. Overdoses account for one fourth of all suicide attempts in England [16].

Hospital Visits

Poisonings typically represent 1–3% of all emergency department visits and account for 10% of all admissions for injuries [17, 18]. Reports of emergency department (ED) visits for poisonings in the United States range from 1.1 to 2.5 million per year, depending on the source, data collection methods, and definitions [19, 20]. The peak age

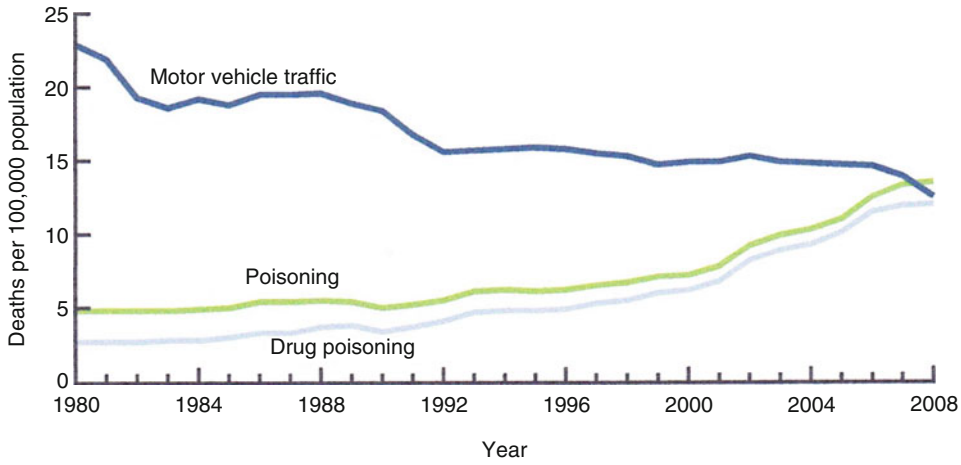

Fig. 2 Motor vehicle traffic, poisoning, and drug poisoning deaths rates: United States 1980–2008. From the US National Center for Health Statistics Data Brief. 81: December 2011

for ED visits for drug poisoning is 20–34 (Fig. 5). Hospital admissions for poisonings in the United States are about 130 per 100,000 population, or about 260,000 poisoning admissions in the United States each year [20, 21]. There are a reported 80,000 poisonings admissions each year in England, which result in about 400 deaths, or 0.5% of all such admissions [16]. According to another report, for all of the United Kingdom, the total admissions are about 170,000 annually [15]. It was reported in 2012 that drug-related admissions in England alone increased by 58% from 2000 to 2001 [22].

Emergency department reporting of poisoning cases is highly variable. In one study, an academic tertiary care emergency department called its regional poison control center (PCC) on 26% of its cases [19]. In many poisoning cases, the exposure was highly reported to the PCC (e.g., 95% for cyclic antidepressants), in contrast to cases of drug abuse (e.g., 5% for cocaine or heroin poisoning), which are not often reported to poison control centers. A review of an entire state's hospital admissions for poisoning indicated that the Oregon Poison Center was contacted for 54%, or 1,352, of 2,486 admissions in 1989 [23].

Drug overdoses typically account for approximately 2.5–5% of all intensive care unit (ICU) admissions in the United States, with an average length of stay (LOS) of 2.5–3.5 days [24, 25]. Poisonings have been reported to represent 11–14% of all ICU admissions in some countries [26–28]. In the 2014 annual report of the National Poison Data System of the AAPCC, 101,141 of the recorded 612,184 patients (16.5%) referred to a hospital were admitted to an ICU [29]. This number of annual US admissions to an ICU can be estimated to be only about one half of all ICU poisoning admissions, based on underreporting of cases to regional poison centers [19, 20]. Mortality

Table 2 Causes of death in the U.S. for 2013

Mortality 2013
All unintentional injury deaths
Number of deaths: 130,557
Deaths per 100,000 population: 41.3
Cause of death rank: 4
Unintentional fall deaths
Number of deaths: 30,208
Deaths per 100,000 population: 9.6
Motor vehicle traffic deaths
Number of deaths: 33,804
Deaths per 100,000 population: 10.7
Unintentional poisoning deaths
Number of deaths: 38,851
Deaths per 100,000 population: 12.3

From: Deaths: Final Data for 2013, Tables 9 and 18. http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64

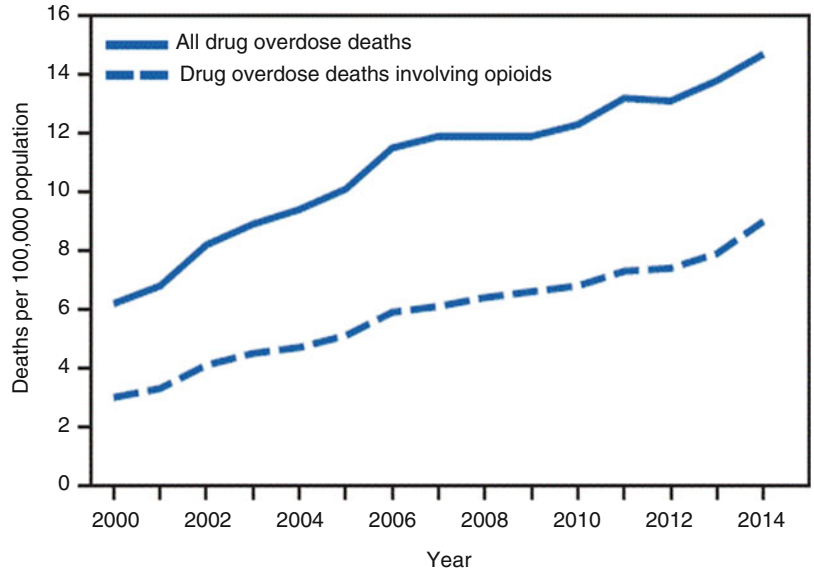

Fig. 3 From Ref. [12]

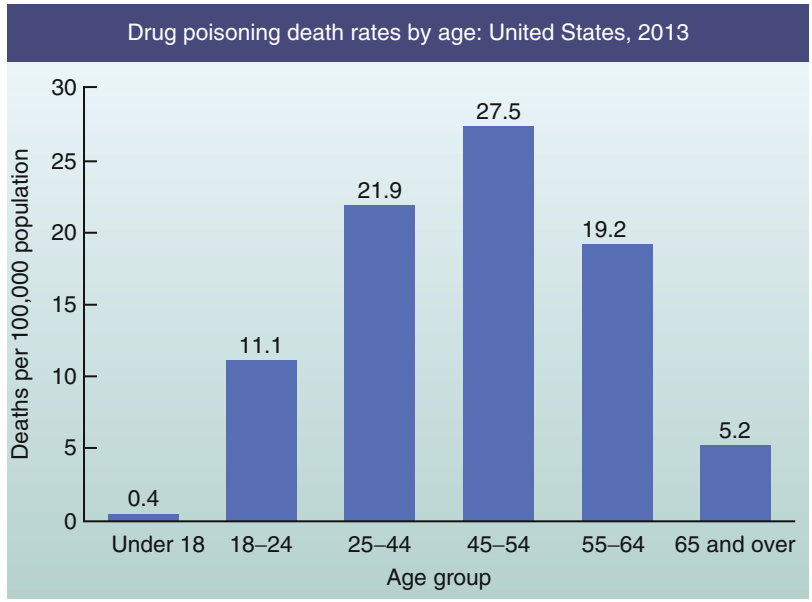

Fig. 4 Source US Centers for Disease Control and Prevention. National Center for Health Statistics, National Vital Statistics System, 2013

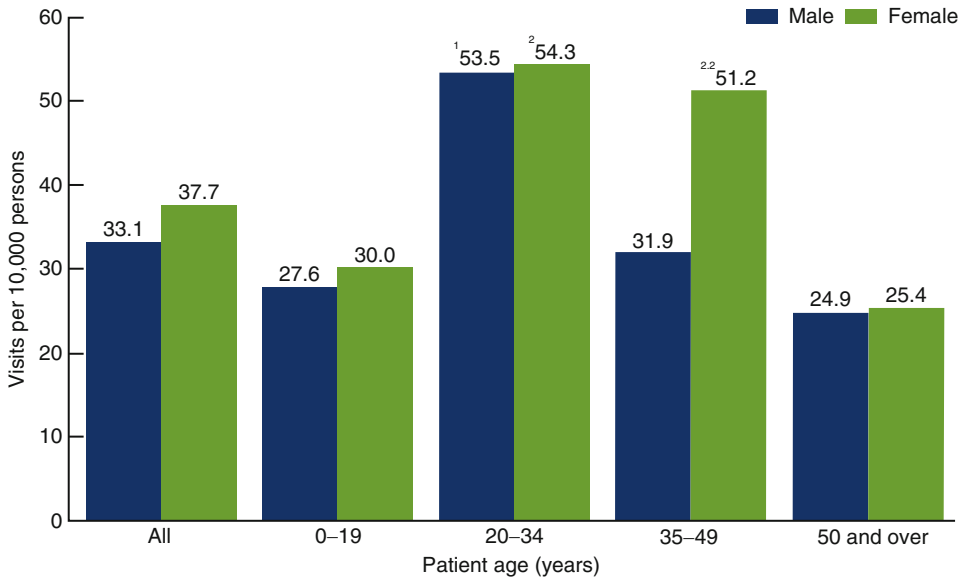

Fig. 5 Emergency Department visit rates for drug poisoning, by age and sex: United States, 2008–2011. From the US National Center for Health Statistics, Data Brief Number 196, April 2015

rates in the ICU for poisoning admissions range from 3 to 6% according to most reports [24–28].

Toxins

The history of drugs and toxins causing hospital admissions have evolved over the last several decades. It is interesting to review historically these changing patterns. Reports from Edinburgh describe the changing patterns of admissions from the 1960s into the 1990s. In 1966, 60% of the admissions to the Royal Infirmary of Edinburgh were for barbiturate poisoning [30]. Only in the teenage group did aspirin surpass barbiturates as a cause of toxicity. In this time period, poisoning

accounted for 10% of hospital admissions. In 1968, 74% of the patients had a LOS of 2 days or less [31]. Proudfoot reported on the subsequent 20-year trend (1967 through 1986) at the same center [9]. During this period, barbiturate poisonings decreased from 30% of admissions in the 1970s to a rare occurrence. Methaqualone was initially responsible for 10% of admissions but by the mid-1970s was almost no longer seen. A predominance of benzodiazepine overdoses subsequently replaced barbiturates and methaqualone, their incidence increasing from 10% to approximately 40% of admissions in the 1970s. Throughout the 1970s, there was also a rapidly increasing admission percentage for paracetamol (acetaminophen), whereas there was a decreasing trend for salicylates.

Benzodiazepines were reported as the predominant ICU admission for poisonings in Stockholm, Sweden, from 1972 through 1985, increasing from 17% to 28% of the total number [32]. In 51% of these cases, a benzodiazepine was part of a polydrug overdose and in 21% of cases, benzodiazepines were the single ingestant. Benzodiazepine-alone admissions were intubated in 37% of cases, whereas the intubation rate was 47% if benzodiazepines were consumed with alcohol or as part of a polydrug overdose. Of the 702 ICU admissions, the complication rate was 9.8%. There were five fatalities related to respiratory insufficiency or aspiration pneumonia or both.

During the 1980s and 1990s, cyclic antidepressant poisoning was a predominant ICU admission diagnosis. In the Netherlands from 1994 through 1998, cyclic antidepressants constituted 33.3% of the total intoxication admissions and 2.4% of total admissions. The average LOS was 3.1 days. Of these patients, 40% were intubated and seven (2.7%) died [26].

In New Zealand in 1992, there was a similar experience [33]. Of all emergency department visits, 1.2% were poisoning related, yet these cases constituted 11% of ICU admissions. The incidence was 17 per 100,000 population. The most common agents ingested were cyclic antidepressants (19.6%), benzodiazepines (18%), acetaminophen (16.9%), and various antipsychotics [33]. The average LOS was 2.4 days. A 6-year review (1986 through 1991) of ICU admissions for poisoning was published in Australia [27]. Poisonings accounted for 13.8% of all admissions. The most common agents were benzodiazepines, ethanol, tricyclic antidepressants, acetaminophen, phenothiazines, and antihistamines. The mean age was 32, the mortality rate was 2%, and 6 of the 14 fatalities were from nonmedicinal products [27].

The introduction of flumazenil, a benzodiazepine antagonist at the γ-aminobutyric acid receptor site, reportedly had an impact on ICU care and LOS in Israel. Leykin and colleagues described acute poisonings treated in the ICU from 1982 through 1984 [34]. The predominant intoxicants were benzodiazepines (51%), tricyclics (25%), barbiturates (21%), and narcotics (11%). Flumazenil was believed to have contributed to a decreased ventilator time and LOS (from 4.8 to 3.1 days). The introduction of the safer antidepressants, selective serotonin reuptake inhibitors, also markedly reduced the ICU admission rates, LOS, and cost of care [35].

In many countries, nonmedicinals such as plants and pesticides remain a significant cause for ICU admissions and fatalities. Over a 15-year period in Hong Kong during the 1980s and 1990s, rates of medicinal poisoning admissions per 100,000 population ranged from 57.3 to 80.9 [36]. In the more recent years of the report, admissions for nonmedicinal poisonings decreased from 53 to 22 per 100,000 population. Overall, poisoning fatality rates have ranged from 2 to 4 per 100,000 population, with an increasing rate into the 1990s.

The climate can have an impact on environmental exposures. In South Africa, 15.5% of toxicology consultations are for plant, spider, snake, scorpion, mushroom, and insect poisoning [37]. In addition, frequent consultations occur for household, agricultural, and industrial agents, including cholinesterase inhibitors and other pesticides, volatiles, corrosives, and soaps. The pattern of pharmaceutical exposures is similar to that in many other countries, however. Acetaminophen is the most common (14.6%), followed by benzodiazepines (13.1%), aspirin and nonsteroidal antiinflammatory drugs (9.4%), antidepressants (6.7%), and cardiovascular agents (5.5%) [37].

In a report from Ecuador, only 26% of the reported poisoning cases were drug related [38]. The leading drugs were benzodiazepines (24%), acetaminophen (23%), aspirin (22%), and carbamazepine (11%). Except for carbamazepine, this experience is not too different from that in many other countries. The top four categories of nonmedicinal substances were organophosphate pesticides, which constituted 18% of all poisonings, followed by phosphorus (14%), rat poison (10%), and solvents (6%). Pesticides are often a leading category of poisoning in some developed and many underdeveloped countries. In one hospital in Turkey, pesticides followed analgesics as the second most common poisoning [39].

A few reports have focused on pediatric poisoning admissions. In a study from Boston during 1981 and 1982, 90 acute poisonings (52 accidental and 38 suicidal) constituted 1.1% of the 8,296 total admissions [40], 64% were medical ICU admissions and 4.5% of the total medical ICU admissions. The average LOS was 2.2 days. There was one fatality due to diphenoxylate. The most frequent agents responsible were alcohol (11), barbiturates (9), cyclic antidepressants (9), theophylline (8), aspirin (8), and benzodiazepines (8). A review of pediatric hospitalizations from the same children's hospital approximately a decade later (over a 4-year period from 1992 to 1995) documented a 0.9% admission rate for poisoning [41]. Two thirds of the 638 admissions for poisonings were medication related. Toddlers, age 1–5 years, accounted for 42% of admissions, and adolescents older than 12 years accounted for 45% of admissions. In the toddlers, lead, caustic agents, and benzodiazepines were the most common agents, whereas acetaminophen predominated in the adolescents. Antidepressants, antihistamines, and salicylates also accounted for a significant number of admissions. The LOS over this period decreased from 5.85 to 3.45 days [41].

The US state of Washington reviewed all hospital pediatric discharges over an 11-year period [42]. The incidence was 45 per 100,000 children per year. Intoxication accounted for 0.6% of the hospitalizations. Children aged 12–18 accounted for 75% of the admissions, whereas toddlers (age $\leq$5 years) accounted for 20% of the admissions. The fatality rate was 0.2%. The average LOS was 1 day (range 1–3 days). ICU issues related to pediatric poisoning are discussed in detail in Intensive Care of Pediatric Posioning Patients.

Currently, the best source for identifying the poisons, toxins, and toxidromes likely to cause hospital admissions is the ToxIC (Toxicology Investigators Consortium) Registry of the ACMT (American College of Medical Toxicology). Although the cases collected are less than the National Poison Data System of the AAPCC (American Association of Poison Control Centers), they better reflect those patients requiring inpatient care by medical toxicologists and intensivists. In 2014, 9,712 cases were entered from 47 medical toxicology services, providing care at 77 clinical facilities [43]. They included 81% of the accredited US medical toxicology fellowship sites, thus capturing the great majority of patients seen at the busier academic medical toxicology facilities. There is likely a bias in this data towards the sickest poisoned patients based on the type of facility and the active presence of a medical toxicology program. The ToxIC Registry recorded the referral services leading to admissions or inpatient consultations and found that almost all (93.5%) came from the emergency department, the admitting inpatient service, or by transfer from another facility [43]. Of concern was that only 0.1% of cases accounted for referral from a poison control center to a medical toxicology service, demonstrating a current lack of collaboration between poison centers and medical toxicology services. This presents a heretofore underutilized opportunity to greatly improve patient care by coordinating initial phone consultations with bedside care by toxicologists.

Pharmaceutical products exposure, particularly intentional, was the most common reason for consultation by a medical toxicologist, accounting for 61.7% of all cases. Accidental exposures to pharmaceuticals or toxins followed with 13.4% and organ system dysfunction at 3.8% [43] (Table 3). Adverse drug reactions represented only five of the total cases for medical toxicology consults, yet are increasing events which could benefit from medical toxicologist consultation. This demonstrates the need for collaboration

Table 3 Reasons for medical toxicology encounter/consultation

	N	(%)
Intentional exposure – pharmaceutical	4,803	(52.4)
Intentional exposure – nonpharmaceutical	913	(10.0)
Unintentional exposure – pharmaceutical	853	(9.3)
Unintentional exposure – nonpharmaceutical	379	(4.1)
Organ system dysfunction	347	(3.8)
Not documented	297	(3.2)
Withdrawal – opioids	270	(2.9)
Envenomation – snake	234	(2.6)
Withdrawal – ethanol	227	(2.5)
Ethanol abuse	194	(2.1)

From Rhyee et al. [43], p. 392

Table 4 Agent classes involved in medical toxicology consultation 2014

	N	(%)
Analgesic (nonopioid)	1,599	(12.8)
Sedative-hypnotic/muscle relaxant	1,546	(12.4)
Opioid	1,311	(10.5)
Antidepressant	1,301	(10.4)
Ethanol	849	(6.8)
Anticholinergic/antihistamine	761	(6.1)
Cardiovascular	713	(5.7)
Antipsychotic	689	(5.5)
Sympathomimetic	684	(5.5)
Anticonvulsant	421	(3.4)
Psychoactive	312	(2.5)
Envenomation	282	(2.3)

From Rhyee et al. [43], p. 393

between the Institute for Safe Medication Practices and poison control centers, medical toxicologists, and emergency departments to decrease the incidence of these events through diagnosis, treatment, reporting, education, and development of prevention strategies [44].

Nonopioid analgesics, particularly acetaminophen, were the most common medication involved (12.8%), as has been the case for many years (Table 4). Sedative-hypnotics were a close second agent class seen in 12.4%, then opioids in 10.5%, and antidepressants in 10.4%. In the category of individual psychoactive drugs of abuse, the rapid emergence of synthetic cannabinoid abuse accounted for 26% of these agents, second only to herbal marijuana (32.4%) in this class.

Table 5 Antidotal therapy

	N	(%)[a]
N-acetylcysteine	921	(31.1)
Naloxone/nalmefene	605	(20.4)
Sodium bicarbonate	322	(10.9)
Physostigmine	156	(5.3)
Thiamine	119	(4.0)
Fomepizole	90	(3.0)
Flumazenil	81	(2.7)
Glucagon	80	(2.7)
Calcium	77	(2.6)
Folate	74	(2.5)

[a]Percentages are of total antidotes administered
From Rhyee et al. [43], p. 406

The treatment required by the patients in the 2014 ToxIC Registry clearly exemplify the intertwined relationship between medical toxicology and critical care medicine. Of the 9,172 patients, antidotes were administered 2,962 times, or 51.8% of all treatments reported [43]. *N*-Acetylcysteine for acetaminophen overdoses and naloxone or nalmafene for opioids accounted together for over one half (51.5%) of all antidotes administered. The only other antidote given that was more than 10% of the total was sodium bicarbonate, usually used for cardiac conduction abnormalities, arrhythmias, or hypotension in sodium-channel blocker toxicity (Table 5). Specific toxicologic care was administered in conjunction with supportive general pharmacologic and nonpharmacologic care, frequently directed by intensivists. General pharmacologic supportive care was given 2,843 times, with benzodiazepines, opioids, and vasopressors being the most common (Table 6). Intravenous fluid administration and mechanical ventilation were the most commonly employed forms of supportive care, used 2,733 times collectively in the 9,172 patients (Table 7). The provision of critical care and medical toxicology together, either by the medical toxicologist or in collaboration with the intensivist, is essential for the recovery of the poisoned patient.

Table 6 Supportive care – pharmacological

	N	(%)[a]
Benzodiazepines	1,624	(7.1)
Opioids	261	(9.2)
Vasopressors	239	(8.4)
Antipsychotics	186	(6.5)
Glucose (concentration > 5%)	165	(5.8)
Anticonvulsants	78	(2.7)
Neuromuscular blockers	66	(2.3)
Albuterol (or other bronchodilator)	63	(2.2)
Corticosteroids	49	(1.7)
Antiarrhythmics	42	(1.5)
Antihypertensives	35	(1.2)
Beta blockers	27	(0.9)
Vasodilators	8	(0.3)
Total	2,843	(100)

[a]Percentages are of total number of treatments
From Rhyee et al. [43], p. 406

Table 7 Supportive care – nonpharmacological

	N	(%)[a]
IV fluid resuscitation	1,937	(67.6)
Intubation/ventilatory management	796	(27.8)
CPR	40	(1.4)
Hyperbaric oxygen	21	(0.7)
Transfusion	21	(0.7)
Pacemaker	15	(0.5)
Therapeutic hypothermia	13	(0.5)
Cardioversion	11	(0.4)
ECMO	7	(0.2)
Organ transplantation	4	(0.1)
Aortic balloon pump	1	(0.0)
Bypass	1	(0.0)
Total	2,867	(100)

CPR cardiopulmonary resuscitation, *ECMO* extracorporeal membrane oxygenation
[a]Percentages are out of the total number of treatments administered
From Rhyee et al. [43], p. 406

Fatalities by Toxin

Carbon monoxide (CO) is the second most common toxin causing poisoning fatalities, with alcohol the leading cause [45]. Most CO fatalities do not present to health care facilities but rather are found deceased and are coroner cases. Historically, in the 1950s and 1960s in Scotland, England, and Wales, barbiturates were the second most common cause. In 1962, there were 4,208 carbon monoxide deaths and 1987 barbiturate, sedative, and salicylate deaths combined [30]. In 1968, the fatality rate for all poisoning admissions at The Royal Infirmary of Edinburgh was 0.7% [31].

The Rhode Island Poison Center reviewed and compared its fatality reports with reports of the medical examiner for a 4-year period (1986 to 1989) [46]. Carbon monoxide was the most common cause of fatality, accounting for 98 of the 369 fatalities. After excluding cases of patients pronounced dead at the scene or dead on arrival, there were 112 cases in which the PCC could have been called; however, they were called on only 33 of these cases. In 10 of these cases, the poison center determined that they would have had additional recommendations that may have altered the outcome.

In Australia, deaths due to poisonings in 1989 and 1990 [47] had an average victim age of 36 years. Opiates primarily accounted for 40% of the cases, cyclic antidepressants accounted for 14%, and benzodiazepines accounted for 6.5%. Only 25 of the 231 patients reached the hospital alive. In a later Australian report, the Hunter Area Toxicology Service reported a 0.6% mortality rate from 1987 to 1995 [48].

Recent data show that most poisonings who are now admitted to a hospital have a low fatality rate. Hospital fatality rates in both the National Poison Data System of the AAPCC and the TOXIC Registry of the ACMT are about 1% in the years 2012–2014 [20, 43]. Currently, the most common causes of death in poisoned patients presenting to a hospital are pharmaceuticals, causing 83% of all deaths. Analgesics, and specifically opioids and acetaminophen, accounted for 39% of all deaths [20, 43]. Prescription opioids as a class were the most common, particularly methadone, followed closely by oxycodone and hydrocodone. However, illicit heroin was the single most common cause of death. From 2000 to 2014, there has been a 200% increase in opioid deaths, particularly heroin (Fig. 6).

Stimulants such as amphetamines and cocaine were the second most common cause of inhospital deaths, followed by cardiovascular drugs, antidepressants, and sedative/hypnotic/antipsychotic agents [20].

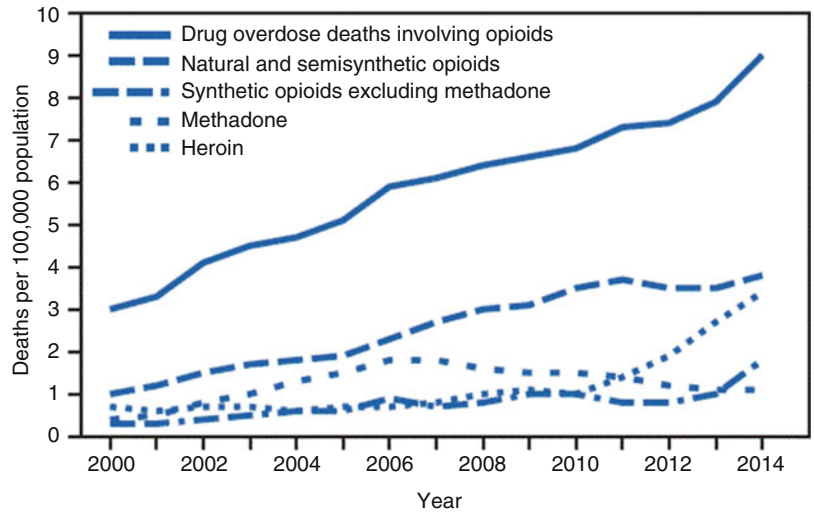

Fig. 6 Opioid deaths by class, 2000–2014 From Ref. [12]

Aspiration syndrome after drug overdose is a common complication and reason for ICU admission. In a study from 1987 through 1995, 39% of all community-acquired aspiration syndromes admitted to the ICU were secondary to drug overdose [49]. The overall mortality rate was 22%, but it was unclear how many of these fatalities followed drug overdose.

The aforementioned reports show that poisoning fatalities, mostly suicidal, continue to be a leading cause of death, especially in young adults. In North America, most of these fatalities occur out of the hospital and are reported by coroners. In-hospital fatalities continue to occur, however. Although some deaths are unavoidable (e.g., post-cardiac arrest or hypoxic brain injury occurring before hospital arrival), avoidable deaths still occur. A validated assessment or predictive tool for poisoned patients does not exist. It is difficult to envision the development of such a tool because of the variability of each potential intoxicant and the diverse pharmacokinetic profiles of drugs and other chemical substances. The time of ingestion and dose taken can be used to predict the course of intoxication. This evaluation must be done individually in each case, however. The medical toxicologist and PCC are resources to help predict severity for each individual case and to provide specific information that may attenuate the severity.

The mental health and social issues that lead to poisoning fatalities need further studies and resources to help reduce poisoning fatality rates. Stern and associates [45] followed 104 consecutive ICU admissions for poisonings [50]. Of these, 88 were followed for 5–24 months. The follow-up mortality rate was 6% by another overdose; 42% were readmitted for another overdose or psychiatric illness.

Ojehagen and colleagues [46] analyzed the repeat overdose patients and the nonrepeaters in a total of 79 patients admitted to a Swedish ICU over an 18-month period [51]. The predominant psychiatric diagnoses were adjustment disorder (31%), alcohol abuse (22%), major depression (19%), dysthymia (14%), and psychosis (9%). Of the patients, 66% were receiving psychiatric care. Repeaters were 58% of the sample and were less educated, had a higher rate of unemployment, and were more likely to be taking psychopharmacologic therapy. In many other series of patients from other countries or regions, the rates of repeaters have been much lower. The psychiatric care of critically poisoned patients is discussed in greater detail in ▶ Chap. 6, "Psychiatric Issues in the Critically Poisoned Patient."

Medical Toxicology Training

Training of health care professionals in toxicology has lagged behind that of other disciplines around the world [52]. Academic toxicology programs are lacking in most countries, although veterinary and pharmacy students receive some background

in the field [52, 53]. It became apparent in recent years in the United States that the fields of emergency medicine, critical care medicine, internal medicine, pediatrics, pharmacology, and occupational medicine could collaborate their basic and clinical science curricula to train physicians in the subspecialty of medical toxicology [54]. Success has been limited so far, owing to inadequate resources in faculty, curriculum guidelines, and clinical training centers. Despite this, in the United States there is a clearly evolving trend of medical toxicology training for medical students, residents, and fellows, particularly at those institutions with medical toxicology attendings.

Medical Students

A 1990 survey of Canadian and US medical schools found that although 88% of US schools reported teaching medical toxicology, only 5% had formal toxicology courses [52]. In Canada and the United States, medical schools averaged only 5 h of didactic toxicology teaching. An MD or PhD toxicologist was on staff at only 51% of the schools. This report represented an improvement, however, from an earlier survey of undergraduate US education [55]. In Great Britain's 24 medical schools, 22 reported formal toxicology teaching for a median of 5 h (range 1–12 h) [56]. Many medical schools have moved away from traditional lecture-based curricula to problem-based, facilitator-guided learning formats. Toxicology is often covered in the neuroscience or pharmacology block in the second year [57].

Residency Training

The experience in medical toxicology obtained in residency programs is highly variable. The formalization of training in medical toxicology varies greatly among countries. In the United States, medical toxicology is a core content area for emergency medicine residencies, so these postgraduate programs provide the most training in the field. Nonetheless, only 26% of the programs in a 1990 survey of US emergency medicine residencies had a board-certified medical toxicology faculty member and 19% offered no toxicology rotations at all [58]. Of the programs, 43% required toxicology training outside of the emergency department, but most of this was at poison information centers rather than bedside experiences. A 2,000 survey of emergency medicine residencies documented an increase in toxicology faculty to 63% of the programs [59]. A toxicology rotation was required at 76% and was an elective at 19%. The experience was widely variable, however, with most still receiving the training primarily at a PCC rather than inpatient care [59]. PCC training has been shown to modestly increase test scores in toxicology [60]. Poison information center experience, however, is limited in its ability to provide the skills necessary to treat critically poisoned patients.

In other US residency training programs, clinical toxicology education is usually lacking any meaningful experience. Only 4% of pediatric and psychiatry programs offer a clinical toxicology rotation, yet only 11% of the pediatric residency directors believed that their residents needed improvement in toxicologic management [61, 62]. Only 41% of psychiatry programs have didactics in toxicology, and only two programs had a toxicology elective [62]. Although internists in their roles as hospitalists, admitting physicians, or intensivists care for most poisoned inpatients, there is no toxicology required in internal medicine residency programs except substance abuse didactics.

Fellowship Training

In the United States, medical toxicology is a formally recognized subspecialty by the American Board of Medical Specialties, the regulatory authority for specialty and subspecialty certification. Postresidency fellowship training programs in medical toxicology emerged in the 1970s in the United States. In 1974, the American Board of Medical Toxicology (ABMT) was established by a subgroup of physician members of the American Academy of Clinical Toxicology (AACT) to set standards in care and training [54]. The primary

function of the ABMT was offering a certifying examination in medical toxicology to physicians, which began in 1975. Entrance to this exam required completion of a fellowship program or a practice pathway of 2 years of clinical experience. In 1989, the ABMT published guidelines for fellowship training in medical toxicology and continued to certify physicians until 1992, when the American Board of Medical Specialties officially recognized medical toxicology as a subspecialty [63]. This new subspecialty board was developed and sponsored by the American Boards of Emergency Medicine, Preventive Medicine, and Pediatrics [54].

Medical toxicology fellowship training requirements in the United States have been developed under the auspices of the American College of Graduate Medical Education (ACGME). Board certification or qualifications are required in a primary medical specialty, and subspecialty medical toxicology training requires 2 years of full-time fellowship in a program accredited by the ACGME. Medical toxicology program requirements are found at www.acgme.org. Fellowship programs grew from 21 in 1997 to 28 in 2016, with 70 fellows in training (www.acmt.net) [64]. The certification examination was first offered in 1994, and accreditation of training programs began in 1999 [64]. In 2000, the grandfather practice route to medical toxicology subboard certification closed. Qualifications to be entered into the ABMS subspecialty examination now require completion of an approved 2-year fellowship. Cognitive expertise examinations are also now required, and a recertification examination is required every 10 years. The core content of medical toxicology, which outlines the knowledge base essential for the practice of medical toxicology, fellowship training, and the framework of the certification and cognitive examinations, was updated in 2012 [64]. The core content includes principles of toxicology, toxins and toxicants, clinical assessment, therapeutics, population health, and analytical and forensic toxicology.

Clinical experience is still variable and often very limited in many programs, despite an ACGME requirement for providing bedside evaluation and management of toxicology patients for a minimum of 12 months. Some programs offer little but the required experience in telephone consultations at a regional poison control center. Bedside experience, although often limited, usually includes consultations on adult and pediatric patients. A few programs have inpatient admitting referral services, but most are consult services. Limitations on bedside training at many fellowships continue to restrict expansion of the specialty and expertise of recent fellowship graduates. In the only study of fellowship training, it was reported that fellows spent only 19% of their time in inpatient encounters. The fellowship programs had a mean total exposure to only 204 (Range 5–1,000) inpatients per program annually [64]. Twenty-four percent of all fellows were required to work in the ED as a part of their fellowship, further diluting their inpatient toxicology experience [64]. Pediatric emergency medicine offers a combined fellowship with medical toxicology [66, 67]. In the United Kingdom, medical registrars receive training in medical toxicology at regional poison treatment centers, in preparation to be consultants in the specialty [9]. They receive extensive bedside experience in the diagnosis and treatment of the poisoned patient, typically well beyond that of fellows in US programs.

With the establishment of the medical toxicology subboard by the ABMS, the American Board of Medical Toxicology (whose primary purpose had been to provide the certifying examination) was no longer necessary and went out of existence, although the ABMT Certification remains a lifetime board certification. The ACMT was founded in 1993 to fill the void left by the dissolution of the ABMT and to provide a physician specialty society for medical toxicologists. Since that time, the College has continued to expand both in numbers and activities, including offering an annual scientific meeting and other educational seminars, publishing the Journal of Medical Toxicology, providing a voice in organized medicine for toxicologists, providing research and training grants, and sponsoring the Toxicology Investigators Consortium Case Registry (www.acmt.net). The College now represents the vast majority of physicians who are Board-Certified in Medical Toxicology. By 2016, there were over

500 members of the ACMT, who were certified by the ABMT or the ABMS subspecialty board. Of these, 221 ACMT members had been recognized as Fellows of the American College of Medical Toxicology (FACMT), meaning they were not only board-certified but also had made significant contributions to the specialty (www.acmt.net).

Medical Toxicologists

Medical toxicologists admit or consult on patients hospitalized or in the ED, staff outpatient occupational and environmental practices, perform research and education, serve industry or governmental agencies, participate in pharmacy and therapeutics committees, and serve as expert witnesses. Most often, however, they still practice by providing telephone consultation for a PCC [68]. There were 209 physician toxicologists certified by the ABMT between 1974 and 1992, having qualified by fellowship training, practice experience, or a combination of both, but by 1992 there were only 183 still practicing in this field [64, 68, 69]. Between 1994 and 2014, 498 medical toxicologists were certified by the ABMS subboard, although 60 certifications have since lapsed. In terms of professional practice, a survey of medical toxicology fellowship graduates in 1998 found that fewer than half spent more than 50% of their professional time in medical toxicology at that time, and one third spent less than 25% [64, 69]. In 2002, there were 315 medical toxicologists, representing 55 solo or group practices serving 125 hospitals in the United States [70]. The average number of in-hospital patients treated annually at that time was 228 per group practice, and 36 of these groups were affiliated with a poison control center. A later survey in 2007 showed that 88% of the respondents were clinically active in toxicology, but only 35% spent an equal or more time in toxicology as compared to their primary specialty [68]. Only 22% saw more than 200 acetaminophen-poisoned patients per year, the most common poisoning seen, and 46% saw less than 50 per year. Of the estimated 260,000 poisoning hospitalizations in the United States each year, only about 12,540 (<1%) are seen by a medical toxicologist. [64, 69–71] Most critically poisoned patients are cared for not by medical toxicologists but by intensivists, hospitalists, or primary care physicians. A barrier to medical toxicology practice has been perceived to be inadequate financial reimbursement. In the early years of the specialty, this was indeed true for most toxicologists. In one study of a solo practice, charges and income were nominal [72]. As the specialty evolved, multiple practices nationally began to succeed in becoming economically feasible [73]. Some of the reasons were the increasing number of adolescents and adults requiring hospitalization due to drug abuse or intentional self-poisoning, increasing complexity and severity of cases, changes in practice methods from telephone consults to bedside care, the increased number of medical toxicologists available to form practice groups, and gradually increased knowledge of these groups in billing practices. Nevertheless, adequate compensation for medical toxicologists is a persistent problem because of the poison control center model of telephone consultations provided with little or no charge [74].

Other Health Care Professionals

Additional training in medical toxicology is needed for other health care professionals worldwide. Critical care and emergency department nurses scored only about 50% on a questionnaire about antidote dosing and indications [75]. Paramedic training programs in the United States devote only 2% of their time to toxicology, and only 11% have a designated experience at a poison center [76]. Poison centers and regional toxicology treatment centers are rich resources for continuing education for health care professionals. These centers have filled this role in industrialized nations and in developing countries, such as Zimbabwe [77]. The poison center may function as a multidisciplinary training site where medical, pharmacy, nursing, paramedic, and school of public health students work together with residents and toxicology fellows in the delivery of clinical advice [78]. Clinical pharmacology

has been combined with clinical toxicology in some institutions [79].

Medical Toxicology Practice Standards

The provision of poisoning treatment throughout the world generally is the responsibility of emergency physicians, pediatricians, internists, occupational physicians, and intensivists. They are supported by a relatively small group of trained clinical toxicologists, consisting of medical toxicologists and pharmacologists, who usually are located at large academic centers or poison centers. In such centers, a medical toxicologist often functions as the primary attending physician for poisoned patients. In the absence of locally available specialists in the field, physicians are forced to rely on telephone consultation, computerized data information systems, or standard texts. The now-disbanded World Federation of Associations of Clinical Toxicology Centers and Poison Control Centers in the 1960s advocated that poison information centers be available and provide the physician with advice tailored to the individual case, but this is not always practical [9]. The American College of Emergency Physicians (ACEP) has stated that poison treatment and information should include consultation with a medical toxicologist or PCC and that there should be regional centers for poison treatment for serious poisonings [80]. Many professional societies, such as the AACT, the European Association of Poison Centres and Clinical Toxicology (EAPCCT), the Society of Critical Care Medicine, the ACEP, and the American Heart Association, have published clinical guidelines for the treatment of poisonings, and these principles are outlined in chapters throughout this book [81–83].

There are multiple demonstrated weaknesses in providing poisoning care with the frequently employed model of care by generalists, such as lack of available medical toxicology care or consultation. Treatment recommended by emergency departments in simulated cases of drug overdoses was found to be correct in only 68% of cases. This included only 50% correct treatment of cases presenting to a teaching hospital and in only 22% of cases when the emergency physician was consulted [84]. A study of poisoning deaths in Massachusetts found that 29 of 60 deaths (48%) had errors in management as judged by an expert panel [85]. In two other studies, it was judged that 20–24% of in-hospital poisoning deaths could have been prevented if a medical toxicologist had been consulted [46, 87]. In England and in the United States, one fourth of all poisoning deaths occur after hospitalization, suggesting that better prehospital or in-hospital care might prevent some of them [85, 87]. An evaluation of the Acute Physiology and Chronic Health Evaluation (APACHE) III showed APACHE III to underpredict drug overdose mortality [88]. In this observational cohort study, APACHE III was used to predict mortality for 1,032 drug overdose admissions to 161 US hospitals. The predicted mortality from APACHE III was 7 (0.7%), but the actual mortality was 25 (2.4%) ($P < 0.0001$). This study suggests that in-hospital poisoning deaths are a greater risk than the APACHE III score can predict, or that there is need for improvement in toxicologic care.

A report from England showed significant variability in the management of poisoned patients. Thomas and coworkers reported this finding by comparing six hospitals in northeastern England over 12 weeks [17]. The catchment area included 1.52 million people. The admission rates for patients presenting to the accident and emergency wards varied from 50% to 87% (average 73%). The LOS varied from 0.8 to 2.1 days. Reasons for this variability were not presented. Only 12% of the patients had an LOS greater than two nights. Being elderly and ingesting benzodiazepines, acetaminophen, or antidepressants seemed to predict a longer LOS. Of the 690 admissions, there were three fatalities (0.4%) [17].

One study has now demonstrated that bedside care by medical toxicologists reduces lengths of stay, cost, and mortality of inpatients as compared to care by nontoxicologists. In this 2-year study of 3,581 patients, the LOS for the patients admitted to a large group's toxicology service were 0.3 days shorter than patients treated by nontoxicologists at both the same and different hospitals. This resulted in a median savings of 1,483 hospital days and

4,269 million dollars [89]. Most importantly, mortality rates were statistically significantly lower under the toxicologists' care, with a projected potential lives saved of 54.7 per 1,000 patients. Unfortunately, in 2014 there were only 42 reported medical toxicology services in the USA, serving 72 individual healthcare institutions [43].

Toxicology Resources

References for toxicology information in the mid-1900s were card files of individuals, poison centers, and the US National Clearinghouse for Poison Control Centers, followed by a computerized version of the Clearinghouse cards [78, 90]. In the 1970s, microfiche technology allowed for the storage and retrieval of larger toxicology databases, which eventually were replaced by computerized information database systems, such as the POISINDEX, which has become one of the standard references for clinicians and poison centers in the United States [78]. In the United Kingdom, the TOXBASE Internet database system is available to emergency departments and individual physicians at www.spib.axl.co.uk [9]. Both database systems contain extensive information on the features and management of pharmaceuticals and toxins.

Clinical toxicology textbooks are another resource for clinicians, although their reliability has been variable. To our knowledge, none before this book has comprehensively focused specifically on critically poisoned patients. The *Physician's Desk Reference* is a frequent source of drug overdose information for 50% of US physicians according to one survey, yet it was judged to include deficient treatment recommendations in 80% of the drugs reviewed, and in 35% of the drug outlines, contraindicated or potentially harmful advice was included [91].

It is often thought that contacting a PCC provides the local physician with reliable assistance in treating poisoned patients, avoiding transfer to a specialty center; some medical organizations even recommend that this be a standard of care [92, 93]. Contacting a PCC has been shown to be useful in cases of minor poisonings and drug or toxin identification, in which PCCs gave correct information 75% of the time in one study [94]. Physicians contact a PCC in only 19–29% of serious cases, however, and even then the recommendations are followed less than half of the time [46, 85, 95, 96]. Although advice from PCCs regarding specific poisonings is generally excellent, the pharmacists or nurses giving most consultations from PCCs are not fully prepared to advise on issues related to the care of seriously ill patients. Contacts with PCCs are increased if a physician toxicologist is available, but experts are frequently not available or accessed for individual cases, and their advice is followed in less than two thirds of these cases [95, 97]. A study of recommendations by a PCC to use two advanced toxicology therapies, hyperinsulemia euglycema (HIE) and intravenous fat emulsion (IFE), showed that only 31 of 70 patients (42%) actually received HIE, and in only 10 of 30 cases (33%) did the physician follow the advice to give IFE [98]. Consultations by telephone have been known to be fraught with hazard, which may account for some of this reluctance, along with unfamiliarity with such treatments. Clinical data recorded at hospitals are often unavailable to PCCs or are significantly different from that provided, and the specialist at the bedside is often in a better position to assess and act on the patient's status than a telephone consultant [9, 99]. For this reason, the ACEP states, "Most medical conditions cannot be accurately diagnosed over the telephone." [93] The ACEP further recommends that "emergency departments do not attempt medical assessment or management over the telephone." [93] The assessment of the circumstantial, laboratory, and clinical evidence requires a high level of clinical and toxicologic expertise on the part of the consultant at the PCC, who is often a nonphysician [9]. Limitations of this model of poison care delivery are exemplified by a study in which treatment advice was sought from US PCCs in a simulated case of serious antidepressant poisoning. The advice was deemed to be correct from only 42% of all the PCCs contacted and from only 60% of the regional centers certified by the AAPCC [94]. In another study, 43% of recommendations by regional PCCs for the use of two antidotes, fomepizole and digitalis FAB fragments, were

improper [100]. Regrettably, most physicians and hospitals must rely on this model of toxicology care for inpatient care due to the relatively small number of medical toxicologists in the USA.

The lack of adequate resources also hampers hospitals in providing care to poisoned patients. Pharmacy stocking of emergency antidotes has been found to be adequate in a wide range of hospitals surveyed (2–98%), depending on the antidote, but only about 1% of hospitals have adequate supplies of all antidotes in amounts necessary to treat even one patient [101, 102]. Most health care facilities have on-site access to qualitative urine drug assays for only a few drugs of abuse and must rely on distant toxicology reference laboratories for more comprehensive drug screens and many necessary quantitative analyses [70]. Specialty poisoning treatment units are available in major cities in some countries, but this is not universally true.

Sites of Care

An ICU is usually recommended to be the most appropriate location for management of poisoned patients requiring hospital admission because of the availability of rapid diagnostic procedures, intense observation and monitoring, and complex treatment modalities [103]. Over 200,000 ICU admissions are due to drug- or toxin-related causes annually in the USA [29]. Caution must be employed in triaging patients with altered mental status to other sites. One study found that 69% of patients with unrecognized medical emergencies inappropriately admitted to a psychiatric unit had a drug overdose or intoxication, or severe drug/alcohol withdrawal [104].

The Society of Critical Care Medicine recommends that overdose patients be admitted to an ICU if they have cardiovascular instability, altered level of consciousness with airway compromise, or seizures [105]. One study found that ICU admission was necessary if in the emergency department the patient required mechanical ventilation or had seizures, coma, a partial pressure of carbon dioxide greater than 45 mmHg, arrhythmias, high atrioventricular block, a QRS greater than 0.11 s, or systolic blood pressure less than 80 mmHg [106]. The Glasgow Coma Scale has been used to predict the need for ICU admission, with a score of less than 13, intubation, or the presence of infectious, cardiovascular, or electrocardiogram complications being sensitive and specific for needing ICU interventions in one study [107]. A smaller study suggested that nonintubated patients with a Glasgow Coma Scale score greater than 6 did not require ICU admission and could be handled on the general medical floors [22]. Intensive care for poisoned patients also may be delivered in an emergency department observation unit with respiratory care capabilities and can result in fewer complications and shorter LOS compared with admission to a general medical floor [108–110].

In severe cases, local resources may be inadequate to meet the patient's needs. Transfer of seriously ill patients to specialty centers is supported in policy statements of the ACEP, ACMT, and Society of Critical Care Medicine [111–113]. Transfer is often necessary to provide access to experienced medical toxicologists, antidotes, and analytic laboratory services not available elsewhere. Specialty poison treatment centers are available in a few cities around the world (see later section on "Poison Centers").

Recommended Equipment and Resources

Care of the seriously poisoned patient requires medical and nursing expertise, an emergency department and critical care unit, analytic toxicology laboratory support, an adequate supply of antidotes, and psychosocial services [31, 114]. Available services should include hemodialysis, a clinical laboratory able to perform routine analyses, plus at least the emergency toxicology laboratory tests listed in the ACMT facility guidelines, a 24-h pharmacy, radiology, respiratory care, and psychiatric and social services [115].

The ACEP has published a clinical policy for the care of patients with toxic exposures, including recommended laboratory tests and common necessary emergency antidotes [83]. Although

intended for facilities serving as regional poison treatment centers, the guidelines of the ACMT also outline the resources deemed necessary in any hospital caring for poisoned patients [115]. The minimal qualitative urine drug assays recommended are listed in Table 8, and the quantitative tests necessary for immediate care are listed in Table 9. In addition to these drug assays, the hospital laboratory must be able to perform rapidly arterial blood gases, a comprehensive metabolic panel, coagulation studies, serum ammonia, serum osmolality, acetone, and lactate.

Table 8 Recommended analytes to be available on qualitative urine screening assays[a]

Amphetamines
Barbiturates
Benzodiazepines
Cannabinoids
Cocaine
Cyclic antidepressants
Opiates
Phencyclidine

[a]This is a recommended list for hospitals in the United States and Canada. It should be modified based on the regional drug use patterns in other locations

Table 9 Recommended analytes to be available for emergency quantitative drug assays (Available within 2 h)[a]

Acetaminophen
Carbamazepine
Carboxyhemoglobin
Digoxin
Ethanol
Ethylene glycol
Iron
Isopropanol
Lithium
Methanol
Methemoglobin
Phenobarbital
Phenytoin
Salicylate
Theophylline
Valproic acid

[a]This is a recommended list for hospitals in the United States and Canada. It should be modified based on the regional epidemiology of poisoning

Antidote needs may vary based on geography and setting; the minimal required antidotes are listed in Table 10.

Poison Centers

The proliferation of accidental and intentional poisonings in the 1940s led to the development of centers for poison information dissemination and treatment around the world. The infancy of such centers was in Copenhagen, the Netherlands, Edinburgh, and Chicago. These specialty centers serve as resources for poison information, public and heath professional education, poison prevention, research, and in some cases tertiary patient care. The increasing number of childhood accidental poisonings and deaths and physicians'

Table 10 Recommended emergency antidotes

Activated charcoal
Amyl nitrate
Antivenin, Crotalidae[a]
Calcium chloride
Calcium gluconate gel
Deferoxamine mesylate
Digoxin immune Fab
Ethanol
Folic acid
Fomepizole
Flumazenil
Glucagon
Leucovorin
Methylene blue 1%
N-Acetylcysteine
Naloxone
Physostigmine
Polyethylene glycol electrolyte solution
Pralidoxime hydrochloride
Protamine sulfate
Pyridoxine
Sodium bicarbonate
Sodium nitrite 3%
Sodium thiosulfate
Succimer
Thiamine hydrochloride
Vitamin K_1

[a]For crotaline endemic areas

general lack of knowledge and resources about drug and chemical ingredients initially highlighted the need for poison centers.

Poison Information Centers

The first poison information service is thought to have been established in the Netherlands in 1949, followed in Europe by similar centers in Paris in 1959, London and Edinburgh in 1962, and Zurich in 1966 [9, 53]. The first information center, or PCC, in the United States was established in Chicago in 1953 and had been preceded by an informal information service in the pharmacy of St. Luke's Hospital [90]. The first PCC was intended to provide information to physicians on ingredient and toxicity information, and the database was a set of small cards. Subsequently a manual was developed outlining the ingredients of common household products and distributed to emergency departments. Similar centers began to appear across the United States, and by 1957, there were 17 PCCs, which now also were taking calls from the public [90]. An initial barrier was the lack of reliable data sources and data collection, so the US Surgeon General designated the National Clearinghouse for Poison Control Centers, which distributed index cards of poison information and collected poison data from centers [90]. There was an uncontrolled growth of PCCs in the United States during the 1960s and 1970s, resulting in 661 PCCs of variable quality [90]. The American Association of Poison Control Centers (AAPCC) was established in 1958 primarily by pediatricians to develop public and professional education programs, promote cooperation between centers, and set standards for operation. In 1978, the AAPCC published strict standards for PCCs, and as a result the number of PCCs declined to 91 in 1995, 73 in 1998, and 55 in 2015 [20, 116]. These centers are staffed around the clock by nurses and pharmacists and usually are directed by pharmacists with some medical direction provided mostly by part-time medical toxicologists [99]. Some centers do not have adequate medical toxicologist availability, and most cases do not involve physician consultation [81, 99]. PCCs have been shown to reduce unnecessary hospital visits and health care expenses, however, and serve as a resource for education, research, poison prevention efforts, and data collection [99, 100]. They also have been shown to be a reliable source of first aid and triage advice for the public and hospitals in cases of nonlife-threatening toxic exposures [84, 94]. Poison center services in the United States to physicians caring for poisoned patients have evolved over the years. Initially, PCCs were primarily consulted for ingredient information. The lack of availability of medical toxicologists at most hospitals has rendered PCCs as the default source of treatment recommendations. Most of this advice comes from nonphysicians working in PCCs, however. The need for medical toxicology resources for information on the treatment of critically poisoned patients is evident.

Likewise, in Europe the EAPCCT was formed in 1964 to share knowledge and to identify toxic hazards. There are now approximately 80 - European PCCs [53]. Networks of multiple centers operate in France, Germany, Italy, and the United Kingdom [53]. In the United States, poison centers can be contacted by the public and health care professionals at 1-800-222-1222, and in the United Kingdom the National Poisons Information Service is available to health care professionals and emergency departments at 0870-600-6266. Health officers, medical toxicologists, and pharmacists staff the centers, and they are often affiliated with poison treatment centers, ICUs, or emergency departments [53]. It has been advocated that these centers be part of a larger toxicology center that includes an analytic laboratory, inpatient treatment center, outpatient services, adverse drug reaction and occupational exposure advice, research, an expanded medical staff, and training [114, 118].

In addition to the United States and Europe, there are poison information centers operating on every continent worldwide except Antarctica. Many of these centers are still in the early stages of development. The Japan Poison Information Center was established in 1986 to serve a population of 124 million and received only about 35,000 calls in 1994 [119]. This represents a

case volume of only 27 per 100,000 population, in contrast to the United States's call volume of 920 calls per 100,000 at that time [119]. Before its dissolution, the World Federation of Associations of Poison Centers and Clinical Toxicologists issued a directory (Yellowtox) of worldwide poison information centers and analytic toxicology services, which still can be found at www.intox.org/pagesource/yellowtox/yellowtoxhtm.

Poison Treatment Centers

Poison treatment centers are highly specialized inpatient units directed by medical toxicologists and are capable of caring for the most complex cases of poisonings. Strong centralized regional poison treatment centers have flourished in some countries and serve as specialty care centers and institutes for toxicologic research, treatment advances, and education. Their origin probably is based in Scotland, where a "delirium ward" was established at the Royal Infirmary of Edinburgh in 1879 (Fig. 7) [30]. This unit gradually evolved into the Regional Poisoning Treatment Centre of Edinburgh, and by 1964 it cared for more than 90% of overdose patients in the Edinburgh area [30]. Another formal treatment center in Europe was founded in 1949 in Copenhagen, followed by other centers in Paris and in Romford, Essex, in the late 1950s [9, 30, 31]. The impetus for further development of centers in the United Kingdom in Birmingham, Dublin, Belfast, Cardiff, and London was the Atkins Report of 1962 and the Hill Report of 1968, in which the United Kingdom Ministry of Health recommended the establishment of regional poisoning treatment centers with consultants in toxicology and associated psychiatric and chemical toxicology laboratory services [31]. Other such centers were developed in Europe and Russia in the 1960s and more recently in the United States and Australia [48, 70, 115, 120].

In 1993, the AACT published standards for toxicology treatment centers [121]. Subsequently the ACMT refined and promoted those standards [115]. The Center for Poison Treatment Facility Assessment Guidelines can be found at www.acmt.net. The rationale for the existence of these treatment centers is cited as the need for a dedicated professional staff to develop expertise, to assess and manage more efficiently medical and psychiatric issues, to advance knowledge rapidly by concentrating patients at dedicated sites for education and research, to focus psychosocial support for the patients' special needs, and to make it efficient to provide analytic laboratory support on-site [30, 31, 48, 114]. These guidelines recommend a medical staff of physicians board-certified in medical toxicology and nurses with toxicology specialty training, adequate beds consistently available for the care of the poisoned patient, quality improvement and teaching programs, and other physician specialists and equipment typically found in university hospitals or regional medical centers. Further details can be found in these guidelines on the ACMT website. There is no mechanism currently to certify centers meeting these standards, but it is known that there are at least 54 medical toxicology services in the USA, most of which would meet these standards [43].

These centers have been found to improve care of the toxicology patient. It was reported that in the first year of operation, the Copenhagen center reduced poisoning mortality by half by centralizing care [30]. The average LOS also has been reported to decrease, compared with general ICU or hospital ward admissions. In Australia, there was a reduction of 2–3 days in hospital stays for complicated poisoning cases at two toxicology centers, but there was not a statistical reduction in mortality [48, 122]. Use of health care resources also has been shown to decrease at these centers without compromising patient care, and the coupling of a treatment center with an aviation medicine service allows for efficient access to therapies unavailable in rural regions [123, 124]. Transfer of such seriously ill patients to specialty centers is supported in a policy statement of the ACEP, which states, "Patients should be transferred to a health care facility that meets their needs." [111] Transfer is often necessary to provide access to experienced medical toxicologists, antidotes, and analytic laboratory services not available elsewhere.

Regional poison treatment centers care for a highly variable number of patients annually.

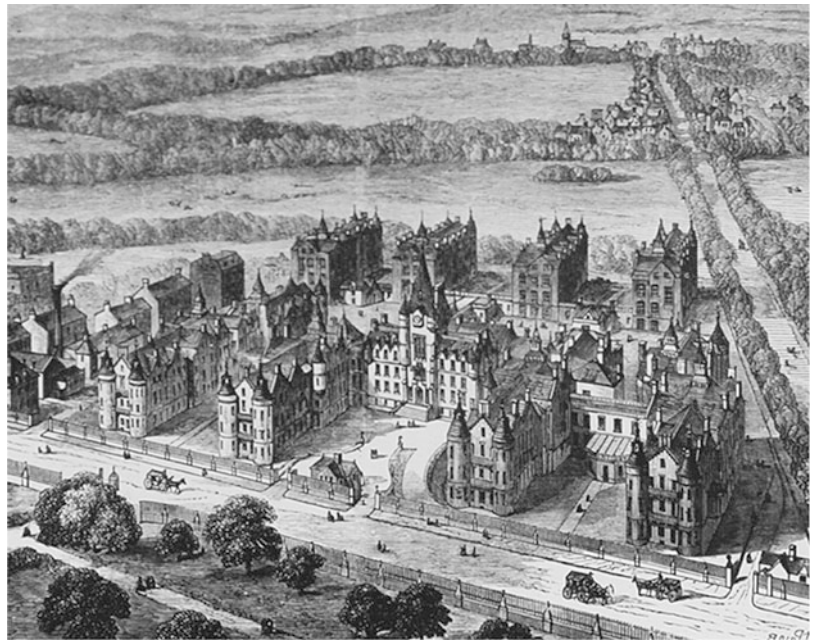

Fig. 7 Royal Infirmary of Edinburgh 1879

Admissions to the Edinburgh center peaked at about 2,200 admissions per year, then declined to about 1,500 annual admissions in 1986 [9]. Two centers in Australia admitted 736 and 192 patients in years reported in the mid-1990s [48, 122]. The center in St. Petersburg, Russia, serves about 7 million people and reported more than 5,500 admissions per year [120].

In the United States, centers in Pennsylvania, Colorado, Arizona, and Utah each had about 500 annual admissions in 2002 [70]. The 54 centers participating in the ACMT ToxIC Registry, representing the busiest toxicology services in the country, treated an average of only 195 patients annually in 2014 [43]. Despite poisonings now causing more deaths than motor vehicle accidents, unlike the proliferation of trauma centers in every state, there has been little growth in medical toxicology specialty services [43, 68]. Even most university hospitals and large regional teaching centers have no toxicologists on their medical staff. This failure of modern medicine to meet this healthcare responsibility is due to a lack of recognition of the need for specialty toxicology care, the relatively low number of medical toxicologists due to a lack of adequately supported fellowship programs, and unfortunately less opportunity to generate profit from these patients for the healthcare system [74]. Despite these barriers, medical toxicology has grown significantly in numbers of board-certified practitioners, peer-reviewed journals, fellowship programs, research, professional society size and activities, and bedside care by an increasing number of clinical sites. Likewise, critical care medicine has established its place as the designated physicians staffing ICUs, developing standardized evidence-based treatment protocols for improved patient care, and published research. The interaction between these two specialties should continue to grow and establish the standard of care for responding to the epidemic of drug overdoses and other critically ill toxicology patients.

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The Diagnostic Process in Medical Toxicology

2

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Contents

This chapter is an update of the chapter on this topic written by Alex T. Proudfoot and J. Ward Donovan in the first edition of this text.

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A medical toxicologist must pay great attention to detail. Unlike other specialties, the toxicologist rarely has a gold-standard diagnostic test to confirm a poisoning or withdrawal condition. Instead, the medical toxicology evaluation requires a thorough history and physical examination and strategically ordered diagnostic testing. Then once all available information is gathered, the medical toxicologist must astutely interpret the findings within the appropriate clinical context. Therefore, the toxicologist can be nothing short of an astute diagnostician.

A key component of medical toxicology is separating the poisoned patient from alternative diagnoses. The Venn diagram of diagnoses for metabolic syndromes, traumatic injuries, infectious diseases, neurologic conditions, cardiac disease, pulmonary disorders, and toxicological illness has much overlap. Therefore, the diagnostic process in medical toxicology must rely heavily upon a detailed history, an astute physical examination, and contextually placed diagnostic testing in order to make the correct diagnosis.

Furthermore, the medical toxicologist must be prepared to exclude nontoxicological diagnoses. When the history is vague, the examination is equivocal, and the diagnostic tests are confusing, the medical toxicologist must have an open mind for alternative diagnoses. We have treated many patients who first present as an "overdose" but are later diagnosed with an ischemic stroke, encephalitis, or other medical condition. Certainly, we have witnessed the opposite scenario as well. Therefore,

constant review and re-review of a clinical picture are paramount to ensure all findings remain consistent with any suspected diagnosis.

History

A detailed history is the most important first step in the diagnostic process in medical toxicology. Therefore, it is critical to gather data from all possible sources. Often, family, friends, and first responders offer great diagnostic clues. Electronic media is a potentially great source of information, including text messages, emails, and social media posts. Electronic media is particularly valuable since it is time-stamped.

When gathering history, where and under what circumstances the patient was found is critically important. Since first responders are trained to "size-up" a scene, they tend to provide the best history. Family and friends may only recognize crucial details when a scene is evaluated on the second attempt after coaching from the medical team. When obtaining history, crucial questions may include:

- Where was the patient found?
- When was the patient last seen in their normal state of health?
- What were the circumstances surrounding the patient's discovery?
- Were any pill bottles, empty wrappers, or chemicals closely available?
- Are any suicide notes, text messages, or social media posts available?
- Is there any history of past drug overdoses, other attempts at self-harm, or substance abuse/withdrawal?

All these questions, and certainly many more, help identify the substances involved with a poisoning. Moreover, the history assists in identifying those at risk for aspiration pneumonia, rhabdomyolysis, compartment syndrome, or concomitant traumatic injuries.

A careful evaluation of available pills is extremely important. When pill bottles are identified, have family, friends, and first responders bring the bottles to the hospital. This will assist in clearly identifying any substances. However, counting pills and attempting to correlate how many are missing is often a fruitless endeavor. Patients may hoard or sell pills and fail to take them as prescribed. Pill counts, therefore, are often unreliable. The mere availability of a particular substance suggests it may have been ingested. When pill bottles are not identified, prescriptions or substances available in the home can provide helpful clues. Patients will often ingest what is most easily available. When obtaining the medication history, it is important to inquire about prescriptions, over-the-counter medications, supplements, herbal preparations, and illicit drugs.

One point of caution is reliability of the obtained history. Patients, family, and friends are easily confused by drug names. For example, patients may be confused when attempting to identify over-the-counter pain relievers, such as ibuprofen and acetaminophen. Therefore, obtaining the exact pill bottles from the scene is the most reliable way to obtain this portion of the history.

Equally important is identification of chemical containers. When a chemical is identified in a possible exposure, obtaining the container from the scene is as important as obtaining specific pill bottles. The only reliable means to identify a substance is a well-labeled container. Using a witness' recall as a means to identify a substance may be helpful in narrowing down the potential chemicals. However, specific chemical products have extreme variability in chemical composition even within the same brand. Therefore, errors in chemical identification are more likely when containers are not obtained.

The history is often the only means to identify a poison as few hospitals have the ability to promptly test all exogenous substances in serum or urine. Most hospitals can quickly obtain serum ethanol, salicylate, and acetaminophen concentrations. Yet, obtaining timely quantification of drugs and chemicals in body fluids remains elusive for most other exposures. Therefore, obtaining a detailed history, where possible, is a critically important element of the diagnostic process when dealing with poisoned patients.

Physical Examination

In conjunction with the history, the examination can confirm or refute the suspected toxicological diagnosis. In the absence of any available history, the examination may be the only initial clue in formulating a differential diagnosis. Furthermore, there is no substitute for a thorough bedside evaluation by a medical toxicologist. Medical toxicologists tend to astutely recognize unique signs of specific chemical intoxications or toxidromes.

Certainly, the examination must be tailored to the particular circumstances and clinical picture. This section is not designed to be all-inclusive. However, we merely highlight clinical signs that are high yield in evaluating the poisoned patient.

Vital Signs

Vital signs are vital! They offer the first picture into a patient's illness severity and determine what immediate actions should occur. In addition, serial vital sign measurements provide valuable information concerning a patient's changing clinical condition or response to treatment. Therefore, vital signs should be monitored closely and frequently.

Since many toxicants, drugs, and withdrawal states affect heart rate, the pulse is extremely important. Even a normal heart rate can suggest specific clinical conditions. In some cases, the heart rate is reflexively altered in a poisoning. For example, a toxicant exposure that results in hyper- or hypotension may result in reflexive brady- or tachycardia, respectively.

Blood pressure is also of utmost importance, and like heart rate, many toxicological diagnoses affect blood pressure. Yet more important than the actual blood pressure is the body's ability to adequately perfuse vital organs. When blood pressure measurements suggest the potential for inadequate perfusion (e.g., mean blood pressures $\leq$65 mmHg), we evaluate perfusion by alternative means. In these circumstances, we have borrowed knowledge gained in the treatment of sepsis. Along with the blood pressure, we will often use serum lactate concentrations and mixed venous oxygen saturations [1]. This topic is discussed in greater detail in ▶ Chap. 14, "The Assessment and Management of Hypotension and Shock in the Poisoned Patient."

Respirations are effected by the patient's acid-base status or drugs/toxicants directly. However, merely looking at respiratory rate is often insufficient. One must astutely assess the depth of respirations as well as the rate of breathing. Many toxicants, drugs, and metabolic conditions may alter the minute ventilation without affecting the respiratory rate. In other words, the respiratory rate may remain normal while the patient is experiencing hyperpnea or hypopnea. These changes in minute ventilation are often revealed during a careful physical examination.

Body temperature measurements are often forgotten in the initial evaluation of the poison patient. Yet, the body temperature evaluation may be critically important. Alterations in body temperature can suggest a specific drug ingestion, chemical exposure, or withdrawal condition. For example, electron transport uncouplers, like salicylate, may cause hyperthermia. In other circumstances, the body temperature is merely a marker of the patient's environmental exposure. If a patient has an altered mental status after a poisoning, the patient is at the mercy of the environment. If left exposed to extreme temperatures, patients often present with hypo- or hyperthermia not from the toxicity, but merely from inability to seek shelter. Therefore, body temperature measurements need careful interpretation.

However, an elevated temperature is most strongly associated with mortality in sympathomimetic poisoning [2]. Therefore, body temperature measurements should not go unnoticed. Moreover, when extremes in body temperature are identified, efforts should be made to make the patient euthermic. Certainly, hyperthermia is a more immediate threat to life than hypothermia. Yet, hypothermia may lead to slower or unpredictable drug metabolism. Therefore, extremely high or low body temperatures are a concern and may offer diagnostic clues in the poisoned patient.

Clinical Signs

There are a number of clinical signs unique to the poisoned patient. One of the first signs encountered in the poisoned patient is odors. Odors are the result of malodorous chemicals, drugs, and drug metabolites. An obvious example is the detection of an ethanol odor, which may assist in identifying an intoxicated patient (See Table 1).

A thorough visual inspection of the patient's skin may be informative. This inspection should include a review of the skin color, dryness, and signs of traumatic injury. The actual poison may affect skin color as seen in the yellow staining after dinitrophenol poisoning. In other cases, the drug may cause a physiologic change resulting in skin coloration as in the flushed reddened appearance from antimuscarinic drugs. Cyanosis to a medical toxicologist does not merely suggest hypoxia but may also indicate methemoglobinemia or sulfhemoglobinemia. Some exposures lead to excessive histamine release, and patients may present with erythroderma such as with scombroid poisoning or the anaphylactoid reactions associated with vancomycin. Skin dryness may help differentiate between toxic syndromes. An old adage in medical toxicology is the toxicologist's handshake, which includes placing the clinician's hand in the armpit. Since antimuscarinic toxicity can result in facial diaphoresis, a dry armpit will more clearly differentiate antimuscarinic from sympathomimetic toxicity. Signs of skin trauma can provide contextual history about a patient. Bruising may suggest concomitant traumatic injuries or the presence of a coagulopathy from liver disease or anticoagulant toxicity. Needle marks also tell much about a patient's social history. Skin necrosis or skin necrosis blisters are helpful diagnostic clues. Skin necrosis lesions are erythematous patches of various shapes that develop after prolonged immobility. One can often recreate the exact positioning of the patient by a careful evaluation of these skin lesions. With more prolonged contact, blisters may develop. These blisters have been called pressure necrosis blisters or even "barb blisters" since they were first noted in the era of barbiturate-associated overdoses. Nonetheless, skin necrosis and skin necrosis blisters inform the clinician that the patient suffered prolonged immobility and is at risk for aspiration pneumonia, skin breakdown, rhabdomyolysis, and compartment syndrome. Therefore, a simple inspection of the skin can provide much information about a patient.

A neurologic examination is of high clinical yield in the poisoned, or potentially poisoned, patient. This includes detection of any focal deficits, level of consciousness, speech, pupil size, muscle tone, and deep tendon reflexes. The importance of a detailed neurologic examination not only helps identify the correct toxicological diagnosis but can often identify alternative diagnoses, such as an ischemic stroke. Identification of any focal deficits should suggest the evaluation for nontoxicological diagnoses.

A patient's level of consciousness may suggest how much and, possibly, what type of poisoning is

Table 1 Odors of drugs and toxicants

Odor	Toxicant	Odor	Toxicant
Acetone	Alcoholic ketoacidosis	Mothballs	Camphor
	Isopropyl alcohol		Naphthalene
Acrid (pearlike)	Paraldehyde		Paradichlorobenzene
	Chloral hydrate	Solvent/glue	Toluene
Bitter almonds	Cyanide		Xylene
Disinfectant	Phenol		Trichloroethane
Garlic	Arsenical insecticides	Smoke	Tetrachloroethylene
	Organophosphate insecticides		Carbon monoxide Cyanide
	Selenium		Clomethiazole
	Thallium	Wintergreen	Methyl salicylate
	Phosphorus	Rotten eggs	Hydrogen sulfide

present. In clinical practice, the terms alert, lethargic, obtunded, stupor, and coma are helpful in describing a patients' mental status. Alert patients are awake and conversant. Lethargic patients require a loud verbal command for arousal. Obtundation requires shaking a patient as if awakening from sleep. Stupor requires a painful stimulus for arousal. Finally, a comatose patient is completely unarousable to multiple painful stimuli. Often the first step in a neurological examination, level of consciousness, also quickly determines who may need a more urgent intervention. This topic is discussed in greater detail in ▶ Chap. 19, "Toxicant-Induced Alterations in Consciousness."

The character of speech is quite telling. Fluency, articulation, and the ability to have an attentive conversation are important factors to review. For example, antimuscarinic patients have a characteristic mumbled and difficult to comprehend speech which, once recognized, helps identify this toxic syndrome. As medical toxicologists, we are often consulted for delirium. One characteristic finding of delirium is the inability to remain attentive. A conversation with a patient filled with distraction can suggest delirium. Therefore, the speech character and the conversation quality assist in the toxicological evaluation of potentially delirious patients.

Pupil size is one of the most commonly utilized neurologic examination findings for toxic patients. Most clinicians examine pupils to assess miosis in case of opioid toxicity. However, large pupils can suggest antimuscarinic or sympathomimetic toxicity. Yet, as a point of caution, the pupillary evaluation can be extremely misleading. For example, meperidine, an opioid, often presents with mid-sized pupils due to competing mechanisms from muscarinic antagonism and opioid agonism [3]. Therefore, interpret the pupil exam with much caution, but when utilized correctly, can provide a wealth of information.

The medical toxicologist must distinctly differentiate neuroleptic malignant syndrome (NMS) from serotonin syndrome. Muscle tone and reflexes are an important part of the neurologic examination. Except for the neurologist, most other specialists fail to include this as part of their standard examination. Since the defining features of many toxic syndromes require an evaluation of tone and reflexes, these should become a routine part of the medical toxicologist's evaluation. The details of differentiating these two syndromes are found in ▶ Chaps. 31, "Neuroleptic Malignant Syndrome" and ▶ 24, "Serotonin Syndrome."

Toxidromes

After exposure to an unknown poison, any single sign, symptom, or laboratory abnormality will rarely permit the medical toxicologist to reach a definitive diagnosis. Rather, pattern recognition, the presence or absence of physical examination findings, and detailed historical evidence, together, will lead to speedy and accurate diagnoses.

In 1974, Mofenson and Greensher coined the term "toxidrome" to describe constellations of signs and symptoms that consistently result from particular classes of toxicants [4]. In clinical practice, however, it is more common to encounter partial toxidromes or mixed toxidromes. For example, toxicity from diphenhydramine, a first-generation antihistamine, often results in profound antimuscarinic findings. However, it is also sedating (due to antihistamine effects) and may not result in significant mydriasis due to both the antimuscarinic properties and alpha-adrenergic antagonism. Furthermore, diphenhydramine is a sodium channel antagonist and can cause QRS and QT prolongation and ventricular dysrhythmias, which are not typically caused by purely antimuscarinic agents such as the plant-derived alkaloids in belladonna. Moreover, many intentional drug overdoses involve more than one agent. Thus, patients commonly present with mixed findings. At times, the toxicities of each agent have additive effects as seen in the coingestion of a benzodiazepine and an opioid. In other cases, an agent may mask findings expected of another. As an example, the sympatholytic effects of clonidine may blunt the expected tachycardia and CNS excitation expected after a significant bupropion overdose [5]. Nevertheless, knowledge of the classic toxidromes provides a sound framework around which to

initiate appropriate evaluation, stabilization, and treatment of the critically poisoned patient. Table 2 provides a summary of the classic toxidromes.

Opioid Toxidrome

The toxidrome associated with opiate or opioid intoxication includes the classic triad of coma, miotic pupils, and respiratory depression. Depending on severity of illness, the clinician may also note modest bradycardia and/or hypotension. This toxidrome is not pathognomonic for opioid toxicity, and a similar presentation may suggest an alpha2-adrenergic agonist (e.g., clonidine, guanfacine, and tizanidine) toxicity, barbiturate toxicity, intracranial hemorrhage, and brain stem stroke.

In the proper historical setting, the triad of coma, miosis, and respiratory depression often prompts the use of naloxone. Naloxone has anecdotally been reported to reverse some cases of clonidine toxicity and yet should have no effect in the setting of intracranial hemorrhage, stroke, or barbiturate toxicity. Thus, naloxone is both diagnostic and therapeutic.

Opioid toxicity is discussed in greater detail in ► Chap. 62, "Opioids."

Sedative-Hypnotic

A wide variety of pharmaceutics characterize this toxidrome and generally stimulate central nervous system GABA-A chloride channels. Among the most commonly prescribed agents associated with the sedative-hypnotic toxidrome are benzodiazepines. Others such as ethanol, barbiturates, gabapentin, pregabalin, and zolpidem present with similar findings. Typically, the toxidrome is best described as "coma with preserved vital signs." Though many sedative-hypnotic agents reduce blood pressure, heart rate, and body temperature, the reductions are often mild to modest depending on the severity of the ingestion or the specific drug involved. For example, barbiturate toxicity is more likely to cause significant respiratory depression, hypotension, and hypothermia than other sedative-hypnotic agents. In general, patients appear deeply sedate and pupils are generally mid-sized, although they may be disconjugate. Contrary to popular belief, patients generally do not exhibit respiratory depression in the setting of isolated oral benzodiazepine ingestions [6]. Hypoxia with respiratory depression more commonly develops after intravenous administration or secondarily from upper airway obstruction in the setting of obesity or impaired chest wall excursion. Overall, the sedative-hypnotic toxidrome is the hardest to characterize due to the wide variety of drugs involved and the nonspecific presentation.

Toxicity form these agents is discussed in great detail in ► Chap. 45, "Anxiolytics, Sedatives, and Hypnotics."

Antimuscarinic Toxidrome

The antimuscarinic toxidrome, also referred to as the anticholinergic syndrome, in full or in part, is commonly evident in intentional drug overdoses or adverse drug reactions owing the ubiquitous nature of xenobiotics that affect muscarinic neurotransmission. Examples of drug classes that frequently exhibit antimuscarinic properties include first-generation antihistamines, antipsychotics, and class 1A antidysrhythmics. Additionally, alkaloids (atropine, scopolamine, and hyoscyamine) derived from many plants in the Solanaceae family – e.g., Jimson Weed (*Datura stromonium*), Angel's Trumpet (*Brugmansia sp.*), Deadly Nightshade (*Atropa belladonna*) – are abused by teens and used in religious ceremonies throughout the Americas.

The effects of antimuscarinic drugs are indicative of competitive antagonism of muscarinic acetylcholine receptors [7]. The constellation of tachycardia, mild hypertension, mild hyperthermia, skin flushing, xerostomia and anhidrosis, mydriasis, urinary retention, delirium, carphologia (picking behavior), and muffled or garbled speech suggests antimuscarinic poisoning. Patients will commonly experience visual or tactile hallucinations too. In clinical practice, rarely do patients present with all these signs as

Table 2 Summary of the classic toxidromes

	Heart rate	Blood pressure	Respirations	Temperature	Pupils	Skin	CNS	Distinctive feature(s)
Opioid	↓	↓	↓↓	↓	Miosis	No change	↓ LOC	Coma, miosis, hypoventilation
Sedative-hypnotic	↓	↓	↓	↓	No change	No change	↓ LOC	Coma with normal vitals
Antimuscarinic	↑↑	↑	↑	↑	Mydriasis	Anhidrosis (except face)	Agitated delirium	Carphologia, mumbling speech
Cholinergic	↓↓	↓↓	↑	No change	Miosis	Diaphoretic	↓ LOC, seizures	Bradycardia, bronchorrhea, bronchospasm
Sympathomimetic	↑↑	↑↑	↑	↑	Mydriasis	Diaphoretic	Agitated delirium, seizures	Mydriasis, agitation, tachycardia, hypertension
Serotonin syndrome	↑↑	↑	↑	↑	Mydriasis	Mild diaphoresis	Agitated delirium, seizures	Lower extremity hyperreflexia
Neuroleptic malignant syndrome	↑	↑↑	↑	↑↑	Varies	Varies	Varies – agitated delirium to coma	Cogwheel rigidity with hyporeflexia