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THIRD EDITION

Karch's Pathology of Drug Abuse

Steven B. Karch, M.D.

CRC PRESS

Karch's Pathology of Drug Abuse

THIRD EDITION

About the first edition:

"Dr. Karch has produced a truly comprehensive and useful reference work that belongs on the shelf of any professional interested in the sequelae of drug abuse."

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About the second edition:

"It is easy today for physicians to become technicians rather than professionals. A technician knows how to respond to a problem. The professional has the depth of knowledge that brings real understanding to a problem. This book presents a comprehensive view of each subject that it discusses. Dr. Karch's book is a book for professionals."

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"... a mine of information about the pathology and toxicology of drugs of misuse. ... It is essential for any healthcare professional involved in the care, clinical management, or autopsy of drug misusers to have a clear understanding of how a particular drug affects the body, short-term and long-term, and what relevance the metabolism of the drug has to its clinical manifestation. This book provides all the answers. ... the best and most readable book I have seen on the subjects included."

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The third edition of **Karch's Pathology of Drug Abuse** continues to provide a comprehensive yet accessible guide to the pathology, toxicology, and pharmacology of commonly abused drugs. As in previous editions, the focus remains on the investigation of drug-related deaths and on practical approaches to the detection of drug abuse. It covers in detail the clinical consequences of drug usage and provides the latest information on clinical aspects of drug abuse. This well-written, extensively referenced resource supplies a mixture of clinical information and pathology findings.

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- Toxicology and pathology of ephedrine
- Neurochemistry of excited delirium
- Psychotic behavior in stimulant abusers

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Dedication

For

Donna, my wife of 25 years, for our friends everywhere, and for Sam.

Preface to the first edition

Physicians deal with the consequences of drug abuse on a daily basis, but information about the basic pathology of abused drugs is hard to come by. Hundreds of papers have been published describing the effects of drug abuse on brain neurochemistry, but practitioners are hard pressed to find out how cocaine affects blood vessels or how heroin affects the lungs. I hope this book supplies the information they need. While far from encyclopedic, I think the book does provide answers to most of the questions physicians ask when they are confronted with cases of drug-related death or disability.

In the course of writing the sections on heroin, I was surprised to discover that more than 20 years have elapsed since the first papers were published by Milton Helpern, Charles Wetli, and Michael Baden. Since that time, our government has done little to foster research into the pathology of abused drugs, and knowledge has advanced very little. With the advent of the great HIV pandemic, there may be a price to pay for this lack of knowledge, and for the failure to foster meaningful research. Perhaps with changing government priorities this situation will some day be rectified.

Finally, readers of the book will notice two important omissions: alcohol and marijuana. The reason for not dealing with the former is that alcohol requires its own book. The reason for not discussing the latter is that there isn't enough good anatomic pathology to write about, although recently there have been some interesting studies dealing with marijuana toxicology. I hope this subject can be added in future editions.

Steven B. Karch, M.D.
Berkeley, California

Preface to the second edition

Nearly 900 new references have been added since the first edition. The large increase in number is explained partly by the addition of new subjects, such as solvent abuse. Most of the increase is simply due to increased interest in drug abuse, which is reflected by an increase in the number of papers being published. This increase became apparent late in 1991, and already seems to have peaked. This edition contains 233 new references from 1993, 224 from 1994, and 110 from the first 6 months of 1995.

There have been some major advances since the first edition was published, but most of these have been in the fields of molecular biology and neurochemistry. The characterization of receptor changes in agitated delirium and the cloning of opiate receptors come quickly to mind. By comparison, advances in the field of pathology have been pitifully few. Fewer than 2% of the new references added to this edition have anything to do with anatomy or pathology. Whether this dismal finding reflects a lack of interest among pathologists, or simply is a function of the fact that pathologists have no voice on the various panels that control drug abuse research funding, is not clear. I suspect, however, it is the latter.

I was gratified by the response to the first edition, and pleased that so many have found the book to be useful. I have tried to make this version even better. Perhaps there will be some new pathology to describe in the next edition.

Steven B. Karch, M.D.
Berkeley, California

Preface to the third edition

Six years have elapsed since publication of the second edition of *The Pathology of Drug Abuse* (now titled *Karch's Pathology of Drug Abuse*). Important advances in the molecular biology of addiction have occurred since then. Some of these advances are directly relevant to the clinical disciplines of pathology and toxicology. Recent discoveries about heritable "channelopathies" and their role in the causation of sudden cardiac death are particularly exciting. Nonetheless, the pathology of drug abuse remains essentially an orphan science.

When the first edition of this book was published in 1992, the Drug Abuse Warning Network (DAWN) survey reported 3465 cocaine-related deaths, and there were 1044 Medline citations for cocaine. The number of cocaine-related deaths had increased to nearly 5000 in 1999, but the number of published studies on cocaine was unchanged. Similarly depressing figures could be quoted about heroin and heroin-related research. Government sponsorship for pathology and postmortem toxicology remains nonexistent. Even so, more than 800 new references have been added to this edition, and there is an emerging acceptance of the notion that toxicology is not the same as therapeutic drug monitoring. Forensic pathologists now understand that measuring the blood concentrations of an abused drug does not explain how and why that drug is toxic or determine a cause of death. Acceptance of this idea is no small thing, and perhaps more progress has been made than appears.

As the author of this book, I continue to be gratified by the response it has received, especially when someone tells me how useful it has been in his or her search for answers to difficult problems. I am hopeful that readers will continue to be pleased by this book, even if our fundamental understanding of the problems has not advanced by quite as much as I would have liked.

Steven B. Karch, M.D.
Berkeley, California

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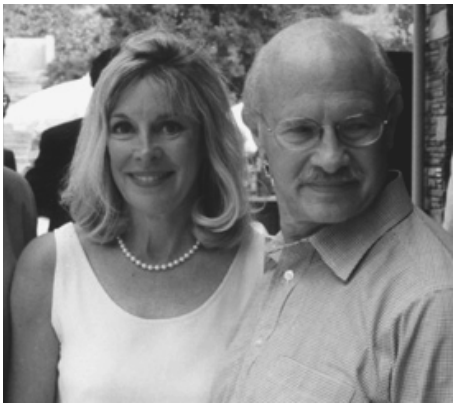
About the Author



Dr. Steven Karch with his wife, Donna.

Dr. Steven Karch earned his undergraduate degree at Brown University in Providence, RI, and attended graduate school in Anatomy and Cell Biology at Stanford University. He received his M.D. degree from Tulane University School of Medicine in New Orleans and did postgraduate training in neuropathology at the Royal London Hospital and in cardiac pathology at Stanford University, Palo Alto. He is currently Assistant Medical Examiner in San Francisco.

Dr. Karch is the author of nearly 100 papers and book chapters, most having to do with the effects of drug abuse on the heart. He has published four books (*The Pathology of Drug Abuse,* first and second editions; *Drug Abuse Handbook*; *A Brief History of Cocaine;* and *The Consumer's Guide to Herbal Medicine*). He is the Forensic Science Editor for Humana Press; the first three titles in that series were released in 2000.

Dr. Karch is a Fellow of the American Academy of Forensic Sciences and a member of both the Society of Forensic Toxicologists (SOFT) and the National Association of Medical Examiners (NAME). He is also a Fellow of the Royal Society of Medicine in London and The Forensic Science Society (U.K.).

Dr. Karch serves as a consultant toxicologist/pathologist to the herbal supplement industry and lectures frequently on the investigation of drug-related deaths. He has testified on drug-related matters in courts around the world.

Contents

chapter one

Cocaine

1.1 Incidence

Cocaine is the most frequent cause of drug-related deaths in the United States. In 1999, across the 40 metropolitan areas included in the federal Drug Abuse Warning Network (DAWN) survey, cocaine was the most frequently mentioned drug (4864 cases, or 48.1%), followed by heroin/morphine (4820) and alcohol-in-combination (3916). These numbers have changed very little in recent years. In 1994, for example, 4134 cocaine-related deaths were reported, accounting for 47% of all drug deaths reported to the government (Kissin et al., 2000).

References

Kissin, W., Garfield, T. et al. (2000). Drug Abuse Warning Network Annual Medical Examiner Data 1998, Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Statistics, Rockville, MD.

1.2 Epidemiology

In 1999, an estimated 1.5 million Americans were current cocaine users. This represents 0.7% of the population age 12 years and older. For that same year, the estimated number of current "crack" users was 413,000. While the number of cocaine users declined from 5.7 million in 1985 (3.0% of the population) to 1.4 million (0.7% of the population) in 1992 and has not changed significantly since that time, a significant increase has occurred in the number of individuals experimenting with cocaine; from 1994 to 1998, the annual number of new users of cocaine (any form) increased from 514,000 to 934,000 (Kissin et al., 2000; Office of Applied Studies, 1998). The increase was most striking among youths ages 12 to 17 years, for whom the rate for first-time use has nearly tripled.

When cocaine users are analyzed by age group, the highest rate of current cocaine use is for those ages 18–25 years (2.0%). This represents a significant increase over the 1.2% observed in 1997. Rates were 0.8% for youths ages 12–17 years, 1.2% for young adults ages 26–34 years, and 0.5% for adults 35 years and older. Rates have not changed for these older groups. According to the federal government's 1999 Household Survey, the rate of current cocaine use is similar in blacks and Hispanics (1.3%) but is much lower (0.7%) among whites (Office of Applied Studies, 1998).

Whether or not a person uses cocaine is highly dependent on how much education he or she has had. In 1998, among adults 18 years and older, those who had not completed

high school had a current use rate of 1.4%. That rate was only 0.8% for those with a high-school education. Among college graduates, the rate was even lower: 0.4%. Employment is another significant predictor of cocaine use. The rate of current cocaine use was highest among the unemployed (3.4% of the unemployed over 18 years old). Cocaine use among individuals with full- or even part-time employment was 0.9%. However, in terms of absolute numbers, most cocaine users were employed. Of the 1.8 million adult current cocaine users in 1998, 1.1 million (70%) were employed either full or part time.

According to the medical examiner component of the DAWN report for 1999, cocaine was the most common cause of drug-related death among blacks (64% of episodes), second among Hispanic decedents (45%), and third among white decedents (32%). Overall, cocaine ranked first among female decedents (33%), and second among males (45%) (Kissin et al., 2000). Cocaine was mentioned in 39% of episodes involving decedents ages 18–54 years, but in only 24% of episodes involving decedents over age 55. Cocaine was mentioned in 16% of deaths involving children ages 6–17 years (Kissin et al., 2000).

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Kissin, W., Garfield, T. et al. (2000). Drug Abuse Warning Network Annual Medical Examiner Data 1999, Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Statistics, Rockville, MD.

Office of Applied Studies (1998). Preliminary Results from the 1997 National Household Survey on Drug Abuse: H-6, Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Rockville, MD.

1.3 History

The word "coca" comes from the Aymara "khoka," meaning "the tree." Coca has nothing to do with the chocolate-producing nut called cocoa, and its only relation to the kola nut is phonetic. Although it is claimed that measurable quantities of cocaine and nicotine have been detected in 3000-year-old Egyptian mummies (Balabanova et al., 1992), these claims remain unconfirmed and unlikely. Cocaine and nicotine are derived from New World plants, and how they would have come to be used in Africa before the discovery of the New World remains a mystery. Even if such plants were known to the ancient Egyptians, Europeans did not hear about them until the Spanish colonized South America. When Spain took Peru in the 1500s, Spanish soldiers and explorers encountered Indians who had been chewing coca leaf for thousands of years.

The experience of the Indians with coca was recounted in Nicolas B. Monardes' monograph, *Joyfulle News out of the New Founde Worlde, wherein is declared the Virtues of Herbs, Treez, Oyales, Plantes, and Stones*. Monardes' book was reprinted many times after first being published in Barcelona sometime in the early 1560s. In 1599, a translation by an English merchant was published in London. Monardes' book contained accurate descriptions of many New World plants, including tobacco and coca. Monardes was fascinated by the fact that coca appeared to allow users to go without food, but he also was aware that coca had undesirable side effects. He observed, "Surely it is a thyng of greate consideration, to see how the Indians are so desirous to bee deprived of their wittes, and be without understanding" (Guerra, 1974).

For a long time the medical community remained unimpressed with coca. Hermann Boerhave favorably mentioned coca in his textbook on medicinal plants, published in 1708 (Mortimer, 1901), but in spite of Boerhave's initial enthusiasm, more than 100 years elapsed

before the first illustration of coca appeared in an English magazine. An article on coca by Sir William Hooker, then curator of the Royal Botanical Gardens at Kew, appeared in 1835. In addition to illustrations of the coca plant, the article also contained Hooker's translation of a book by the German explorer and naturalist, Edward Poeppig. Poeppig thought that coca chewers were very much like opium addicts, and warned against the immoderate use of coca (Poeppig, 1835). Other travelers and explorers had more positive impressions, but the potential toxicity of coca was known even before it became widely available in Europe.

Johan von Tschudi was one of the early explorers of the Amazon. He was a prolific writer, and his travel books were widely read in Europe and the U.S. He, too, was impressed with the apparent ability of coca to increase endurance, but he was concerned that Europeans might develop a "habit." His book *Travels in Peru*, first published in 1847, contains the first accurate description of cocaine "binging" (von Tschudi, 1847). The term describes the tendency of cocaine users to consume, in one session, all the drug in their possession. According to von Tschudi, "They give themselves up for days together to the passionate enjoyment of the leaves. Then their excited imaginations conjure up the most wonderful visions. …I have never yet been able to ascertain correctly the conditions the Coquero passes through on returning to his ordinary state; it, however, appears that it is not so much a want of sleep, or the absence of food, as the want of coca that puts an end to the lengthened debauch."

In 1857, von Tschudi persuaded a professor of chemistry at the University of La Paz, Enrique Pizzi, to try to isolate the active principle of coca. Pizzi thought he had succeeded and gave von Tschudi a sample to take home to Europe. Returning to Göttingen, von Tschudi gave the sample to his friend, Carl Wöhler, the chemist who had first synthesized urea. Wöhler gave the sample to Albert Niemann, his graduate student. Niemann found that the sample contained only gypsum. Wöhler remained curious, and when he heard that Archduke Ferdinand was sending a frigate on an around-the-world training cruise Wöhler approached Carl von Scherzer, chief scientist of the expedition, and asked him if he could bring back enough coca leaves to analyze (von Scherzer, 1861). von Scherzer returned three years later with 60 pounds of leaves and gave them to Wöhler, who again gave them to Niemann.

Given an adequate supply of leaf, purification of cocaine proved relatively simple. Niemann published his Ph.D. thesis, "On a New Organic Base in the Coca Leaves," in 1860 (Niemann, 1861a). Even after the purification of cocaine, interest in its therapeutic applications remained slight, and reports in journals were still mostly anecdotal. Other than the fact that he was the first to isolate cocaine, very little is known about Niemann, and he died shortly after his thesis was published.

A *Lancet* editorial published in 1872, 12 years after cocaine had been purified, stated that "there is considerable difference of opinion as to its effects upon the human subject, and the published accounts are somewhat conflicting; but we think that there is strong evidence in favor of its being a stimulant and narcotic of a peculiar kind, and of some power" (Anon., 1872). Coca-containing wines became popular in France and Italy during the late 1860s (Figure 1.3.1). The most famous of these was manufactured by Angelo Mariani. It contained 6 mg of cocaine per ounce and was advertised as a restorative and tonic; that seems to be how it was used. Satisfied customers endorsing *Vin Mariani* (Figure 1.3.2) included Thomas Edison, Robert Louis Stevenson, Jules Verne, Alexander Dumas, and even Pope Leo III. Within 10 years of its introduction in Paris, Mariani's wines were in much demand throughout the U.S. (Mariani, 1872). The amount of cocaine contained in these products was modest. It is now known that when alcohol and cocaine are combined, a new metabolite called *cocaethylene* is formed. It has the same affinity for the dopamine receptor as cocaine itself, which means that it should be just as psychoactive.

Figure 1.3.1 **Coca-containing wines.** These wines became popular during the 1860s. Among the many competitors, the most famous was *Vin Mariani*. The average product contained 5 to 10 mg of cocaine per ounce. (From the National Library of Medicine.)

Figure 1.3.2 **Newspaper advertisement for *Vin Mariani*.** Angelo Mariani was a master at self-promotion, and it is difficult to decide for which of his two great inventions he should be remembered: the popularization of coca wine or the invention of the modern publicity campaign. *Vin Mariani* was immensely popular. Mariani sent cases of free wine to celebrities, who would then write thank-you notes or even endorsements which Mariani collected and published. Thomas Edison and Sarah Bernhardt wrote endorsements, as did Pope Leo III. President William McKinley's secretary, John Addison Porter, wrote Mariani to thank him and assured Mariani that the wine would be used whenever the occasion required. This advertisement, featuring a picture of the Pope, appeared in a London newspaper in 1899.

Because it has a half-life that is many times longer than that of cocaine, combinations of alcohol and cocaine may be quite intoxicating.

In the early 1880s, Parke Davis and Company began marketing a fluid extract containing 0.5 mg/mL of semi-purified cocaine. At about the same time, physicians began prescribing elixirs containing cocaine for treatment of a variety of ailments, including alcohol and morphine addiction. In spite of the inappropriate use of these mixtures, reports of toxicity and cocaine-related disease were rare. Concurrent with the increased dispensing by physicians, patent medicine manufacturers began adding cocaine extract to nearly all of their products. One such promoter was John Styth Pemberton. He went into competition with Mariani and began selling "French Wine Cola." His initial marketing efforts were not very successful. In what proved to be a wise marketing move, Pemberton dropped the wine from the product and added a combination of cocaine and caffeine. The product, reformulated in 1886, was named "Coca-Cola."

Two events occurred in 1884 that significantly changed the pattern of cocaine use in the U.S. and Europe. The first was the publication of Freud's paper, *Über Coca* (Freud, 1884; Andrews and Solomon, 1975). The second was Köller's discovery that cocaine was a local anesthetic (Figure 1.3.3) (Noyes, 1884). By the time Freud sat down to write his paper, American physicians had already published more than a dozen papers recommending cocaine in the treatment of morphine addiction (Bently, 1880). Freud enthusiastically accepted this American notion and even elaborated on it, recommending cocaine as a remedy for a host of conditions that are not even recognized as diseases today. Köller's discovery was far more important. The availability of an effective local anesthetic had tremendous impact on the way medicine was practiced.

Physicians around the world were soon experimenting with the use of cocaine in a wide range of conditions. Some of the applications, such as eye and hemorrhoid surgery (Anon., 1886c), were quite appropriate. Other applications, such as the treatment of hay fever, were more questionable (Anon., 1886a). Still other uses were bizarre and potentially dangerous (Anon., 1886b). With so many physicians experimenting with the drug, not much time elapsed before the first reports of cocaine toxicity began appearing. Less than one year after Köller's and Freud's papers were published, an article in the *British Medical Journal* described the toxic reactions associated with cocaine use in ophthalmologic surgery (Anon., 1885b). About the same time, the popular press began carrying accounts of cocaine-related deaths (Anon., 1885a). The first cocaine-related cardiac arrest was reported in 1886 (Thompson, 1886), as was the first cocaine-related stroke (Catlett, 1886). In 1887, Mattison reviewed 50 cases of cocaine toxicity, four of which were fatal. Each of the fatalities had the characteristics associated with cardiac arrhythmias (Mattison, 1887a,b). The following year Mattison published data on an additional 40 cases, including two more fatalities (Mattison, 1888).

None of these negative reports appeared to have much impact. Patent-medicine manufacturers continued to cash in on the popularity of coca by replacing low-concentration cocaine extracts with high concentrations of refined cocaine hydrochloride. Thousands of cocaine-containing patent medicines flooded the market, some with truly enormous amounts of cocaine. Dr. Tucker's Asthma Specific, for instance, contained 420 mg of cocaine per ounce and was applied directly to the nasal mucosa. Absorption was nearly total. As the cocaine content of the products increased, so did the number of reported medical complications. The situation rapidly deteriorated when users learned they could "snort" cocaine. Until the early 1900s, cocaine had been taken mainly by mouth or by injection. The fact that the first cases of septal perforation and collapse (saddle nose deformity) were not reported until 1904 suggests that "snorting" had only become popular a year or so earlier (Maier, 1926).

THE OPHTHALMOLOGICAL CONGRESS IN HEIDELBERG.

(From our Special Correspondent.)

MURIATE OF COCAINE AS A LOCAL ANÆSTHETIC TO THE CORNEA—NO RADIATING MUSCULAR FIBRES IN THE IRIS—ACTUAL CAUTERY IN SUPERFICIAL CORNEAL ULCERATIONS—OPTICO-CILIARY NEURECTOMY—IS CATARACT THE RESULT OF CHRONIC BRIGHT'S DISEASE?—PROFESSOR ARLT AND HIS RECENT WORK IN GLAUCOMA.

KREUZNACH, GERMANY, September 19, 1884.

SIR: The usual Ophthalmological Congress in Heidelberg has just closed its session, and a few cursory notes at this early date may interest some readers. At this meeting elaborate papers are not read, but condensed statements are presented of the subjects introduced. The notable feature of this Society is that only new things or new phases of old topics are presented. This is not from any expressed rule, but is from the tacit understanding which controls men who are so diligently investigating the unknown in science as are these eager workers. These men have no patience with mere reiterations. Perhaps the most notable thing which was presented was the exhibition to the Congress upon one of the patients of the Heidelberg Eye Clinic, of the extraordinary anæsthetic power which a two per cent. solution of muriate of cocaine has upon the cornea and conjunctiva when it is dropped into the eye. Two drops of the solution were dropped into the eye of the patient at the first experiment, and after an interval of ten minutes it was evident that the sensitiveness of the surface was below the normal, then two drops more were instilled and after waiting ten minutes longer there was entire absence of sensibility, a probe was pressed upon the cornea until its surface was indented, it was rubbed lightly over the surface of the cornea, it was rubbed over the surface of the conjunctiva bulbi, and of the conjunctiva palpebrarum; a speculum was introduced to separate the lids and they were stretched apart to the uttermost; the conjunctiva bulbi was seized by fixation forceps and the globe moved in various directions. In all this handling the patient declared that he felt no unpleasant sensation, except that the speculum stretched the lids so widely asunder as to give a little discomfort at the outer canthus. Before the experiment his eye was shown to possess the normal sensitiveness, and the other eye, which was not experimented on, was in this respect perfectly normal. The solution caused no irritation of any kind, nor did it at all influence the pupil. The anæsthetic influence seemed to be complete on the surface of the eye, and it lasted for about fifteen minutes and the parts then resumed their usual condition. This first experiment was done in the presence of Professor Arlt, of Professor Becker, of the clinical staff, of Dr. Ferrer of San Francisco, of some other physicians, and of the writer. The next day the same experiment was performed on the same patient in the presence of the Congress and with the same results. This application of the muriate of cocaine is a discovery by a very young physician, or he is perhaps not yet a physician, but is pursuing his studies in Vienna, where he also lives. His name is Dr. Koller, and he gave to Dr. Brettauer, of Trieste, a vial of the solution, to be used in the presence of the Congress by Dr. Brettauer. Dr. Koller had but very recently become aware of this notable effect of cocaine, and had made but very few trials with it. These he had been led to make from his knowledge of the entirely similar effect which it has for some year or more been shown to have over the sensibility of the vocal cords, and because of which laryngologists pencil it upon their surface to facilitate examinations.

The future which this discovery opens up in ophthalmic surgery and in ophthalmic medication is obvious. The momentous value of the discovery seems likely to prove to be in eye practice of more significance than has been the discovery of anæsthesia by chloroform and ether in general surgery and medicine, because it will have therapeutic uses as well as surgical uses. It remains, however, to investigate all the characteristics of this substance, and we may yet find that there is a shadow side as well as a brilliant side in the discovery. Professor Kühne, who in the Heidelberg Physiological Laboratory worked out the details of Boll's discovery of the visual purple of the retina, received the news of this new discovery with the liveliest interest. We may, perhaps, get from him a further investigation into its properties. The substance makes a clear solution, and is found in Merck's catalogue.

Another notable statement came from Dr. Eversburch, of Munich, as the result of very exact and elaborate studies, to the effect that there are no radiating muscular fibres in the iris; in other words, that the dilator iridis has no existence in man. It is found, he says, in some animals, and especially in those which have oblong pupils, whether vertical or horizontal, and in the form of fasciculi at the extremities of the slit. He absolutely denies the existence of such fibres in the human eye, and asserts that the fibres hitherto described under this name are nerve-fibres. These revolutionary assertions were received with respect and attention, because the investigator was known to be a careful and competent anatomist. If his declarations should be confirmed, and they will not be lightly accepted, we must find out a new theory for the active dilatation of the pupil. A good deal of physiology will have to be cast into a new form. It is true that the anatomical discussion has not been closed on this point, but in favor of the existence of the dilator stand the names of Merkel, Henle, and Iwanoff among recent investigators. Eversburch has in his possession the preparations of Iwanoff, who died a few years ago, and he knows the nature of the contest into which he enters.

The uses of the actual cautery in superficial forms of corneal ulceration and in some other superficial processes, especially in those of micrococcic origin, were discussed both here and in Copenhagen. There seems to be a general consensus as to the usefulness of this treatment in selected cases of superficial corneal disease, viz., in ulcus rodens, in superficial suppurative processes, in atonic ulcers, and by Nieden in xerophthalmus. Nieden will shortly announce his views in full in an article in the *Archives for Ophthalmology*. He presented a most delicate and elegant form of galvano-cautery which he had devised, and to which he had applied a very delicate and promptly acting key invented by Professor Sattler. Another form of cautery is in use in the Heidelberg Eye Clinic, which has been devised by Professor Becker, and is a very small and utilizable Paquelin cautery. Both these instruments can be handled with nicety and delicacy, and without frightening the patient, and also in most cases without giving him any pain. This treatment, as well as the scraping of such ulcers by a sharp spoon, as does Meyer, of Paris, is founded on the micrococcic theory of the pathology of these processes, and marks another forward step in ophthalmic therapeutics.

Optico-ciliary neurectomy as a preventive of sympathetic ophthalmia has not passed out of practice, as to a considerable degree has become the case among us. So able an observer and logical a reasoner as Professor Schweigger, of Berlin, recommends its performance and holds it in higher esteem than enucleation. He divides the internal rectus muscle to gain easy approach to the nerve, and he lifts it from its bed by a sharp double hook and excises 10 mm. of it. He is said to be extremely skilful in this proceeding, and the very small disturbance which he causes in the structures of the orbit may perhaps explain the success which he has had and the confidence which he expresses in its prophylactic virtue. Among over a hundred cases which furnished the material for his conclusions, in two cases he saw occur in the opposite eye an acute neuro-retinitis, with opalescent infiltration, etc. There was no reduction of vision either central or peripheral. In two weeks the appearance

Figure 1.3.3 **Cocaine as a local anesthetic.** The discovery that cocaine was a potent local anesthetic revolutionized surgery. It was first reported at an ophthalmology congress in Heidelberg. Shortly thereafter an account appeared in the *Medical Record* of October 11, 1884. (From the Medical Library at the University of California, San Francisco.)

Figure 1.3.4 **Indonesian coca production.** During the 1920s, Indonesian plantations exported more coca leaf than producers in South America. This photograph, taken in 1927, shows workers sorting coca leaf. (Photograph courtesy of the Tropen Museum Photo Bureau, Amsterdam.)

As demand for cocaine grew, alternate sources came on line, and a Southeast Asia cocaine industry came into existence. Coca was also grown in Nigeria, Sri Lanka, Malaysia, Indonesia, Taiwan, and Iwo Jima (Figure 1.3.4). But the Javanese plantations were the main suppliers, and Japanese pharmaceutical companies were the main buyers. European drug manufacturers, such as Merck, even bought their own Javanese plantations, shipping dried coca leaves back to Germany for refining. In order to remain competitive, Dutch coca growers, along with The Dutch Colonial Development Board, formed a joint venture and built their own refinery in Amsterdam. The Nederlandsche Cocaine Fabriek (NCF) opened on March 12, 1900, in Amsterdam (Figure 1.3.5). The Amsterdam plant was so successful, that a second floor was added to the factory in 1902. By 1910, coca exports from Java exceeded those from South America (Karch, 1998; Musto, 1998; Gootenberg, 1999).

The first histologic studies of cocaine toxicity were published in 1888. Vasili Zanchevski of St. Petersburg, Russia, studied the acute and chronic effects of cocaine in dogs. After a single lethal dose (24 mg/kg), the animals had changes typical of acute asphyxia. Smaller daily doses given for several weeks caused a "marked hyperemic condition of the central nervous system, in contrast to the rest of the organs, which were anemic." There were focal degenerative changes in the spinal ganglia, heart, and liver. In some cases, the myocytes had "lost their striae and [were] intensely granular" (Zanchevski, 1888). Although illustrations are lacking, Zanchevski's descriptions suggest that he was the first to observe a form of contraction band necrosis (CBN) occurring as a result of cocaine toxicity.

French researchers were the first to systematically study cocaine's psychological effects, largely because cocaine and morphine addiction were such a major problem in Paris. In 1889, at a meeting of the Biological Society of Paris, Valentine Magnon presented three cases illustrating that cocaine users were subject to tactile hallucinations. The symptom

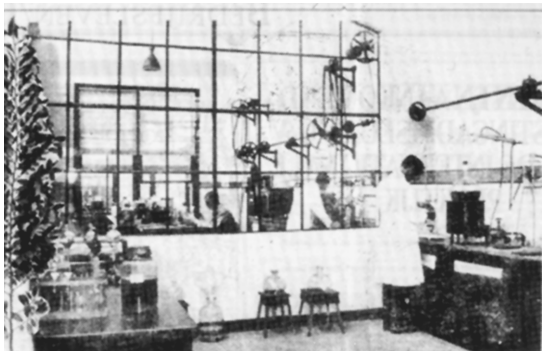

Figure 1.3.5 The Nederlandsche Cocaine Frabriek: The Dutch Colonial Development Board and coca growers in Java formed a joint venture and built a refinery to better compete with Merck and the other German cocaine manufacturers. The Nederlandsche Cocaine Fabriek (NCF) opened in Amsterdam on March 12, 1900. The Dutch plant was so successful that a second floor was added to the factory in 1902. By 1910, NCF claimed to be the largest cocaine manufacturer in the world, producing more than 1500 kg of refined cocaine per year. This photograph is from a trade publication, *Het Pharmaceutisch Weekblad*, published in 1925. (Courtesy of Marcel de Kort, Netherlands Ministry of Health.)

complex became known as "Magnon's symptom." In 1914, Georges Guillain contrasted the differences between cocaine and alcoholic hallucinations, commenting on how variable the effects of a given dose of cocaine could be (Maier, 1926).

One psychiatric disorder that has only recently been rediscovered is cocaine-associated excited delirium (some use the term *agitated* instead of *excited*, but the terms are used interchangeably). This cocaine-related disease first came to widespread public attention in 1914 when the *New York Times* carried a front-page article written by an American, Edward Williams. The article described "crazed Negroes" who were threatening the women of the New South (Williams, 1914). Because Williams' writings were patently racist, and because he observed the syndrome only in blacks, later historians wrote off his observations as racist hysteria (Kennedy, 1985).

New reports of the syndrome (hyperthermia, followed by agitated psychosis, respiratory arrest, and death) began to appear again at the start of the current pandemic. Although the disorder has nothing to do with race, it is quite real (Wetli and Fishbain, 1985), and the underlying neurochemical changes have now been characterized (see Section 1.12.2.12). Excited, or agitated, delirium was, in fact, recognized long before the *New York Times* headlined its dire warnings. In 1849, 25 years before cocaine became commercially available, a physician named Lester Bell published a paper describing exactly the same sort of symptoms in hospitalized psychiatric patients. Journal editors today would probably not have allowed Bell quite as much latitude in the title of his paper, but it was descriptive: "On a form of disease resembling some advanced stages of mania and fever, but so contra distinguished from any ordinarily observed or described combination of symptoms as to render it probable that it may be an overlooked and hitherto unrecorded malady" (Bell, 1849).

The first human autopsy study of a cocaine-related death was published in 1922. Bravetta and Invernizzi described a 28-year-old man who had been sniffing cocaine regularly for some months prior to his death. He neither drank nor used other drugs (Bravetta and Invernizzi, 1922). Hyperemia of the brain, lungs, and adrenals was noted, and the

heart was described as "flaccid" (cardiomyopathy?). The accompanying illustrations of the autopsy showed lesions similar to those described by Zanchevski. Animal studies by the same authors confirmed the autopsy findings and also demonstrated widespread endothelial injuries. These studies were reprinted in Maier's classic text on cocaine abuse, published in 1926 (Maier, 1926).

The tissue disposition of cocaine was studied at an even earlier date. In 1887, a German chemist, Helmsing, published his technique for the detection of cocaine in urine and tissues. The technique was fairly sensitive, and Helmsing was able to detect cocaine in urine from a cat that had been given 8 mg of cocaine (Anon., 1887). In 1951, Woods and his colleagues developed a calorimetric technique capable of detecting levels of cocaine as low as 500 ng/mL (Woods et al., 1951). A quarter century later, Jatlow and Bailey (1975) used gas chromatography to lower the limits of detection down to 5 ng/mL.

Shortly after Maier's text was published, case reports simply stopped appearing. Between 1924 and 1973, there was only one cocaine-related fatality reported, and it involved a surgical misadventure. In 1977, Suarez first described the "body packer" syndrome, where death results from the rupture of cocaine-filled condoms in the smuggler's intestines (Suarez et al., 1977). The absence of case reports no doubt reflected a decline in use, but the decline itself is difficult to explain. Certainly the passage of laws restricting the sale of cocaine (the Pure Food and Drug Act of 1906 and the Harrison Narcotic Act of 1914) had a great deal to do with it, but other factors were involved (McLaughlin, 1973).

Perhaps the most important factor may have been the introduction of amphetamines. Although amphetamines share important mechanisms of toxicity with cocaine, the former appear to have a higher therapeutic index, and, based on the number of case reports appearing in the medical literature, the incidence of myocardial infarction seems to be much lower with amphetamine and methamphetamine use than with cocaine. This may have to do with the fact that methamphetamine induces the production of heat shock protein, making myocytes more resistant to ischemic damage (Maulik et al., 1995). Methamphetamine is also much less expensive than cocaine, is easier to obtain, and appears to be more socially acceptable.

Significant toxicity from the use of coca leaf and coca extract was never a problem in Europe or the U.S. Toxicity only emerged when purified cocaine became readily available and individuals could increase their dosage by an order of magnitude. The small amounts of cocaine in *Vin Mariani* were apparently harmless, but the huge amounts in Dr. Tucker's formula were occasionally lethal. With the appearance of "crack" cocaine in 1986, another order of magnitude increase in dosage occurred (Jekel et al., 1986). That cocaine-related illness is now a significant cause of morbidity and mortality should not be surprising. It is not just that more people are using the drug; they are using more of it and using it more effectively.

The number of reported cocaine-related deaths rose rapidly during the late 1980s and continued to rise during the early 1990s. From 1990 to 1992, the number of cocaine-related deaths increased by nearly 25% (from 2408 to 3220), but the process now appears to have leveled off. In 1999, the most recent year for which complete statistics are available, medical examiners reported 4864 deaths, amounting to 41.8% of all reported drug-related deaths. That number is essentially unchanged from the previous two years (Kissin et al., 2000). Because the medical examiners participating in the DAWN survey perform only 60% of all autopsies done in the U.S., the total of all cocaine-related deaths must be substantially higher. Worse still, the methodology used by the DAWN survey is such that the total number of cocaine-related deaths is underestimated, even by districts that file reports with the survey (Brookoff et al., 1993).

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1.4 Cultivation and manufacture

1.4.1 Cultivation and crop yields

Coca leaf has been grown in the Andean subregion for thousands of years. Early explorers found it all along the eastern curve of the Andes, from the Straits of Magellan to the borders of the Caribbean. Coca grows best on the moist, warm slopes of mountains ranging in elevations from 1500 to 5000 feet. Coca shrubs grow to heights of 6 to 8 feet (Figure 1.4.1.1). The trunk of the plant is covered by rough, somewhat glossy bark that has a reddish tint. Its flowers are small and usually white or greenish yellow. Leaves are elliptical, pointed at the apex, and dark green in color. All cultivated coca is derived from two closely related species that grow naturally only in South America, *Erythroxylum coca* Lam and *Erythroxylum novogranatense* Hieron. Each species has one distinct variety designated as *E. coca* var. *ipadu* (Plowman) and *E. coca novogranatense* var. *truxillense* (Rusby) Plowman (Plowman, 1985). All four types are cultivated, although the alkaloid content of the different plants varies considerably (Plowman and River, 1983). *E. coca ipadu* is cultivated only in the Amazon valley of Brazil, Colombia, and Peru. Of all the cultivated varieties, *E. coca ipadu* contains the least alkaloid, less than 0.5%, and very little of that is cocaine. *E. novogranatense* is cultivated more widely and is better adapted to growth in hotter, drier climates.

Although there is some controversy, it seems likely that *E. novogranatense* was the variety cultivated in Java, Ceylon, India, and Taiwan. This variety may contain anywhere from 1 to 3% total alkaloid, with cocaine constituting as much as one half of the total alkaloid present (Lee, 1981; Bohm et al., 1982; Plowman and River, 1983; Plowman, 1985; Schlesinger, 1985). A strain of *E. novogranatense* cultivated in the desert coast region of Peru, near Trujillo, is the plant used to flavor Coca-Cola and other cola beverages.

Figure 1.4.1.1 **The first illustration of cocaine.** The first illustration of coca to appear in an English magazine (*Companion to the Botanical Magazine*) was published in 1836. It was drawn by Sir William Hooker, then director of the Royal Botanical Gardens at Kew. (Illustration courtesy of the library at the Royal Botanical Gardens at Kew, England.)

As recently as 1998, Colombia was still the world's leading producer of cocaine, accounting for 75% of all the cocaine production. That situation could change, as there really are no barriers to the re-establishment of cocaine growing in Southeast Asia. Some of the cocaine is produced from locally grown leaves, and the balance from semi-refined cocaine base imported from Peru and Bolivia. According to reports from the Drug Enforcement Agency (DEA), there was a 28% increase in the number of potentially harvestable coca plants in Colombia in 1998.

Major coca growing areas in the Andes share many characteristics. Yungas, which is close to La Paz, has an average annual rainfall of 45.7 inches. Chaparé, which is close to Cochabamba, has an annual rainfall of 102 inches. The plantations in Yungas can be harvested three times per year. Each harvest yields from 2 to 2.7 tons per hectare per year. Chaparé leaf contains, on average, 0.72% cocaine. It is estimated that the currently used

refining techniques are only 45% effective (less than half the cocaine is actually recovered from the leaf). As a result, 390 kg of Chaparé leaf are required to produce 1 kg of cocaine base.

The alkaloid content varies from area to area, depending on the local conditions and the strain cultivated. Coca leaf from Yungas, for example, has an alkaloid content of 0.85% (DEA, 1991). The average coca plantation will produce for about 20 years, but after the tenth year its yield steadily declines. Yields throughout South America are comparable. Both the yield per acre and the alkaloid content of the leaf were much higher in the Southeast Asian plantations (at one time, Indonesia exported more coca leaf than Peru). More than 60% of all coca leaf is grown in Peru, with another 22% coming from Bolivia and 15% from Colombia. Minor amounts come from Ecuador. When processed, 400 lb of leaf will yield between 1 and 2 kg of coca paste, depending on the quality of the leaf and how efficiently the coca has been extracted (Abruzzese, 1989).

It is estimated that in 1991 Andean coca producers had 201,700 hectares under cultivation, with more than half of that in Peru. This acreage would have produced 291,000 metric tons of leaf, yielding 820–850 tons of refined cocaine (DEA, 1991). In the interim, a U.S. State Department report published in 1999 noted a decrease in total acreage under production in 1998, with overall coca cultivation in the Andean countries falling 17% to 190,800 hectares. According to another recent U.S. State Department report, Peruvian coca cultivation in 1999 had decreased by 24% from 1998 levels (from 51,000 to 38,700 hectares), lowering the total amount of potential cocaine production to 175 metric tons, down from 240 in 1998 (U.S. Department of State, 2001).

1.4.2 Paste production

Cocaine extraction is a two- or three-step process carried out in a series of laboratories. The first steps occur on site. Immediately after harvesting, coca leaves are placed in a shallow pit lined with heavy plastic. The leaves are then soaked in a dilute solution of water and strong alkali, such as lime, for three or four days. An organic solvent is added. Methyl isobutyl ketone (MIBK) is the solvent of choice for this purpose, but nearly a dozen other solvents have been identified in samples that have been confiscated by the DEA and other agencies (International Narcotics Control Board, 1999). In recent years, the use of ethyl acetate and *n*-propyl acetate has become increasingly popular, but kerosene, gasoline, or even acetone can be used if no other solvents are available.

Extracted coca leaf is discarded and sulfuric acid is then added to the extract, dissolving a complex mixture of alkaloids in the aqueous layer. If the alkaloid content of the leaves is very high (as in Bolivia), hydrochloric acid may be used instead of sulfuric. The organic solvent is then removed, and the remaining aqueous solution is made alkaline by the addition of lime, ammonia, or the equivalent, causing the more basic alkaloids to precipitate out. This crude form of cocaine, called coca paste, is allowed to dry in the sun. The site where the initial steps occur is referred to as a "paste lab" (Figure 1.4.2.1). Laborers, called *pisacocas*, keep the alkali–coca leaf mulch mixed by stirring it with their hands and walking through it with their bare feet. The fluid is quite corrosive, and the workers quickly develop large extremity ulcers. The *pisacocas* tolerate the ulcers only because they are given a constant supply of coca paste to smoke (Weatherford, 1988).

The dried product is a mixture of cocaine, *cis*- and *trans*-cinnamoylcocaine, tropine, tropacocaine, hygrine, cuscohygrine, ecgonine, benzoylecgonine, methylecgonine, and isomers of truxillines. The mixture also contains a host of soluble organic plant waxes and benzoic acid. Depending on the alkaloid content of the coca leaves and on how the leaves

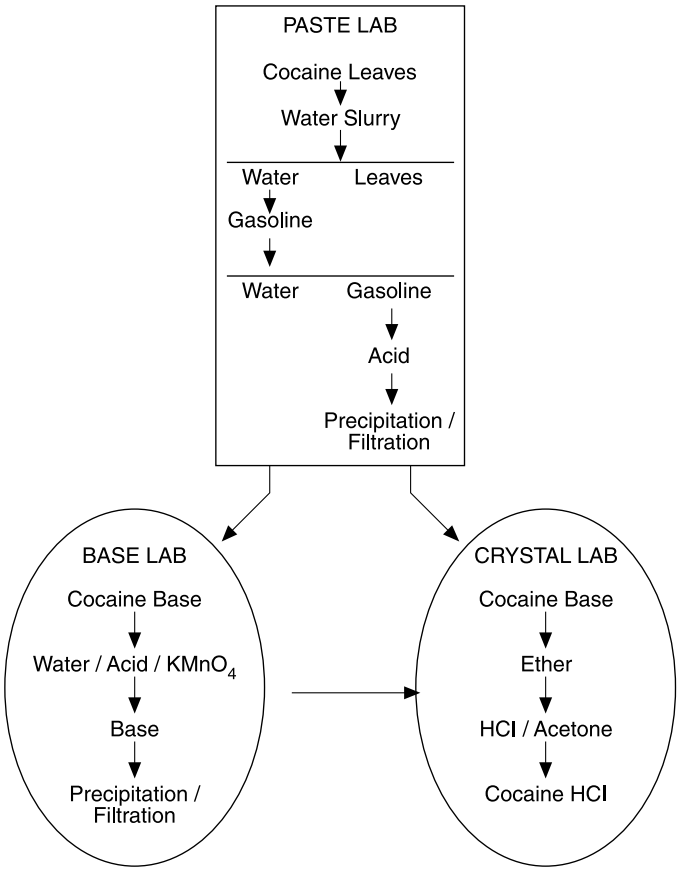

Figure 1.4.2.1 **Flow chart of illicit cocaine processing.** The preparation of purified cocaine from leaf. (Adapted from the *WHO Bulletin*.)

were processed, it takes between 100 and 150 kg of dry leaf to produce 1 kg of coca paste (Montesinos, 1965; Brewer and Allen, 1991).

Once the paste is prepared, the clandestine manufacturer has two options. The paste may be further purified at a base lab, or the producer may go directly to a "crystal lab." At base labs, paste is dissolved in dilute sulfuric acid. Potassium permanganate (potassium dichromate or sodium hypochlorite can be used just as effectively) (Figure 1.4.2.2; International Narcotics Control Board, 1999) is added until the solution turns pink, thereby destroying the cinnamoylcocaine isomers present as impurities in the paste. The isomers of cinnamoylcocaine are converted to ecgonine and, because ecgonine is very water soluble, it is easy to separate it from the cocaine. The job of the clandestine chemist is to stop the oxidation process (usually by adding ammonia or some other alkali) before the cocaine starts to oxidize and the yield drops. Analysis of impounded samples suggests that permanganate oxidation is used only about 60% of the time.

The reddish-pink solution is allowed to stand, then it is filtered and the filtrate is made basic with ammonia. The cocaine base precipitates out. The precipitate is filtered, washed with water, and then dried. Finally, it is dissolved in diethyl ether or acetone. After filtering, concentrated hydrochloric acid and acetone are added, causing purified cocaine hydrochloride to precipitate out. This final step may be done on site or the semi-purified cocaine

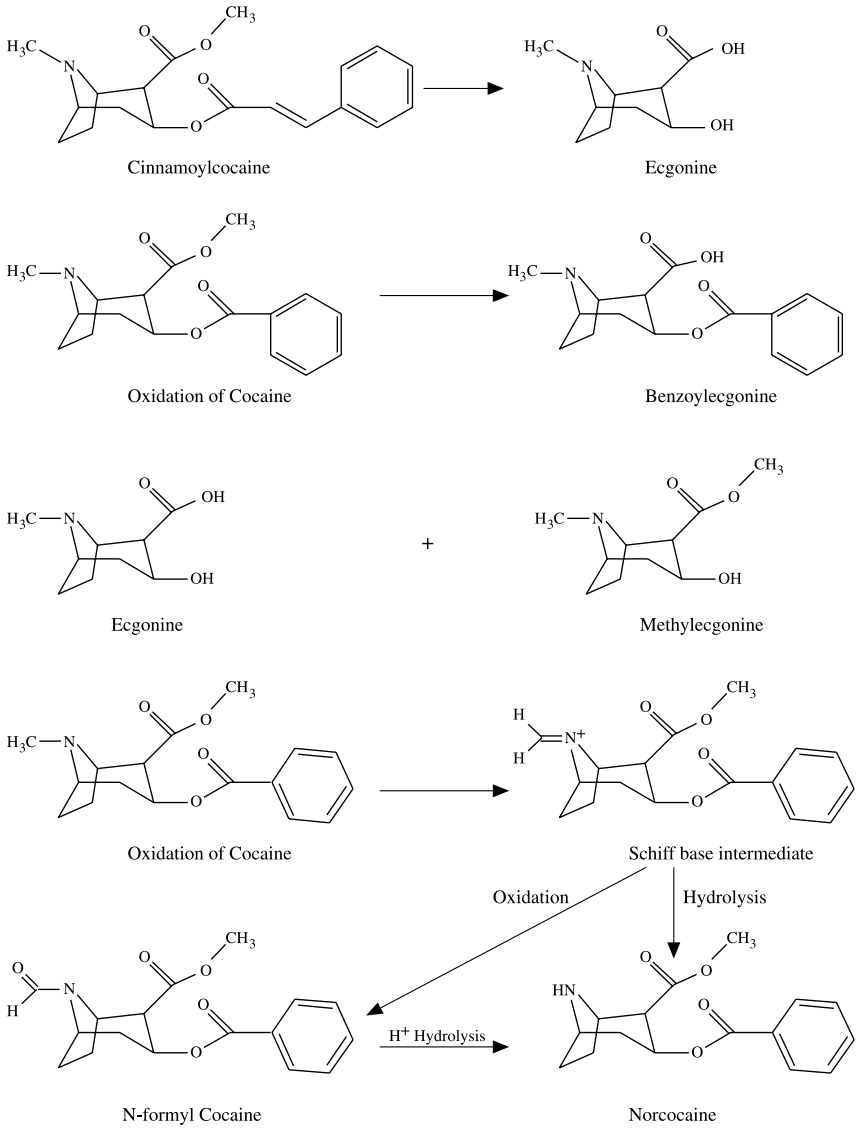

Figure 1.4.2.2 **Cocaine refining.** Cocaine refiners often add potassium permanganate to remove impurities. Cinnamoylcocaine is converted to ecgonine, which is water soluble and easy to separate from cocaine. If the process is allowed to continue for too long, the cocaine itself is degraded and the yield drops. Norcocaine, which may be hepatotoxic, is formed at the same time.

may be transported to a "crystal lab," usually located in one of the larger Colombian cities, although some drug producers have begun to set up labs in the U.S. As much as 50 kg may be processed at one time (Lee, 1981). The semi-purified cocaine is dissolved in a solvent, often ether. Hydrochloric acid is then added, along with a bridging solvent such as acetone, and white crystals precipitate out. The crystals are collected by filtration. Traces of the solvent remain, and their presence can sometimes be used to identify the origin of cocaine samples. In coca-producing countries, there is a significant market for the semi-purified paste itself. Paste is smoked, rolled up in pieces of newspaper, or packed into

cigarettes. Many of the ingredients introduced during the manufacturing process are still present in the coca paste and are inhaled as pyrolysis products. Coca paste smoking is a major cause of morbidity in coca-producing countries, but there is a paucity of scientific data about it (Paly et al., 1980).

When permanganate is added during the refining process, the *N*-methyl group of cocaine is oxidized, leading to the formation of *N*-formyl cocaine. Hydrolysis of *N*-formyl cocaine leads to the formation of norcocaine. The presence of these last two compounds can have forensic and clinical significance. Because *N*-formyl cocaine is a product of permanganate oxidation, it is not present in coca paste. Accordingly, the presence of this compound may yield valuable information about how, and possibly where, the cocaine sample was produced (Brewer and Allen, 1991).

Norcocaine is potentially hepatotoxic but, as a rule, only small amounts are formed by humans, and then usually only when ethanol is also present. Analysis has shown norcocaine concentrations in illicit samples ranging from 0.01 to 3.70% (Kumar, 1991). As may be expected, chemical analysis of coca paste has disclosed the presence of all the elements used during its manufacture, including benzoic acid, methanol, kerosene, sulfuric acid, cocaine sulfate, and other coca alkaloids (Jeri et al., 1978; Jeri, 1984; Moore and Casale, 1994). Impurities may constitute from 1 to 40% of a given paste sample. Paste can be broken down into neutral, acidic, and basic fractions. Gasoline residues are particularly common in the neutral fraction (El Sohly et al., 1991).

Unlike amphetamines, which may occasionally be contaminated with lead during the course of manufacture, coca paste samples, when analyzed, have always been found to be lead free. However, paste can contain large amounts of manganese, and the amount of manganese present is a marker for where the paste was produced. Colombian paste is manganese-rich while Peruvian is not (El Sohly et al., 1991). Limited studies of blood levels suggest that the results of coca paste smoking are not much different than those for "crack" smoking (Paly et al., 1980).

The total synthesis of cocaine is possible, and clandestine cocaine laboratories have been confiscated. The process is, however, a great deal more demanding than the synthesis of amphetamine and has never been attempted on a large scale. The synthetic origin of the cocaine will be evident from the contaminants found along with the cocaine. Diastomers of cocaine, such as pseudococaine, allococaine, and the *d,l*- form (which does not occur in nature) of cocaine, are not found in cocaine refined from coca leaf (Soine, 1989).

1.4.3 Quality and availability

The purity of confiscated cocaine is considered to be a good general indicator of availability. At wholesale levels, the purity levels of kilogram quantities which had been averaging 80% during 1990 increased to 87% during 1991. There is no recent indication that these purity levels are declining. At the retail level, the purity of gram-sized specimens which had been less than 50% in 1981 rose to nearly 80% in 1988, but has now fallen back into the high-60% range. At the same time, the street price has dropped from $275/g in 1981 to less than $95/g in 1996. Figure 1.4.3.1 illustrates the price and purity trends. The information is from the STRIDE (System To Retrieve Information from Drug Evidence) database maintained by the DEA. Although it was generally believed by many that the underlying cause of the current cocaine pandemic was the cheaper price of "crack" cocaine, an analysis by research economists suggests that, on a milligram-per-milligram basis, "crack" is not, and never was, less expensive than cocaine hydrochloride (Caulkins, 1997).

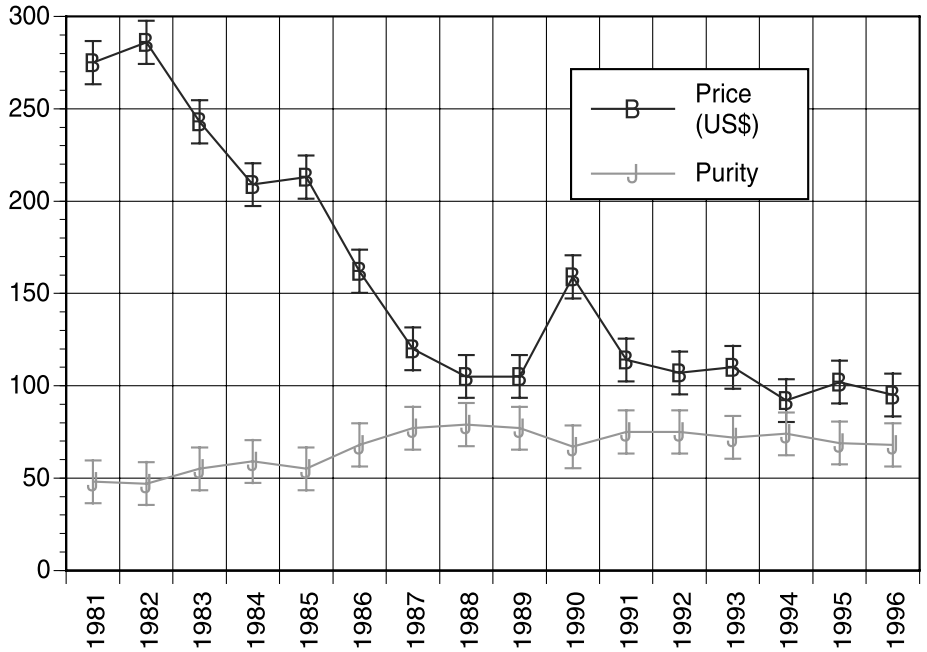

Figure 1.4.3.1 **Cocaine purity and prices, 1981 to 1996.** Estimates based on data from the Drug Enforcement Administration, 1999.

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1.5 Drug constants

Cocaine is [1R-(exo,exo0]-3-(benzoyloxy)-8-methyl-8-azabicyclo[3,2,1]octane-2-carboxylic acid methyl ester. The free base has the formula $C_{17}H_{21}NO_4$, and it has a molecular weight of 303.4 (Figure 1.5.1). It contains 67.31% carbon, 6.98% hydrogen, 4.62% nitrogen, and 21.10% oxygen. Pure cocaine forms colorless crystals or white crystalline powder. It is odorless and has a bitter taste. Its melting point is 98°C; however, it becomes volatile at temperatures over 90°C. Aqueous solutions are alkaline to litmus. The pKa at 15°C = 5.59. One gram dissolves in 600 mL of water, 6.5 mL of alcohol, 0.7 mL of chloroform, 3.5 mL of ether, or 12 mL of olive oil. It is also soluble in acetone and ethyl acetate. Cocaine hydrochloride, referred to in the older literature as cocaine muriate, has the formula $C_{17}H_{22}ClNO_4$. Its composition is 60.08% carbon, 6.53% hydrogen, 4.12% nitrogen, and 10.43% chloride, and its molecular weight is 339.81. Powdered, crystalline, or granular cocaine is water soluble and has a slightly bitter taste. The pKa is 8.6, and the melting point of pharmaceutical-grade material is 195°C. One gram dissolves in 0.4 mL of water or 3.2 mL of cold alcohol. It is also soluble in chloroform (1 g in 12.5 mL), glycerol, and acetone. It is insoluble in ether or oils. When heated in solution, it will decompose. Cocaine hydrochloride, stored in a tightly closed container at room temperature, will not decompose for at least five years. Solutions are stable for at least 21 days, provided the temperature is below 24°C and the pH is below 4.0. Above 4.0 pH, hydrolysis rapidly occurs (Muthadi and Al-Badr, 1986; Budavari et al., 1996).

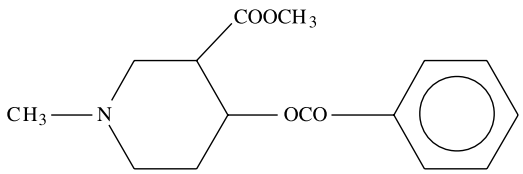

Figure 1.5.1 **Cocaine,** m.w. = 300.4.

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1.6 Routes of ingestion

1.6.1 Overview

Until quite recently, plasma concentrations of cocaine and its metabolites, after administration of realistic doses, had never been published. Ethical considerations prevent physicians from administering anything near the amount of cocaine consumed by addicts during a binge. As a consequence, cocaine pharmacokinetics in real cocaine abusers remained largely unstudied and uncharacterized. In 2000, several important studies addressing this issue were published. One was a clinical study in which plasma cocaine concentrations in 111 symptomatic cocaine users were measured and correlated with clinical symptoms (Blaho and Winberry, 2000). In a second study, the half-life of cocaine was estimated in a group of addicts admitted to a closed ward (Moolchan et al., 2000). The results of these studies suggest that (1) chronic users may consume multigram quantities of cocaine with relative impunity; (2) a variety of cocaine metabolites, previously thought to be insignificant (ecgonine methyl ester, norcocaine), are actually formed in fairly substantial amounts; and (3) in chronic users, the half-life of cocaine may be many hours longer than had previously been thought. All of these variables are partially a function of the route of administration (Figure 1.6.1.1).

1.6.2 Coca leaf chewing

Coca has been chewed for over 3000 years, but the pharmacokinetics of the process have only been partially characterized. Habitual users chew an average of 12 to 15 g of leaf three or four times a day. Depending on the quality of the leaf, the alkaloid content is usually less than 0.5%. Thus, the total amount of coca consumed at any one time is unlikely to amount to more than 75 mg. In one experiment, novice chewers who spit out their saliva had average peak blood levels of 38 ng/mL at 1 hour. Experienced users, who swallow their saliva, had mean values of 249 ng/mL; however, the range was from 130 to 859 ng/mL (Paly et al., 1979; Holmstedt, 1979). These levels probably are toward the lower end of the spectrum of levels attained when the drug is snorted.

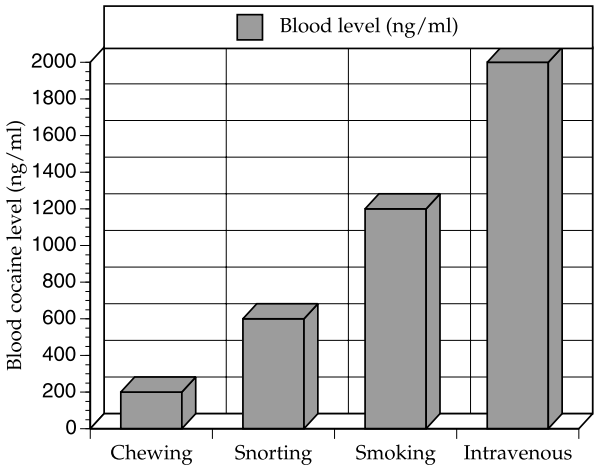

Figure 1.6.1.1 **Blood levels and routes of administration.** The route of ingestion determines cocaine blood levels. "Crack" smokers may have blood levels three or four times as high as leaf-chewing Indians. Levels after snorting are intermediate.

1.6.3 Coca tea drinking

Coca teas are popular in many areas of South America and are even sold commercially. The average coca tea bag contains approximately 1 g of dried coca leaves. The content of the commercial tea bags is quite variable, depending on where they are manufactured. Products from Peru and Bolivia generally contain 1 g of dried, shredded coca leaf containing 4 to 5 mg of cocaine plus variable amounts of benzoylecgonine and ecgonine methyl ester, along with trace amounts of *trans*-cinnamoylcocaine. Depending on the origins of the coca tea, urinary benzoylecgonine concentrations in tea drinkers range from just under 4000 ng/mL to almost 5000 ng/mL 3.5 to 10 hours after ingestion (Jenkins et al., 1996).

1.6.4 Snorting (insufflation)

When cocaine is snorted, peak plasma concentrations are proportional to the amount of cocaine ingested (Wilkinson et al., 1980). Because cocaine is a vasoconstrictor, it inhibits its own absorption, and the time required to reach peak concentration gets longer as the dose gets larger. One hundred milligrams, which is approximately the equivalent of two to three "lines," will produce a blood level of 50–100 ng/mL, sufficient to cause transient increases in pulse and blood pressure (Fischman et al., 1983; Javaid et al., 1983; Foltin et al., 1988). In one study, intranasal application of 1.5 mg/kg (equivalent to 90 mg in a 60-kg man, or roughly the amount of cocaine found in 15 g of leaf) produced peak plasma concentrations of 120–474 ng/mL within 30–60 minutes (Van Dyke et al., 1976). When somewhat larger doses were given (2 mg/kg), peak plasma concentrations ranged from 131 ng/mL up to 1012 ng/mL, with an average of 370 ng/mL at 30 minutes, falling to 295 ng/mL at 60 minutes, and 223 ng/mL at 90 minutes (Brogan et al., 1992).

In the laboratory setting, nasal insufflation has been shown to be the least efficient way of administering cocaine, at least when compared to intravenous use or smoking. A 42-mg dose of cocaine hydrochloride produces peak plasma concentrations of 65 ± 8 ng/mL, barely one quarter the level produced by smoking only 32 mg of base or injecting 25 mg intravenously.

In practice, the amount of cocaine taken by users is considerably greater than test doses given in the laboratory. Blaho et al. reported that plasma concentrations in four symptomatic cocaine "insufflators" ("snorters") was .21 ± 0.20 mg/L. That value is not significantly different than a mean cocaine concentration of 0.18 ± .06 mg/L measured in 46 symptomatic "crack" smokers who presented at hospital emergency departments for treatment (Blaho and Winberry, 2000). Resultant plasma concentrations from the symptomatic patients are surprisingly close to results observed in volunteers in a controlled setting.

1.6.5 Surgical application

Cocaine is still used by otorhinolaryngologists and cosmetic and plastic surgeons, often in combination with epinephrine, to maintain a dry operative field. The recommended maximum dose is 200 mg per patient or 2–3 mg/kg. However, a survey carried out in the late 1970s found that most practicing head and neck surgeons routinely exceeded these recommendations, occasionally with untoward, or even fatal, results (Johns and Henderson, 1977). As the dangers of this practice have become more apparent, cocaine/epinephrine combinations are used much less often, but the combination is still used, and the occasional myocardial infarct occurs as a result (Laffey et al., 1999). Even when cocaine-

soaked pledgets are applied, plasma concentrations may exceed 600 ng/mL within the first half hour (Liao et al., 1999).

Topical cocaine may be combined with submucous injections of lidocaine/epinephrine. Because pH has a significant effect on local anesthetic activity, bicarbonate is occasionally mixed with the cocaine to increase its efficacy (Sollman, 1918). Cocaine mixed with an epinephrine solution is referred to as "paste." When a mixture of cocaine and epinephrine is used, with or without the addition of bicarbonate, the resultant plasma levels can be quite high. Concentrations of over 2000 ng/mL have been observed (Lips et al., 1987; Bromley and Hayward, 1988).

Injected epinephrine is, of course, absorbed along with the cocaine, and this may lead to toxicity. The toxic effects of cocaine on the heart are at least partly mediated by catecholamine excess, and the potential for the occurrence of an untoward event such as myocardial infarction is very real when cocaine is combined with epinephrine (Meyers, 1980; Chiu et al., 1986; Littlewood and Tabb, 1987; Ross and Bell, 1992; Ashchi et al., 1995; Noorily and Noorily, 1996; Laffey et al., 1999). At the turn of the century, cardiac arrest was a relatively frequent complication of cocaine and cocaine/epinephrine anesthesia (Mayer, 1924), but now that the inherent toxicity of the combination is better understood, serious complications are uncommon.

Malpractice suits have alleged that either too much epinephrine or too much cocaine had been given, but the probability is that both agents combined to cause coronary artery spasm (Ascher et al., 1988; Karch, 1989; Flores et al., 1990; Wilkerson et al., 1990). Both cocaine and epinephrine can also induce lethal cardiac arrhythmias, at least in animal studies, but the mechanisms involved remain largely uncharacterized (Kabas et al., 1990; Laster et al., 1990; Schwartz et al., 1988).

Catecholamine measurements have been made in postmortem urine specimens, but physiological stress is common before death, and urine catecholamines in healthy subjects, when normalized to creatinine concentrations, overlap concentrations of patients with pheochromocytoma and are of little diagnostic significance (Tormey et al., 1999). Even measurements made during life, especially in the post-arrest state, would be impossible to interpret, as it is impossible to distinguish parenteral epinephrine from epinephrine released in response to the maximal physiologic stress of infarction or successful cardiac resuscitation (Worstman et al., 1984; Prengel et al., 1992).

It is occasionally alleged that excessive amounts of epinephrine have been administered as a means of attempted murder. Unfortunately, the dose of epinephrine administered cannot be calculated either in living patients or in the postmortem setting, as the volumes of distribution for epinephrine and its metabolites have never been measured. Postmortem measurements of epinephrine concentrations, or metanepherine/normetanepherine concentration ratios, are equally without value, because nothing is known about catecholamine postmortem redistribution.

Another reason why postmortem epinephrine measurements cannot be interpreted is the tremendous concentration variations that normally occur in different tissues. For example, in areas of the brain such as the hypothalamus, high norepinephrine concentrations would be anticipated, while other areas of the brain not linked to the sympathetic nervous systems would normally be expected to contain more epinephrine and less norepinephrine (Mefford, 1988). Similar considerations apply in the heart, where catecholamine concentrations appear to be much higher within the conduction system than in the rest of the myocardium (Reuter, 1974; Lurie et al., 1995), and in the kidney, which actually synthesizes epinephrine from norepinephrine. Isotope tracer studies have shown

that more than half of the epinephrine detected in urine is actually synthesized in the kidney (Ziegler et al., 1997).

Some individuals with uncomplicated infarction will have higher catecholamine levels than others with cardiac arrest who have been given exogenous epinephrine (Worstman et al., 1984). Similarly, cocaine levels, in and of themselves, do not appear to correlate with the probability of developing coronary artery spasm, and infarction can occur when only metabolite is present (Del Aguila and Rosman, 1990; Levine and Nishikawa, 1991). Demonstration of pre-existing cocaine-related lesions provides at least a plausible mechanism for infarction. Cocaine and epinephrine increase oxygen consumption. Previous asymptomatic lesions can suddenly become symptomatic if the demand for increased blood supply becomes too great.

The surgical application of even small amounts of cocaine will cause patients to have positive urine tests for as long as three days. In one study, patients undergoing lacrimal duct surgery were anesthetized with less than 3 mL of topical 4% cocaine hydrochloride. In almost every instance, urine specimens obtained 24 hours later exceeded the 300 ng/mL National Institute on Drug Abuse (NIDA) cutoff, and some still exceeded the cutoff at 48 hours. In a few patients, cocaine was still detectable 72 hours later, though at levels less than 300 ng/mL (Cruz et al., 1991). In another, more recent study, where either 160 or 400 mg of cocaine were applied to the nasal mucosa of patients undergoing septoplasty, 90% of the drug was absorbed within the first 15 minutes. Plasma from the group receiving 400 mg, drawn 20 minutes after application, had a mean concentration of 0.608 ± 0.09 mg/L (Liao et al., 1999).

The use of cocaine as a local anesthetic also carries with it the risk that the surgeon may inadvertently contaminate himself and test positive for cocaine (see Section 1.6.7). One study considered several possible scenarios for exposure (Bruns et al., 1994). The study involved 22 patients who had routine nasal surgery and the surgeons who operated on them. The surgeons participating in the study used their fingers to mix 4 cc of 4% cocaine into cotton pledgets which were then inserted into the patients' nostrils. The surgeons wore masks at all times. In six cases they also wore gloves, and in six cases they did not. In order to test for cumulative effects, a separate experiment was done; a single physician handled cocaine on Day 1 once every 2 hours for 6 hours, and on Day 2, once every hour for 6 hours. Cotton-soaked pledgets were prepared as if surgery was to be performed. The cotton was handled for 2 minutes, and the surgeon then washed his hands 15 minutes later.

When surgeons wore gloves, no cocaine metabolite was detected. When the surgeons did not wear gloves, benzoylecgonine (BE) appeared in their urine, although at levels well below NIDA or Department of Defense (DOD) cutoffs, either for screen assays or gas chromatography/mass spectrometry (GC/MS) confirmation. The mean BE concentration was 30.1 ng/mL at 8 hours and 18.8 ng/mL at 24 hours. The highest BE level recorded was 53 ng/mL. However, much higher levels were observed when one surgeon handled the cocaine-soaked cotton for the 2-day study, and a cumulative effect was definitely observed. Twelve hours after the first exposure (once every 2 hours for 6 hours), BE levels were approximately 90 ng/mL. Eighteen hours after the second exposure, levels measured by GC/MS had risen to 245 ng/mL, a positive result by either military or civilian standards.

1.6.6 Intravenous use

Intravenous use of cocaine results in much higher blood cocaine concentrations than coca leaf chewing, which is almost certainly why intravenous users are more likely to become ill than leaf chewers. Kumor et al. (1988) found that a 40-mg intravenous bolus given to a human volunteer resulted in plasma concentrations of between 204 and 523 ng/mL at

10 minutes. Chow et al. (1985) gave a 32-mg dose of cocaine to volunteers and observed peak levels of approximately 250 ng/mL with a maximum increase in heart rate at 7.3 minutes. Barnett et al. (1981) observed levels of 700–1000 ng/mL, 5 minutes after injecting 100 mg. The levels exceeded 2500 ng/mL after an injection of 200 mg. Blaho et al. (Blaho and Winberry, 2000) reported that typical symptomatic emergency room patients, presenting after injecting unknown amounts of cocaine, had relatively low plasma cocaine concentrations of 170 ± 0.24 ng/mL, but much higher concentrations of BE, with a median plasma concentration very near 2000 ng/mL.

One important aspect of intravenous cocaine use is that it requires multiple frequent injections to get "high." Narcotic users, by comparison, inject infrequently. The increased number of injections places the cocaine user at greater risk for human immunodeficiency virus (HIV) infection and for all the other infectious complications of intravenous drug use. Whether any of these observations have any bearing on clinically apparent toxicity is difficult to say, especially because intravenous cocaine use (as opposed to intravenous heroin use) seems to have largely been supplanted by "crack" smoking. In fatal cases of "speedballing" (combining cocaine and heroin), death-scene investigators generally find that the heroin has been injected and the cocaine smoked. The practice remains unexplained.

1.6.7 Genital application

Genital and rectal application of cocaine serves two purposes. Absorption is prompt and relatively complete, so high blood levels are reached very quickly. In addition, cocaine used in this manner also acts as a local anesthetic. Fatalities have been reported after vaginal application. Except for a pregnant woman who died of air embolism after her partner blew "crack" smoke into her vagina (Collins et al., 1994), the clinical histories in these patients suggest that death was due to arrhythmia, but, interestingly, reported blood levels have not been high (Doss and Gowitt, 1988; Ettinger and Stine, 1989; Greenland et al., 1989; Burkett et al., 1990). Occasionally, genital application may be inadvertent. There are two reports in the literature of women smuggling drugs in their vaginas. In one instance, the woman was found dead with two plastic bags, each containing 85 g of cocaine, in her vagina. The external genitals were necrotic (Mebanex and De Vito, 1975; Benjamin et al., 1994). In a second case, a woman detained by customs agents was found to have a 16-cm × 10-cm × 1-cm elliptical packet of cocaine wedged so tightly in her vagina that obstetric forceps were required for removal.

Toxicity from genital application is not limited to females. Priapism has been reported in men after application of cocaine to the glans (Rodriguez-Blaquez et al., 1990), occasionally leading to serious surgical complications (Altman et al., 1999). For obvious reasons, rectal application has become popular among homosexual abusers, and fatalities have been reported (Shook et al., 1985). Drugs and alcohol, not just cocaine, are commonly introduced into the rectum to promote sphincter relaxation and to ease the discomfort of anal dilatation. Resultant blood concentrations after any of these practices have not been studied.

1.6.8 Dermal absorption

Cocaine adheres to the skin and can be absorbed through it. Controlled experiments showed that cocaine can remain on the skin for at least three days after external exposure (Kidwell et al., 1997), and it is not easily removed. The most reasonable explanation for this phenomenon is simply that positively charged drugs will ionically bond to skin proteins, just as they bond to protein in hair (Kidwell and Smith, 2000). Such an interaction

would explain why cocaine can be recovered from the skin of individuals who have handled "crack" cocaine, even after thorough hand washing, or swabbing with 70% isopropyl alcohol. It is quite unlikely that anyone would absorb enough cocaine via this route to cause a NIDA positive urine test (although that can occur when an individual has handled bulk cocaine) (Maloney et al., 1994).

When 5 mg of cocaine hydrochloride and 5 mg of cocaine free base, dissolved in alcohol, were painted on the forearm skin of a volunteer, the maximal urinary BE concentration of free base was 55 ng/mL at 48 hours. Much less of the cocaine hydrochloride was absorbed, with a peak urine level of only 15 ng/mL at 48 hours (Baselt et al., 1990). Unpublished data, cited in the study by Baselt, showed that 2 mg of cocaine hydrochloride, dissolved in water and placed on the palms of the volunteers' hands, resulted in EMIT® d.a.u. assay positives in all five participants. In one case, the resultant urine level was actually above the 300-ng/mL cutoff (in Baselt's study cited here), which means that a charge of cocaine use, based only on the urine test, could very well have been sustained in court. A third study, done with cocaine paste, yielded much the same result (Elsohly, 1991).

The testing of medical personnel is not federally regulated, which means that a zealous administrator might pursue charges against an individual with BE in his urine in concentrations below federally set cutoffs. Fortunately, the concern is mostly academic, because two separate studies have shown that physicians, unless they violate all rules of infection control, are not likely to accidentally absorb sufficient quantities of cocaine via the skin, or even via an aerosol, to test positive. Placing two drops of 4% cocaine on the skin, breathing deeply when spraying a patient with 4% cocaine aerosol, or squeezing cocaine-soaked cotton pledgets between the fingers did not cause any of 11 volunteers to test positive (Zieske, 1992).

In a 1994 study, three different scenarios were tested; the urine of physicians was tested after they had soaked cottonoid pledgets in a 4% cocaine solution and then inserted them into patients' nares. The physicians wore masks for all the trials, but wore gloves for only six. No metabolite was found in the urine of physicians wearing gloves, and only low levels of BE were detected in the six who wore no gloves (mean concentration of 30.1 ng/mL at 8 hours, 18.8 ng/mL at 24 hours). In the third scenario, a single physician handled cocaine-soaked cottonoids three times a day for two days, then washed his hands 15 minutes later. After the first day of testing, urine levels were below 100 ng/mL, but after the second day, urine levels rose to 245 ng/mL on GC/MS testing (Bruns et al., 1994).

Of course, environmental skin contamination is not the only explanation for the presence of cocaine in or on the skin. Cocaine has a relatively large volume of distribution (V_d) (various reports suggest values of 2–5 L/kg), which means that cocaine will distribute throughout the tissues in the body, including the skin. Studies of tissue obtained at autopsy have shown high concentrations of abused drugs in abdominal skin and subcutaneous fat, even of drugs that are generally not thought of as being highly lipophilic. The rate at which such drugs move from subcutaneous skin to the surface, if they do at all, is simply not known (Levisky et al., 2000).

Absorption through the skin is also of theoretical concern for convicted drug takers who are being monitored with sweat-collection patches. It has been suggested that exposure to low levels of drug in the environment could lead to skin absorption, entrance of very small amounts of drug into the bloodstream, subsequent secretion of the drug into the sweat, and eventual collection of that drug-containing sweat by the patch. The results of several studies suggest that this scenario, while logically possible, simply does not occur. However, the possibility of absorption through the patch has not been entirely ruled out (Kidwell and Smith, 2000).

1.6.9 Inhalation

By 1986, the practice of smoking free base that had been extracted with volatile solvents (an innovation of the early 1980s known as "freebasing") gave way entirely to the practice of "crack" smoking (Washton et al., 1986). In order to make "free base," cocaine dissolved in ether has to be heated, a practice even skilled chemists would approach with caution. Many of the less-skilled "freebasers" sustained life-threatening burns. Perhaps the most famous of these was the American comedian Richard Pryor.

The origins of "crack" smoking are not entirely clear. It has been alleged by conspiracy theorists that the introduction of "crack" was either (1) a genocidal plot to destroy the black community, or (2) a cynical approach towards fundraising, adopted by an administration badly in need of cash to support covert military operations in South America. Neither theory is supported by any substantial body of fact, though it must be said that the financing of wars by selling drugs is a very old tradition, first introduced into North America by the Spanish more than 500 years ago (Karch, 1998). Another popular theory, that "crack" is cheaper than cocaine hydrochloride, has been disproved by economists (Caulkins, 1997).

The first medical reports describing "crack" smoking came from the Bahamas in 1983 (Jekel et al., 1986). The first mention of "crack" smoking in the U.S. came from New York City in 1985 (Gross, 1985). "Crack" prepared on the streets contains variable amounts of bicarbonate and other contaminants. The composition has clinical significance, not only because of the amount of cocaine that is finally delivered, but also because, when faced with arrest, many "crack" smokers will swallow their supply. If the "crack" they are smoking contains substantial amounts of bicarbonate, the "rock" is likely to pass through the stomach without dissolving and without producing symptoms. If the "crack" contains more cocaine than bicarbonate, it may dissolve rapidly and produce toxicity.

For clinical experiments, "crack" is prepared by mixing cocaine hydrochloride with an equal weight of sodium bicarbonate in sterile water and then heating the mixture in a boiling water bath. Cocaine base precipitates out and forms small pellets or "rocks" when the water is cooled. Prepared in this manner, smoking 50 mg of base delivers between 16 and 32 mg of cocaine to the subject (Paly et al., 1980, 1982; Perez-Reyes et al., 1982; Foltin and Fischman, 1991).

In one study, plasma concentrations, measured 6 to 12 minutes after a subject smoked one 50-mg "rock," ranged from 250–350 ng/mL. In a second study, from the same laboratory, two 50-mg doses of free base, smoked 14 minutes apart, produced a peak plasma concentration of 425 ng/mL 4 minutes after the last dose (Foltin and Fischman, 1991). Smoking a 50-mg dose every 14 minutes, for a total of four doses, produced a plasma concentration of over 1200 ng/mL in one subject. In both human and experimental animals, changes in heart rate and blood pressure are dose dependent and correlate temporally with peak cocaine plasma concentrations (Boni et al., 1991), but there is a great deal of variation between experimental subjects.

In clinical practice, drug concentrations in symptomatic users seeking emergency treatment are very similar to those reported in the earlier controlled trials. In the study by Blaho et al. (Blaho and Winberry, 2000), plasma cocaine concentrations in symptomatic "crack" smokers were indistinguishable from blood concentrations of individuals who prefer to insufflate their drug and, regardless of which route had been used, there was no correlation between blood concentrations and symptoms.

Side-stream exposure to cocaine vapor can cause measurable quantities of cocaine metabolite to appear in the urine. When a 73-kg adult male was confined in a closed space

approximately the size of a closet and was exposed to 200 mg of volatilized free base, urine concentrations over the succeeding 24 hours ranged from 10 to 50 ng/mL (Baselt et al., 1991). Environmental exposure to cocaine is also a real hazard for inner-city children. Nearly 2.5% of children examined at a metropolitan emergency department tested positive for cocaine or cocaine metabolite. The number would probably have been higher, but children with signs of cocaine toxicity or a history of cocaine exposure were specifically excluded from the survey (Kharasch et al., 1991).

1.6.10 Gastrointestinal absorption

A significant proportion of the cocaine found in the blood of coca leaf chewers gets there as a result of gastrointestinal absorption. Chewers who swallow their saliva have higher cocaine levels than those who do not. While it is widely believed that cocaine is not absorbed from the gastrointestinal tract, quite the opposite is true (Wilkinson et al., 1980; Jenkins et al., 1995), at least for the hydrochloride salt.

Gastrointestinal absorption of pure cocaine has been studied in at least two controlled clinical trials. Oral dosing, provided that (1) the initial dose is not massive, and (2) large doses are given over the course of many hours, appears to be quite safe. In a recent trial, dosage was increased over the course of several weeks so that participants were receiving up to 2000 mg of cocaine hydrochloride per day. Oral administration results in peak plasma concentrations approximately one hour after administration. The maximum concentrations produced by doses ranging from 1250 (five separate doses of 250 mg each) to 2000 mg/day (five separate doses of 400 mg each), ranged from 653 to 1899 ng/mL (Jufer et al., 1998, 2000).

One reason for the wide variation in observed peak concentration is the accumulation of cocaine in plasma over time; the first dose of the day produces lower plasma concentrations than the last. A variety of cocaine metabolites were also identified in Jufer's study, including ecgonine methyl ester (EME), often in concentrations greater than that of BE. Both BE and EME were detected within 1 to 2 hours of drug administration. Peak concentrations for the minor metabolites occurred later (Jufer et al., 1998). In a second trial, concerned mainly with psychological effects, oral doses of up to 300 mg of cocaine hydrochloride were well tolerated and had only transient and insignificant effects on blood pressure. Interestingly, the subjects of the second trial rated the stimulant effects higher, and more pleasurable, after oral dosing than after smoking or insufflating (Rush et al., 1999).

Gastrointestinal absorption assumes particular importance in the "body packer" syndrome (Figures 1.6.10.1 and 1.6.10.2). "Body packers," as opposed to "body stuffers" (another name for drug users who swallow the evidence when faced with imminent arrest), smuggle large quantities of drugs, sometimes approaching a total of 1 kg, in their intestines and other bodily orifices (Figure 1.6.10.3). The drug is usually wrapped in latex (Figure 1.6.10.4), but if the package leaks, results can be fatal (Bednarczyk et al., 1980; Fishbain and Wetli, 1981; McCarron and Wood, 1983; Caruana et al., 1984; Beck and Hale, 1993; Hierholzer et al., 1995a,b; Meyers, 1995; Cobaugh et al., 1997; Teijink et al., 1997; Gomez Antunez et al., 1998; Nihira et al., 1998).

The practice of "body packing" was first described in 1977 (Suarez et al., 1977). Low-level smugglers ("mules") swallow packets containing hundreds of grams of cocaine. The drug to be smuggled is wrapped in a condom, plastic bag, or aluminum foil. Packets generally contain 3 to 6 g of drug. The x-ray density of cocaine is very close to that of stool, and that can make detecting smugglers difficult (Wetli and Mittlemann, 1981;

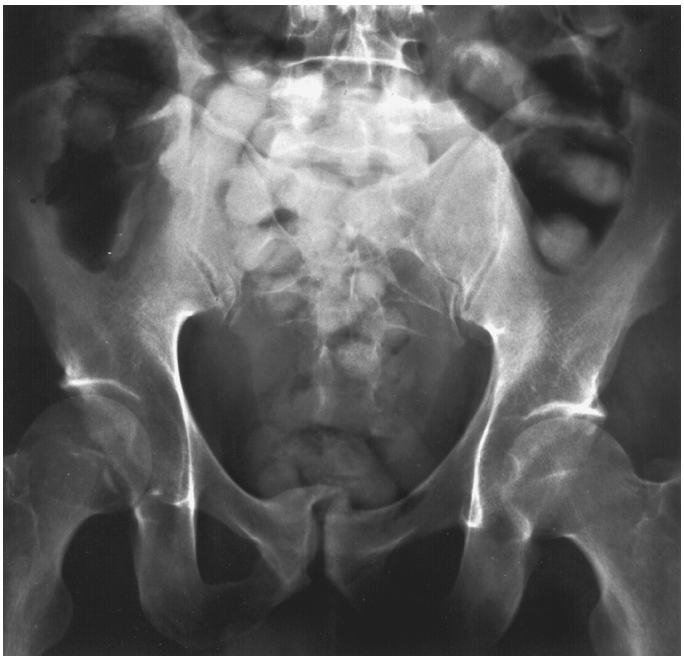

Figure 1.6.10.1 **"Body packer" syndrome.** Drug couriers can be diagnosed with plain abdominal x-rays, although occasionally CT scanning is required. This plain film clearly demonstrates cocaine-containing packets. (From *Abdom. Imaging*, 20, 339, 1995. With permission. Courtesy of Dr. M. Meyers, State University of New York, Health Sciences Center.)

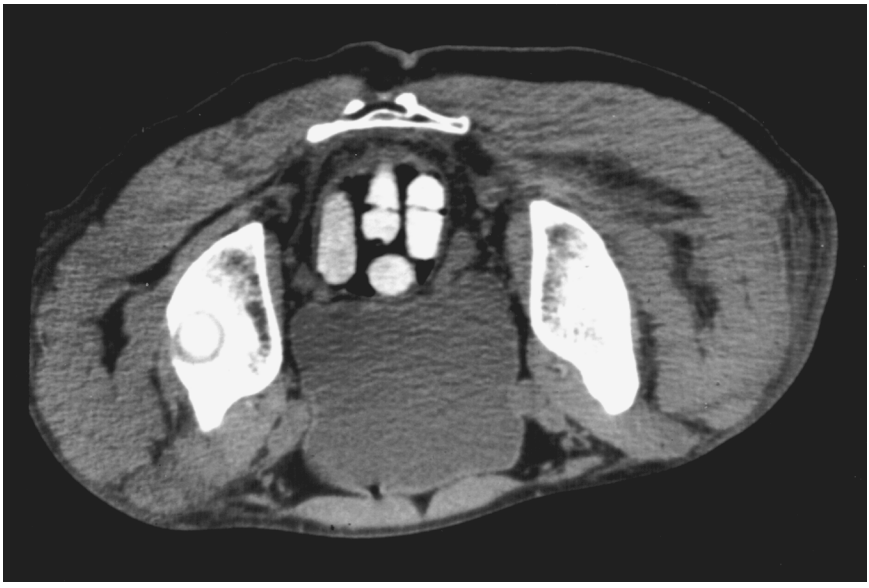

Figure 1.6.10.2 **"Body packer" syndrome.** This syndrome was first described in 1977. Smugglers who swallow multiple, rubber-coated packets of drugs are at grave risk for massive overdose. (From *Abdom. Imaging*, 20, 339, 1995. With permission. Courtesy of Dr. M. Meyers, State University of New York, Health Sciences Center.)

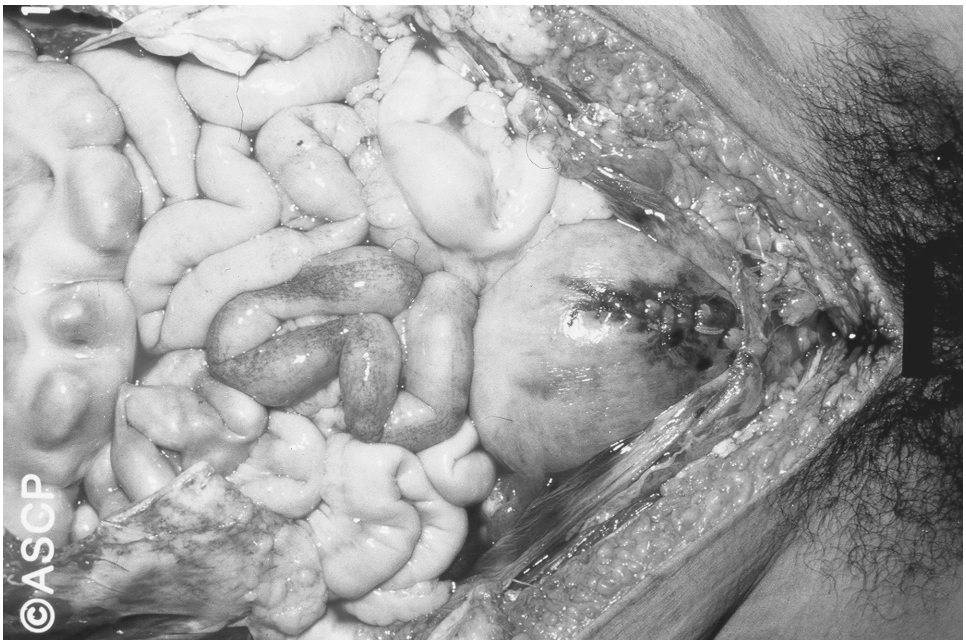

Figure 1.6.10.3 **Pregnant drug courier.** Pregnant uterus is visible in lower section of picture, while cocaine-filled condoms are apparent throughout the intestinal tract; see Figure 1.6.10.4. (Photograph courtesy of the College of American Pathologists, Northfield, IL.)

Figure 1.6.10.4 **Drug packets.** Cocaine packets removed from decedent shown in Figure 1.6.10.3. Reports suggest that some may ingest up to half a kilogram in this fashion. (Photograph courtesy of the College of American Pathologists, Northfield, IL.)

Karhunen et al., 1991). If a packet should rupture, the smuggler will quickly absorb a very large amount of drug. Seizures commonly result and appear to be the mechanism of lethality in experimental animals given huge amounts of cocaine (Catravas et al., 1978). Humans may also develop pulmonary edema and heart failure. But, if the drug courier is a regular user with some degree of tolerance, even a massive overdose may not produce the classical symptoms, and the outcome is not necessarily fatal (Bettinger, 1980; Howell and Ezell, 1990). The occasional body packer may present first with toxic psychosis, rather than fever and hyperpyrexia (Fernandez Moyano et al., 1998).

Blood concentrations in body packer fatalities have ranged from 3 to 11 mg/L, well in excess of levels normally seen after intravenous abuse. Even if the cocaine-containing packets do not rupture, small amounts of cocaine may still appear in the urine, and urine testing may be diagnostic for the syndrome (Gherardi et al., 1990; Nihira et al., 1998). Other diagnostic techniques that have been advocated included plain x-ray films, barium contrast studies, and computerized tomography (CT) scanning. As smugglers have become more sophisticated, they have improved their packing techniques to prevent leakage. They have also attempted to avoid x-ray detection by ingesting mixtures of oil that will reduce the contrast difference between the packets and the surrounding bowel contents (Pinsky et al., 1978; Sinner, 1981; Gherardi et al., 1990). Most major international airports are now equipped with facilities for on-site EMIT® urine testing, and special toilet facilities with which to collect the contraband.

Gastrointestinal absorption can also occur via mothers' milk (Sturner et al., 1991; Dickson et al., 1994; Golding, 1997). While there is no question that such transfers occur, their significance is not known.

1.6.11 Special maternal/fetal considerations

Few human data have been collected, although maternal/fetal drug ratios for cocaine (and other drugs) are regularly reported. The usefulness of these ratios is not really known. By mid-pregnancy, the fetus may come into direct contact with high concentrations of cocaine that have been absorbed in the amniotic fluid (Woods, 1998). How much, if any, cocaine is actually absorbed in this fashion is not known, nor is it known whether such contact has any medical significance (Dempsey et al., 1999). What is known with certainty is that nearly all of the data on maternal/fetal drug pharmacokinetics have been derived from experimental animals (Bailey et al., 1998; Collins et al., 1999), or from the *in vitro* study of placental function (Cejtin et al., 1999). The relevance of these studies to humans has yet to be convincingly demonstrated.

Pregnant ewes appear to provide one of the best experiment models. In the ewe model, fetal blood concentrations five minutes after a maternal cocaine infusion are only 12% of the values seen in the mother (Moore et al., 1986). In near-term Macaque monkeys, 1 mg/kg injected intramuscularly in the mother resulted in peak plasma concentrations of 132–312 ng/mL, 10 to 20 minutes after injection. Fetal levels lagged behind, peaking from 30 minutes to 2 hours later, but peak levels were the same (18–329 ng/mL) (Binienda et al., 1993). The pharmacokinetics of cocaine has also been studied in pregnant and lactating rats (Wiggins et al., 1989). From 30 minutes to 3 hours after injection, cocaine levels are three to four times higher in the brain and three to five times higher in the liver than in the blood. During the period from 30 to 90 minutes after injection, fetal brain concentrations were 50 to 90% of the mothers' and 1.5 times as high as the blood concentration in mothers or pups.

In vitro studies of human placenta have demonstrated high-affinity binding sites for cocaine (Ahmed et al., 1990). In isolated perfused cotyledons of normal-term human placenta, cocaine is passively but rapidly transported, without undergoing metabolic transformation. The same holds true for cocaethylene and norcocaine. In this *in vitro* model, the direction of transport seems to depend entirely upon the relative concentration of cocaine in the mother and fetus; when fetal levels are higher than maternal levels, equally rapid transport back across the placenta occurs (Schenker et al., 1993), but results are often unpredictable (Bailey et al., 1998).

Studies in humans are far more limited. In one study, amniotic fluid from 450 women between 12 and 39 weeks of pregnancy was screened for cocaine or its metabolites. Only five samples out of 450 were positive for cocaine, BE, and/or EME by GC/MS. In addition, one sample was also positive for cocaethylene, yielding a positivity rate of 1% (Ripple et al., 1992). In a second study, cocaine or BE was detected in 74% of amniotic fluid samples taken from 23 known cocaine abusers. In the 23 cases described, concentrations in the amniotic fluid ranged from 400 to greater than 5000 ng/mL for BE and from trace amounts to 250 ng/mL for cocaine (Jain et al., 1993). Interestingly, BE concentrations were significantly greater in the amniotic fluid than in the newborn's urine (1800 and 280 ng/mL, respectively; $p = .0001$), suggesting that not a great deal of drug had been absorbed, either via the skin or through the gastrointestinal tract. In another case report, the amniotic fluid cocaine and BE concentrations were measured in a stillbirth case and found to be 3.3 mg/L and 1.6 mg/L, respectively (Apple and Roe, 1990).

The results of a third study suggest that absorption occurs, but not necessarily in every case. Cocaine and its metabolites were measured in urine, meconium, and amniotic fluid specimens collected from 30 maternal–infant pairs with histories of prenatal cocaine use. There was qualitative, but not quantitative, agreement between the results of drug determinations in maternal urine, amniotic fluid, infant urine, and meconium. And, even though all of the mothers in this study admitted to using cocaine during their pregnancy, cocaine or its metabolites were detected only in the 20 cases in which cocaine was used within three weeks before delivery (Casanova et al., 1994).

Results of published case series indicate that maternal cocaine exposure does not necessarily guarantee a particular fetus will absorb the drug cocaine. A 1994 publication described a 26-year-old woman who bore a 4-pound infant at 32 weeks of gestation (Potter et al., 1994). The mother was an admitted intravenous cocaine user who injected herself daily throughout the course of her pregnancy. She also used hashish on a weekly basis during the first trimester of the pregnancy, drank an occasional beer, and smoked one to two packs of cigarettes a day throughout the pregnancy. Hair samples from the mother obtained two months after delivery contained nicotine, cotinine, and BE (concentrations in various segments of hair ranged from 0.8 to 2.3 ng/mg). Urine from the child was negative for benzoylecgonine and cannabinoids, and only cannabinoids were detected in the meconium. Hair samples obtained from the child at birth were negative for cocaine and benzoylecgonine, but did contain nicotine and cotinine. Thus, maternal cocaine use cannot be said to guarantee transfer to her unborn child, at least not in any particular isolated case.

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1.7 Metabolism of cocaine and its metabolites

1.7.1 Cocaine

Except in the newborn (Dempsey et al., 1999), cocaine is rapidly cleared from the bloodstream (Figure 1.7.1.1) (Inaba et al., 1978; Barnett et al., 1981; Javaid et al., 1983; Chow et al., 1985; Kumor et al., 1988). Its elimination clearance rate is at least 2.0 L per minute. The half-life of the drug in humans is variously reported as being between 0.5 and 4.0 hours, depending on whether or not the individual is a chronic or naïve user (Chow et al., 1985; Jatlow 1987; Kumor et al., 1988; Moolchan et al., 2000). In the newborn, it is on the order of 11–12 hours (Dempsey et al., 1999). Previously reported laboratory measurements made in healthy volunteers (usually chronic cocaine users admitted to detoxification programs) given relatively small doses of cocaine probably do not accurately reflect the situation in real life. For one thing, enrollment in the pharmacokinetic studies is almost always contingent on the individual being drug free at the time of the study. But, the results of both animal and human studies suggest that cocaine is stored, that its rate of excretion changes as cocaine accumulates (Weiss and Gawin, 1988; Jufer et al., 1998), and that the amount of cocaine consumed by "crack" smokers is measured in multiple gram quantities, not milligrams (Gossop et al., 1994). Autopsy studies certainly show that to be the case in humans (Karch et al., 1998; Blaho and Winberry, 2000).

The terminal half-life and elimination clearance differ markedly from species to species. In the rat, for example, the plasma half-life is only 18 minutes. In ewes, the preferred model for maternal/fetal distribution studies, the half-life of inhaled cocaine is only 1.6 ± 0.5 minutes (mother) and 3.4 ± 0.9 minutes (fetus) when injected intravenously (Burchfield et al., 1991; DeVane et al., 1991). Anatomic differences can have equally profound effects. Unlike humans, the coronary arteries of dogs are highly anastomotic. Like humans, the hearts of swine contain no important anastomotic connections. Experiments designed to determine the effects of cocaine on the heart by transient occlusion of a coronary artery

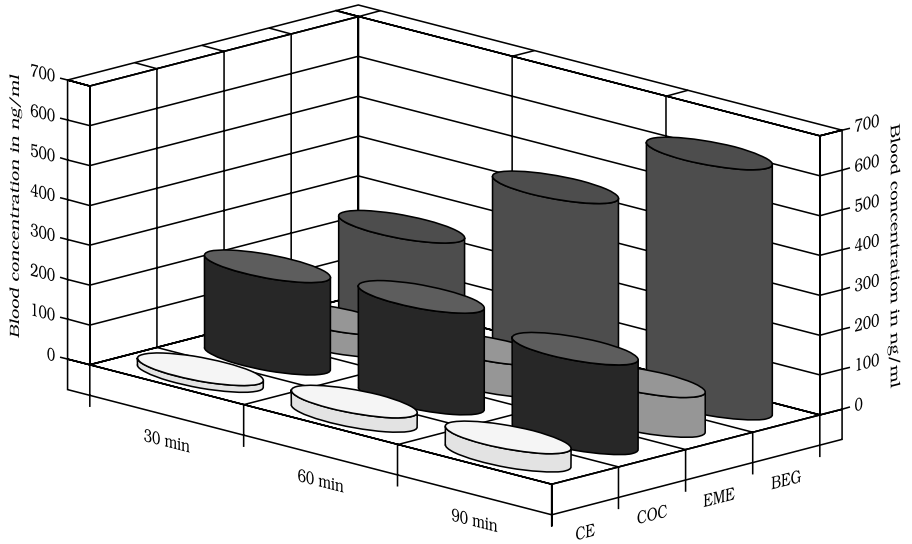

Figure 1.7.1.1 **Blood concentrations of cocaine and its metabolites in humans.** Average blood concentrations of cocaethylene (CE), cocaine (COC), ecgonine methyl ester (EME), and benzoylecgonine (BEG) in eight subjects given 2 mg/kg of intranasal cocaine and 5 mL/kg of 10% ethanol. (Data adapted from Pirwitz, M. J. et al., *Arch. Intern. Med.,* 155, 1186–1191, 1995.)

may produce different, or even contradictory results, depending on which experimental animal is used (Greaves, 1998).

In the early days of the current cocaine pandemic, many believed that only a very small percentage of cocaine was excreted unchanged in the urine and that it was only detectable there for 3 to 6 hours (Jatlow, 1988). That simply is not the case. An analysis of 104 postmortem urine specimens that had tested positive for cocaine metabolite (either BE or EME, or both) disclosed cocaine in 66% of the specimens, sometimes in very high concentrations (0.07–78 mg/L). In this same study, when the BE concentration of the urine sample was greater than 2.0 mg/L, cocaine was detected in 83% of the specimens, but the detection rate dropped to only 30% when BE levels were under 2.0 mg/L (Ramcharitar et al., 1995). In an even more recent study of 99 cocaine-related deaths, the mean urine cocaine concentration in 48 individuals actually dying of cocaine toxicity was 40.1 ± 83.7. The urine concentration in the other 51 decedents, for whom the presence of cocaine was an incidental finding unrelated to the cause of death, was 30 ± 83.0 mg/L. The difference was not statistically significant (Karch et al., 1998).

More than a dozen different cocaine breakdown products have been identified, but they are rarely measured, mainly because their presence seems to be of little clinical significance. In the 46 symptomatic "crack" smokers studied by Blaho and Winberry (2000), the mean concentration of cocaine and its principle metabolites, listed in decreasing order, were as follows: benzoylecgonine (1.4 ± .19 mg/L) > ecgonine methyl ester (.53 ± .05 mg/L) > ecgonine (.53 ± .07 mg/L) > cocaine (.18 ± .06 mg/L) > norcocaine (.04 ± .03 mg/L) > cocaethylene (.02 ± .01 mg/L).

In the clinical setting, most hospital laboratories use commercial immunoassay kits designed to detect only BE. Other metabolites, even if they are present, remain undetected and unstudied. However, techniques now exist for the simultaneous measurement of cocaine, cocaethylene, their metabolites, and even pyrolysis products using GC/MS (Cone

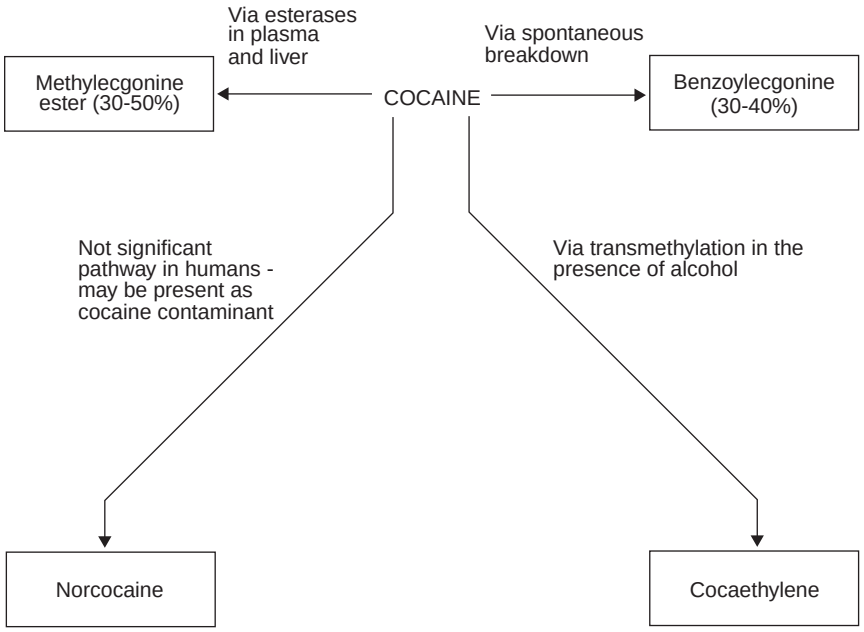

Figure 1.7.2.1 **Metabolic fate of cocaine.** In the absence of alcohol, benzoylecgonine (BEG) and ecgonine methyl ester (EME) are the principal breakdown products of cocaine. Cocaine is converted to EME by hepatic esterases and by plasma cholinesterase. Benzoylecgonine forms spontaneously. In cases of cholinesterase deficiency, more cocaine is shunted via the BEG route. There is very little evidence, however, that cholinesterase levels affect toxicity.

et al., 1994; Jenkins and Goldberger, 1997). More information may become available in the near future, but for the moment, at least in humans, it appears that there are only two important cocaine metabolites: BE and EME, and very little evidence exists showing that either exerts toxicity in its own right.

1.7.2 Benzoylecgonine and ecgonine methyl ester

In the absence of alcohol, the principal metabolites of cocaine are benzoylecgonine and ecgonine methyl ester (Figure 1.7.2.1). The relative proportion of the metabolites detected seems to have very little to do with the route of administration. In Blaho and Winberry's (2000) study of 111 emergency room patients, BE concentrations were consistently the highest (generally by a factor of 10) of all metabolites detected (1.4 mg/L in "crack" smokers, 1.9 mg/L in insufflators, 1.9 mg/L in intravenous users, and 1.6 mg/L in subcutaneous injectors). In controlled laboratory studies, less than a third of a given dose of cocaine was converted to BE (Cone, 1989), but some other early studies found that as much as 85–90% of the cocaine administered was converted to BE (Jatlow, 1988). This discrepancy is probably explained by the relatively small amount of drug given and by the fact that it was given intravenously.

The observation that many cocaine-related myocardial infarcts occur hours after last cocaine use, coupled with the knowledge that BE has a much longer half-life than cocaine itself, has led some to speculate that benzoylecgonine is vasoactive and the actual cause of infarction (Kurth et al., 1993). Clinical support for the idea is entirely lacking (Morishima

et al., 1999a; Pan and Hedaya, 1999), and the observed time lag between cocaine use and infarction may have more to do with the time it takes plaque rupture to become symptomatic than with any chemical property of BE or EME.

The half-lives of both BE and EME are much longer than the half-life of cocaine (Brzezinski et al., 1994). EME has a half-life of about four hours, while the half-life of BE is closer to 6 hours. In neonates, the half-life of BE appears to be 1.5 to 2.1 times longer than in adults (Dempsey et al., 1999). As a consequence, BE is likely to still be detectable in plasma for at least 24 hours after ingestion (Javaid et al., 1983; Jatlow, 1987). Initially, it appeared that the ratios of BE and EME to each other, and to the parent compound, depended on the route of administration (Brogan et al., 1992; Isenschmid et al., 1992a,b; Cone et al., 1994); however, actual clinical experience with symptomatic cocaine users, taking large amounts of drug, suggests very little difference in metabolite ratios, no matter what route of drug administration has been used (Blaho and Winberry, 2000).

Benzoylecgonine is stable in frozen specimens, but cocaine is not (Dugan et al., 1994), and the amount of BE and EME measured in urine will vary depending on how the specimen is stored. EME is stable for as long as three years in urine samples with pH ranges of 3 to 5, but at pH 9, 100% will have disappeared in 30 days (Vasiliades, 1993). Under alkaline conditions, EME will hydrolyze to form ecgonine and thus will not be detected.

Most postmortem urine samples contain more BE than EME (Clark and Hajar, 1987; Howell and Ezell, 1990), but changes in sample acidity can also lead to the measurement of inaccurately high ratios of EME to BE in postmortem blood samples. During life, EME circulating in the blood is rapidly converted to ecgonine and levels remain quite low, but, after death, anaerobic metabolism continues and the pH of serum becomes progressively lower. As a result, conditions are not suitable for spontaneous hydrolysis, and the conversion of cocaine to BE and EME to ecgonine stops. At the same time, enzyme-mediated hydrolysis continues, albeit at a slower rate, and EME continues to accumulate. The resultant high EME levels and relatively low BE levels will give a false impression of the situation before death (Logan and Peterson, 1994; McKinney et al., 1995).

Cocaine is a weak base and a small molecule that diffuses freely across the placenta. BE does not. It is highly ionized at physiological pH ranges and barely crosses the placenta. As a consequence, all the BE detected in a fetus is derived from cocaine metabolized in the fetus. And, because the fetus cannot clear BE as quickly as the mother, maternal/fetal ratios are just the opposite of those observed with cocaine. In Meeker's autopsy study, the ratio in six cases was 2.44, with a range of 1.17–6.80 (Meeker and Reynolds, 1990).

Spontaneous hydrolysis of cocaine to BE certainly accounts for much of the BE detected in blood or urine, but it is now clear that humans possess two distinct hepatic cocaine carboxylesterases: one catalyzes the conversion of cocaine to EME, and the other catalyzes the hydrolysis of the methyl ester group of cocaine to form BE and, in the presence of alcohol, causes transesterification of the cocaine to form cocaethylene (Dean et al., 1991; Brzezinski et al., 1994). What remains to be determined are the relative roles played in BE production by carboxylesterase systems, plasma cholinesterase, and spontaneous hydrolysis.

Another source for BE in the urine is "spiking" (the purposeful contamination of a specimen in order to cause a false-positive test). This is a defense sometimes used by athletes who test positive after a competition. This argument is easily disproved by analyzing the specimen for other cocaine metabolites, particularly those that only occur *in vivo*: *m*-hydroxybenzoylecgonine, *p*-hydroxybenzoylecgonine, and *N*-desmethylbenzoylecgonine. Recovery of any of these compounds proves that cocaine was metabolized

to BE and then to one of the other derivatives *in vivo* (Poch et al., 1999). Another variation on this theme, used by some athletes, is to claim that cocaine was surreptitiously added to their food. In such an event, the presence of normal *in vivo* metabolites would be expected, but if they are present in high concentrations, it stretches credulity to suppose that the victim would not have noticed something wrong at the time the food was eaten.

Some authors have suggested that low plasma cholinesterase levels explain cocaine toxicity (Jatlow et al., 1979; Handler et al., 1991; Morishima et al., 1993a,b; Om et al., 1993; Konkol et al., 1994; Kump et al., 1994), but little evidence supports this idea.

Normal plasma cholinesterase (PCE) levels vary tremendously from individual to individual and change depending on the physiologic state. In one study purporting to show that "complications" were more common in individuals with low PCE levels, some of the individuals with "complications" had higher PCE levels than controls (Om et al., 1993). Clearly, individuals with genetic defects and atypical forms of cholinesterase, as indicated by low dibucaine numbers, will metabolize cocaine more slowly than individuals without that defect, but that does not prove toxicity is any more likely. One cocaine abuser, however, believed strongly enough in this relationship to take an organophosphate insecticide in hopes of prolonging his high (Herschman and Aaron, 1991).

Suggestions that a reduction in cholinesterase activity increases the chances for toxicity are not strengthened by the utter lack of evidence that the complications of chronic cocaine abuse are dose related (Smart and Anglin, 1987; Karch and Stephens, 1991). There is, in fact, complete overlap between blood cocaine concentrations in fatal cases of cocaine toxicity and in trauma deaths, where the presence of cocaine is an incidental finding (Karch and Stephens, 1991). Cholinesterase activity is not even necessary for EME production. Small amounts of EME continue to form in hepatectomized animals, and BE concentrations continue to rise after hepatectomy, even when plasma cholinesterase inhibitors are given (Kambam et al., 1992a,b; Garrett et al., 1994).

1.7.3 Cocaethylene

Clinical and epidemiologic studies indicate that 60–90% of cocaine users also consume ethanol at the same time (Grant and Harford, 1990; Hearn et al., 1991b; Andrews, 1997), and DAWN lists the combination of ethanol and cocaine as the most frequent cause for drug-related emergency room visits (Kitchell, 1998). The significance of these observations lies in the fact that, when ethanol is combined with cocaine, a unique cocaine metabolite called *cocaethylene* is formed (de la Torre et al., 1991; Hearn et al., 1991; Jatlow et al., 1991). Whether or not the formation of this novel metabolite is the cause of increased toxicity in humans is not known.

In experimental animals, simultaneous administration of cocaine and ethanol results in higher plasma cocaine concentrations than does the same amount of cocaine given alone, and it also leads to cocaethylene formation. Not only does cocaethylene block dopamine re-uptake as effectively as cocaine (Hearn et al., 1991a; McCance-Katz et al., 1993), but it also has a longer half-life. Largely as a consequence of these observations, and because the entire issue of cocaine toxicity is poorly understood, it is believed by many that cocaethylene is inherently more toxic than cocaine, and that its presence explains many, if not most, cases of severe cocaine toxicity or death. This notion has become entrenched in the literature. For example, a review article published in 1997 claimed that cocaethylene "carries an 18- to 25-fold increase over cocaine alone in risk for immediate death" (Andrews, 1997). Evidence derived from human clinical and autopsy studies does not support this conclusion.

When the clinical outcomes of 190 emergency room patients with positive urine tests for just BE alone were compared with the clinical course and outcome of 125 other patients where both BE and ethanol were detected, little morbidity was observed in either group. In fact, the only substantial difference between these two groups was that alcohol-positive patients had, as might be expected, more marked decreases in level of consciousness (Signs et al., 1996). Other clinical studies of cocaine users visiting emergency rooms have also failed to demonstrate alcohol-associated increases in the severity of either neurologic or cardiovascular findings in cocaine users (Vanek et al., 1996).

The failure to find convincing evidence of cocaethylene-mediated human illness, in spite of such convincing experimental evidence, could be explained in several ways. For one thing, the concurrent use of cocaine and alcohol may be much less common than is generally believed. A recent autopsy study of 268 deaths where cocaine was detected (including individuals for whom the presence of cocaine was an incidental finding and cases where cocaine was the cause of death), morphine was detected slightly more often than ethanol (37.3 vs. 39.5%) (Karch et al., 1999). Even if cocaethylene was responsible for death in one third of the cases, that would still leave another third for which morphine was the cause, and yet another third completely unexplained.

Alternatively, it may be that cocaethylene is just more toxic to animals than to people. Evidence to that effect is beginning to emerge. Dogs and rats are important animal models for studying the role of cocaethylene, but when dogs are given a cocaine dose of 3 mg/kg intravenously (i.v.) and ethanol dose of 1 g/kg i.v. they fail to produce detectable plasma concentrations of cocaethylene (Song et al., 1999). And, when studied *in vitro*, human microsomal formation of cocaethylene is not nearly as efficient at converting cocaine to cocaethylene as are microsomes from dogs and rats (Song et al., 1999). There is even evidence that different species of rats, exposed to equivalent doses of cocaine and ethanol, synthesize cocaethylene at different rates and respond differently once cocaethylene has been produced (Horowitz et al., 1999). Other species' differences are also recognized, such as differential effects of cocaethylene on dopamine and on serotonin receptors (Baumann et al., 1998).

Cocaethylene is synthesized in the liver by a transesterification reaction which adds an extra ethyl group to cocaine (Figure 1.7.3.1). The reaction occurs in the microsomal fraction, and is catalyzed by a nonspecific carboxylesterase that not only catalyzes the transesterification of cocaine to cocaethylene, but also converts cocaine to BE (Brzezinski et al., 1994). In some experimental animals, there is evidence for the presence of similar esterases in the kidneys (Boyer and Petersen, 1992), but in humans the only tissue capable of producing cocaethylene appears to be the liver (Bailey, 1994). Once formed, cocaethylene can be further metabolized to benzoylecgonine, norcocaethylene, and ecgonine methyl ester (Cone et al., 1994).

Cocaethylene is detectable for much longer than cocaine because the same carboxylesterases involved in cocaethylene and BE formation can also exchange ester groups with ethanol, leading to the more or less continuous breakdown and reformation of cocaethylene, and prolongation of the time cocaethylene remains detectable in tissues. In studies with rats, cocaethylene incubated with liver homogenates had a measured half-life of only 13 minutes. When ethanol was added, however, the apparent half-life increased fivefold, to more than one hour (68 minutes). When esterase inhibitors were added at the same time as the ethanol, no prolongation was observed (Bourland et al., 1998).

Evidence also exists for a third route of cocaethylene formation. Fatty acid ethyl ester synthetase normally esterifies ethanol with fatty acids, but it may also utilize cocaine as a substrate in a reaction that yields cocaethylene (Heith et al., 1995). Fatty acid ethyl ester

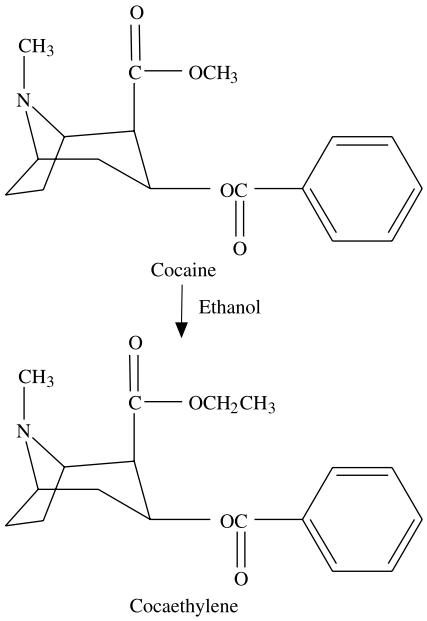

Figure 1.7.3.1 **Cocaethylene formation.** Cocaethylene is formed in the liver by a transesterification reaction which adds an extra methyl group to cocaine. Cocaethylene has a much longer half-life than cocaine, but cocaethylene binds to the dopamine receptor with the same affinity as cocaine.

synthetase has a wider distribution in the body than does the nonspecific carboxylesterase, but its relative role in cocaethylene production in humans is not known. When animals are treated with cocaine and alcohol, they convert 2–10% of the cocaine to cocaethylene (Dean et al., 1992; Levine and Tebbett, 1994; Miller et al., 1994) and other, potentially toxic, *N*-demethylated cocaine metabolites (Dean et al., 1992). The situation in humans is more confusing.

Not only is the concurrent use of cocaine and alcohol less common than had previously been thought, but findings in emergency room patients (Buaho and Winberry, 2000) suggest that the effects of ethanol co-ingestion may be exaggerated, as well. The reason that co-ingestion of the two drugs seems to have such negligible clinical effects is that the amount of alcohol present may be rate limiting in cocaethylene production. Most cocaine users simply do not ingest enough alcohol for cocaethylene to be formed, or at least formed in significant quantities. And, in the case of the developing fetus, it appears that, even when cocaethylene is produced in significant quantities, the placenta prevents its passage (Morishima et al., 1999b) from mother to child.

In Hearn's original autopsy study, cocaethylene was detected in only 62% (77/124) of decedents testing positive for both cocaine and ethanol. Further analysis showed that, in the 47 cases where cocaethylene could not be detected, ethanol concentrations were usually significantly less than 0.1 mg/L (Hearn et al., 1991). Using a somewhat different but very sensitive technique, Jenkins and Goldberger (1997) found cocaethylene in the blood of only one of 13 decedents who tested positive for cocaine (range 23–2088 ng/mL), and that individual had died of a gunshot wound, not cocaine toxicity. In a study of 41 patients with detectable cocaethylene concentrations, no significant correlation between plasma ethanol and plasma cocaethylene concentrations was observed. The lack of correlation

was thought to be a consequence of the very high ethanol concentrations in most of the patients, which made the cocaine concentration the rate-limiting step in cocaethylene formation (Bailey, 1996).

The relationship between cocaine and alcohol has now been evaluated in several studies using healthy volunteers (Farré et al., 1993; McCance-Katz et al., 1993). In the first study, individuals with a history of recreational drug use were given cocaine alone or a drink containing 1 gm/kg of vodka followed by a 100-mg dose of cocaine hydrochloride (snorted). Cocaethylene was detected only in the samples from the alcohol-pretreated group. The peak cocaethylene concentration was 55 ± 8 ng/mL, and serial blood measurements were consistent with a half-life of 109 minutes. Norcocaine levels were also much higher in the group that had been pretreated with alcohol.

An observation difficult to explain was that the alcohol group had higher peak cocaine levels than those who had used cocaine alone (352 ± 111 ng/mL vs. 258 ± 115 ng/mL). It may be that spontaneous conversion to BE, the normal route by which 40% of a given dose of cocaine would be metabolized, is in some way inhibited by alcohol-induced pH shifts. With less of a given dose being metabolized to BE, more is available for hepatic metabolism, leading to increased norcocaine formation.

In a second study, patients with clinical signs of cocaine intoxication and positive alcohol screening tests were found to have cocaine concentrations ranging from 50 to 4360 ng/mL, and blood alcohol levels ranging from 0.09 to 0.84 g/dL. The mean cocaethylene level was 710 ± 0.100 ng/mL (Mash et al., 1991). Cocaethylene does not appear in the bloodstream until 20 to 30 minutes after cocaine and alcohol are ingested (McCance-Katz et al., 1993), so the time of specimen collection may make some difference. In studies using tracer quantities of C^{11}-labeled cocaine, no cocaethylene could be detected until 10 minutes after the simultaneous administration of alcohol and intravenous cocaine (Fowler et al., 1992).

When healthy human volunteers were treated with various combinations of 1 g/kg of ethanol and 100 mg of intranasal cocaine, alcohol alone impaired psychomotor performance, but cocaine alone produced, in addition to euphoria, improved reaction times. When the alcohol and cocaine were taken together, the degree of cocaine euphoria increased, but the psychomotor impairment induced by the alcohol was substantially reversed. Heart rate and blood pressure increases were greater when cocaine was taken with alcohol than when it was taken alone. Plasma cocaine levels were higher when cocaine was taken with alcohol (225 vs. 344 ng/mL), and norcocaine levels doubled (1.5 vs. 3.5 ng/mL); however, alcohol ingestion had no measurable effect on BE or EME production. The peak plasma cocaethylene level was 53 ± 12 ng/mL, or roughly 15% of the parent compound level (Farré et al., 1993).

In a follow-up to these studies, Farré et al. (1997) found that cocaine combined with ethanol produced measurable increases in heart rate, rate–pressure product, and pleasurable-related subjective effect. Plasma cortisol concentrations were significantly higher after concomitant alcohol and cocaine use than with cocaine alone, but ethanol-induced hyperprolactinemia was relatively unaffected.

In still another human study, utilizing nearly the same doses of cocaine and alcohol, cocaethylene was first detected in plasma 30 minutes after the cocaine was given. The initial concentration was 10 ng/mL, and the peak level was 62 ng/mL, reached at two hours. The peak cocaethylene level was 20% of the peak cocaine level, but both levels were equal after six to seven hours had elapsed (McCance-Katz et al., 1993). The calculated half-life in this study was 148 ± 15 minutes, which is generally in agreement with earlier measurements. Cocaine and preformed cocaethylene have been given to volunteers in controlled studies (Perez-Reyes, 1994). With the volunteers acting as their own controls,

cocaethylene had a longer elimination half-life (1.68 vs. .67 hours) but, on a weight-for-weight basis, produced less of a "high."

The detection of cocaethylene in tissue, blood, or hair samples is not, as previously believed, proof positive of cocaine use. It is, instead, proof of exposure. When ethanol is used for refluxing, cocaethylene can be generated as a by-product during extraction of cocaine from the coca leaf (Turner et al., 1979). Cocaethylene can be found in street samples of illicitly prepared drug and even in samples of pharmaceutical-grade cocaine (Casale and Moore, 1994).

Finally, the pharmacologic properties of cocaethylene and cocaine, though largely similar, do differ in some important aspects. The results of *in vitro* studies suggest that cocaethylene is a more potent blocker of the inward sodium channel than the parent compound (Xu et al., 1994). If that is the case in humans, then high levels of cocaethylene would be more likely to produce cardiac conduction abnormalities than would high levels of cocaine. There is also evidence that cocaethylene decreases myofilament Ca^{2+} responsiveness and may produce more severe negative inotropic effects than cocaine (Qiu and Morgan, 1993).

1.7.4 Anhydroecgonine methyl ester (methylecgonidine)

Another metabolite of forensic interest, anhydroecgonine methyl ester (AEME) is the major pyrolysis product of cocaine. It is excreted only in the urine of "crack" smokers (Jacob et al., 1990) and can also be detected in their blood, although plasma concentrations are generally quite low (3–34 ng/mL when measured in 13 admitted "crack" smokers) (Toennes et al., 1999). Its identification may be of some forensic significance, as its presence proves the route of ingestion, although "crack" smoking can also be proven by demonstrating the presence of ecgonidine, an AEME metabolite (Paul et al., 1999).

The pharmacology and pharmacokinetics of this compound have not received much attention. Structurally, AEME shares features with other chemicals, such as anatoxin and arecoline, which have cholinergic properties, raising the possibility that this compound may be toxic in its own right. Studies in animals confirm that AEME inhalation decreases airway conductance (Chen et al., 1995). Preliminary data suggested that AEME-induced bronchoconstriction might have more to do with the physical properties of AEME than with any cholinergic effect. AEME forms in "crack pipes" when the volatilized cocaine begins to cool, forming particles approximately 1 micron in diameter. But, depending on the design of the pipe, the particles can be considerably larger. Particle diameter influences where they are deposited in the respiratory tract. It follows that whether or not a "crack" smoker becomes symptomatic and develops bronchospasm may well have something to do with how the "crack" is smoked (Wood et al., 1996).

Other evidence suggests that cholinergic mechanisms are involved. AEME has negative inotropic effects on human myocardium, reversible by atropine, consistent with the idea that it is stimulation of cholinergic receptors in heart and lung that results in both decreased cardiac output and bronchospasm. The results of other studies suggest that cocaine cardiotoxicity is due to its antimuscarinic effects, which reduce membrane electrical stability and act synergistically with other (sympathomimetic) effects of cocaine to promote arrhythmias (Xiao and Morgan, 1998). Still, additional mechanisms must also be involved, as the negative inotropic effects of AEME are also reversed by treatment with nitric oxide inhibitors (Woolf et al., 1997).

Cocaine, itself, causes a negative inotropic response because of calcium overload within individual myocytes but, in the case of AEME (whatever the underlying mechanism), the

negative inotropic effects are a consequence of decreased myofilament Ca^{2+} responsiveness and also structural damage to myocytes by some as yet unidentified, direct toxic effect (Huang et al., 1997). Once AEME is formed, liver microsomes convert it to ecgonidine, which is then excreted in the urine. In a recent study, ecgonidine was detected in more than 95% of BE-positive urine specimens from a random drug-testing program, indicating that smoking is the major route of cocaine administration (Paul et al., 1999). Even though blood levels tend to be very low, AEME can be detected in other matrices, including sweat, hair, and saliva (Kintz et al., 1997). Kintz et al. identified AEME in 32 hair specimens of "crack" abusers, including fetal hair; hair concentrations ranged from 0.20 to 21.56 ng/mg. These results suggest that AEME can be a useful marker for the detection of cocaine smoking in both clinical and forensic settings.

1.7.5 Norcocaine

In animals, cytochrome P-450 and flavin adenine-dinucleotide-containing monooxygenase metabolize cocaine to norcocaine. Further enzymatic breakdown yields *N*-hydroxynorcocaine and norcocaine nitroxide (Shuster et al., 1983). Norcocaine nitroxide, once thought to be a highly reactive free radical, is now known to be stable; however, further oxidation to the norcocaine nitrosodium ion produces a compound that is highly reactive with glutathione. If glutathione stores fall below a certain level, lipid peroxidation is unopposed and cocaine metabolites bind to hepatic proteins, eventually leading to cell death (Evans, 1983; Kloss et al., 1984a,b). It had been thought that, in humans, only minute amounts of cocaine underwent oxidative metabolism, which would explain why liver lesions have only rarely been reported in cocaine users. However, the study by Blaho et al. (2000) clearly demonstrated that fairly substantial amounts of norcocaine can be detected in the plasma of symptomatic cocaine abusers. In their study of 111 cocaine users presenting for emergency room treatment, the mean norcocaine concentration was 30 ± 17 ng/mL. The higher levels of norcocaine seen when alcohol use is combined with cocaine have yet to be explained. Other effects observed in animals that may or may not occur in humans include elevation of serum adrenaline concentration and increased production of both atrial naturetic factor and tumor necrosis factor. In rats, cocaine and norcocaine both lead to increased concentrations of all three hormones, but a much greater amount of cocaine must be given to produce elevations comparable to those produced by norcocaine (Mahlakaarto et al., 1998).

1.7.6 Fetal metabolism

Human placenta has considerable cholinesterase activity (Sastry, 1997). There is some variation from individual to individual in the ability to metabolize cocaine, which means that some fetuses may be affected to a greater or lesser degree than others (Roe et al., 1990). In animal studies, newborns develop higher blood levels than adults receiving the same dose of cocaine, and their plasma and tissue levels decline more slowly than adults (Morishima et al., 1990). Infants born to cocaine-using mothers may have persistently elevated cocaine levels for days (Chasnoff et al., 1987). However, a causal relationship between persistently elevated levels and the occasional case reports of perinatal stroke and intraventricular hemorrhage in the newborn has not been demonstrated.

The fetus handles BE differently than the mother. Because BE is excreted primarily in the urine and both renal blood flow and glomerular filtration rates double in pregnant women, the mother clears metabolite much more quickly than her fetus. In one study where

BE concentrations were measured in mother and child shortly after birth, the mother's BE concentration was nearly 20 to 30 times higher than that of the fetus (240 vs. 12.2 ng/mL to 378 vs. 10.8 ng/mL) (Meeker and Reynolds, 1990). Though unproven, the possibility also exists that the enzymatic pathway for conversion of cocaine to methylecgonine may not be fully developed in the newborn. In newborns, the plasma half-life of BE during the first day of life, based on measurements in 13 infants, was 16 hours. During the first week of life, the urine half-life of BE measured in 16 subjects decreased to 11.2 hours (Dempsey et al., 1999).

Possibly because of differences in placental function, concentrations of cocaine and its metabolites in umbilical cord blood may vary considerably, and in some cases no cocaine may be detected at all (see Section 1.8). When umbilical cord blood from 36 neonates at risk for prenatal cocaine exposure was studied prospectively, only 18 of the samples were plasma positive for BE, and only half of those (nine, or 25% of the sample) were also positive for cocaine. The maximum plasma cocaine concentration in cord blood was 88 ng/mL (mean, 39 ng/mL). The maximum plasma BE concentration was 3880 ng/mL (mean, 844 ng/mL). Other drugs were also detected. In infants testing positive for BE, the mean plasma drug concentration of nicotine was 1.7 ng/mL; cotinine, 94 ng/mL; and caffeine, 1205 ng/mL. Mean plasma drug concentrations were not significantly different in the infants that were BE negative (nicotine, 5.2 ng/mL; cotinine, 97 ng/mL; and caffeine, 1440 ng/mL). No cocaethylene was detected in any of the women (Dempsey et al., 1998).

The failure to detect cocaethylene is a good example of the difficulties involved in trying to generalize from animal or even *in vitro* toxicity data to humans. *In vitro* studies with human placenta indicate that the placenta does not serve as a significant physical or metabolic barrier to cocaethylene transfer from mother to child (Simone et al., 1997), yet none was detected when a large group of children born to cocaine-using mothers was tested (Dempsey et al., 1998).

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1.8 Problems of test interpretation

1.8.1 Introduction

Modern techniques allow for the detection of drugs in quantities as small as parts per billion, in an ever-growing list of alternative tissue matrices. Unfortunately, these technical advances have done little, if anything, to help identify those deaths that are due to drugs and those deaths where the presence of drugs is simply an incidental finding. Why are such precise measurements of so little value? Because, except for episodes of massive overdose (Fishbain and Wetli, 1981; Wetli and Mittlemann, 1981), when the mechanism of death is perfectly clear, most cocaine-related deaths occur in chronic drug users, where

death is a consequence of neurochemical and anatomic changes that have been induced over a period of months or even years (Karch et al., 1998). Long-term cocaine users have changes in their hearts (Karch et al., 1998) and brains (Volkow et al., 1993) that favor the occurrence of sudden death. The existence of these changes explains why, in the living or the dead, it is absolutely impossible to correlate a specific blood or plasma concentration with toxicity (Jenkins and Goldberger, 1997; Karch et al., 1998; Blaho and Winberry, 2000).

In addition to problems of direct toxicity, less privileged drug users, such as sex workers or those without access to sterile syringes, are at increased risk for a host of lifestyle diseases, such as hepatitis, tuberculosis, and HIV (Persaud et al., 1999). Given these realities, the accurate certification of drug-related death requires knowledge of (1) the decedent's past medical history, (2) an account of what happened at the scene, (3) a thorough postmortem examination, and (4) the results of toxicology testing. Reliance upon only one of these elements, to the exclusion of the others, is almost certain to result in misdiagnosis.

Except, perhaps, for research studies, there seldom is any reason for clinicians to measure plasma concentration of cocaine or its metabolites. No matter what the measured cocaine concentration, treatment is based on the patient's symptoms, although just what that treatment should be remains controversial. Unlike alcohol, where specific blood concentrations do, generally, correspond to specific physiological and psychological states, cocaine blood concentrations do not relate to symptoms (Blaho and Winberry, 2000), not even in the laboratory setting. When cocaine is given to volunteers, correlations can be drawn between the degree of mood elevation and peak blood levels, but only when concentrations are rising. If blood concentrations are falling, the exact same concentration that results in a "high," can be associated with a dysphoric reaction. Both cardiovascular effects and feelings of euphoria decline more rapidly than do cocaine blood concentrations (Javaid et al., 1978), but the "rush" experienced by cocaine users follows a different time course than the cardiovascular changes (Kumor et al., 1988).

1.8.2 Tolerance

The interpretation of postmortem blood concentrations is even more complicated than attempts at making such correlations in the living. Before the current cocaine pandemic, blood concentrations of more than 5 mg/L were thought to be uniformly fatal (Wetli and Mittlemann, 1981). With more experience, it has become apparent that isolated postmortem blood concentrations cannot be used to determine the cause of death. Tolerance on a massive scale occurs, and concentrations well in excess of 5 mg/L can be encountered in cases of trauma death where the presence of cocaine is clearly an unrelated finding (Pagel et al., 1994; Shannon et al., 1996; Karch et al., 1998).

A case report describing a man shot while drinking in a local bar is illustrative. Prior to being shot, the man's behavior was said to have been normal. When autopsied several hours later, after having undergone aggressive fluid replacement, multiple blood specimens showed a blood cocaine concentration of 30 mg/L (Howell and Ezell, 1990). In a similar case, a young woman with a history of chronic cocaine abuse was found dead at home. The woman was not a body packer attempting to smuggle drugs, and there was no evidence that she had purposefully overdosed; the blood concentration was over 300 mg/L (Peretti et al., 1990).

On the other hand, for individuals who are chronic abusers with established changes in their heart and brain (and perhaps elsewhere), death and toxicity can occur after the

ingestion of trivial amounts of drug, and can be associated with very low blood and plasma concentrations (Smart and Anglin, 1987; Jenkins and Goldberger, 1997; Karch et al., 1998). These considerations would not apply in naïve users, without underlying or undiagnosed heart or brain changes. In an early autopsy study of 59 cocaine-associated deaths, postmortem blood cocaine levels ranged from 0 to 12.2 mg/L with a mean of 1.2 mg/L. Benzoylecgonine concentrations were from 0.09 to 30.6 mg/L (Goggins et al., 1990). A decade later, in a series of 99 cocaine-associated deaths (of which roughly one-half were a direct consequence of cocaine toxicity and one-half incidental findings), blood and urine cocaine and BE concentrations in the two groups were indistinguishable. The mean blood cocaine concentrations were 1.12 mg/L in the group for which death was attributed to direct cocaine toxicity and .487 mg/L in the group for which cocaine was an incidental finding (not significantly different). Interestingly, concentrations of the principal metabolite, BE, were significantly higher in the group dying of cocaine toxicity than the other group (1.54 vs. .946 mg/L) (Karch et al., 1998). Tolerance is certainly one explanation for the overlap; the other is the occurrence of postmortem redistribution.

1.8.3 Postmortem redistribution

Basic drugs such as tricyclic antidepressants, narcotic analgesics such as heroin and morphine, local anesthetics, and stimulants such as methamphetamine and cocaine, all tend to accumulate in heart muscle. When measured in heart blood, concentrations of these drugs increase after death. It had always been assumed that much of the rise was a consequence of the drug being released from heart muscle and diffusing into blood within the heart (Ottosson et al., 1988).

It is now apparent that more is involved than the simple release of drug from heart muscle. In an experimental model designed to explain these changes, rabbits were given amphetamine or morphine and then sacrificed 20 minutes to one hour later. The great vessels of the heart were ligated in half the animals. The rabbits were then placed on their backs, and after six hours had elapsed multiple specimens were taken from the left and right sides of the heart of all the animals. In those with the ligated vessels, the drug concentration ratio in the left and right ventricles remained unchanged after six hours. In the group of rabbits in which the vessels were not ligated, concentrations were the same in the left and right ventricles at time zero, but by six hours, the concentration in the left ventricle had increased to twice the concentration of the right ventricle. The highest concentration of methamphetamine was found in the lungs, followed by myocardium, then pulmonary venous blood, cardiac blood, inferior vena caval blood, and liver (Moriya and Hashimoto, 1999).

The study demonstrates that basic drugs, sequestered in the lungs, are redistributed rapidly into the pulmonary venous blood and then into the left cardiac chambers, provided that the blood remains liquid after death. Because of the lung's very great blood supply, the absolute amount of drug in the pulmonary circulation will be much greater than in other organs. Postmortem, drug temporarily sequestered in the pulmonary circulation may diffuse through the thin-walled pulmonary veins, falsely elevating blood concentration within the left ventricle (Moriya and Hashimoto, 1999). Accordingly, left ventricular blood should never be used for toxicological evaluation. Blood taken from the right ventricular cavity, however, is unlikely to be subject to the same sort of postmortem concentration increase seen on the left. Unfortunately, most autopsy reports still do not specify from which organ the blood sample was obtained, let alone from which side of the heart.

1.8.4 Cocaine-related deaths

Isolated blood cocaine levels cannot be used to explain the cause of death, because cocaine-associated sudden death is not dose related. Chronic cocaine users may have alterations in their hearts (Karch and Stephens, 1991; Brickner et al., 1991; Karch et al., 1995; Sutliff et al., 1996) and possibly their brains (Murray, 1986; Volkow et al., 1993) that make arrhythmias more likely (see Section 1.10.2). Given the presence of appropriate morphologic changes in the heart, in conjunction with a positive history of cocaine abuse, there is nothing unreasonable about declaring cocaine the cause of death even when no cocaine or cocaine metabolite is detectable in the bloodstream. It is vital to emphasize, however, that the observation does not apply to naïve users. Very low drug blood and tissue cocaine concentrations may even be detected as a consequence of environmental contamination. Drugs are universally present in our environment (Oyler et al., 1996; Mieczkowski, 1997). The detection of low levels of cocaine, or cocaine metabolite, in the absence of any anatomic alteration is only evidence of cocaine exposure. It is not evidence of cocaine-related disease. Because of the possibility of side-stream exposure, even the presence of so-called unique metabolites such as anhydroecgonidine and cocaethylene in low concentrations would not necessarily constitute proof of use.

1.8.5 Estimating time of ingestion

Many believe that the ratio of cocaine to benzoylecgonine can be used as an indicator of when the drug was taken. It is argued that, because cocaine has a half-life of only one hour, very high levels of cocaine in the presence of small amounts of BE prove ingestion just before death. Conversely, the detection of high blood concentrations of metabolite but a low concentration of cocaine suggests relatively remote use. Although this approach sounds reasonable, two problems argue strongly against making such inferences. This approach assumes that all of the cocaine and all of the metabolites are to be found circulating only in the blood, but the volume of distribution for BE and EME, the two principle metabolites, has never even been measured, and it may well be that they are quite different. The other confounding factor is the very great inter-individual differences in the rate of metabolism. Moolchan et al. (2000) have shown that in chronic users the half-lives of both cocaine and BE are longer than had previously been thought, probably because the enzyme systems used for the conversion become saturated. If the half-lives of the two compounds are, in fact, not very different, then the ratio between the two cannot be used to determine the time elapsed since ingestion.

The situation is quite different if brain cocaine and cocaine metabolite are measured. Cocaine rapidly crosses the blood–brain barrier, but BE does not; any benzoylecgonine found in the brain is a breakdown product of brain cocaine (Spiehler and Reed, 1985). Postmortem redistribution is not an issue, because, except for the blood already present in the cerebral circulation, after death there is no source of new drug. A decedent with high brain BE concentrations, and no cocaine, must have taken the drug several days before death. Conversely, a decedent with a very high brain cocaine level, and very low BE concentrations must have taken the drug just before dying.

1.8.6 Low cocaine concentrations

Very low cocaine levels are difficult to interpret. Chronic cocaine users sequester cocaine in deep body stores. Small amounts of this sequestered cocaine can leach back into the

bloodstream and saliva for days after the drug was last used (Cone and Weddington, 1989; Burke et al., 1990). Failing to take into account this situation can have important forensic consequences. The National Transportation Safety Board's (NTSB) analysis of the only commercial airline crash ever blamed on drug intoxication is a good example. In 1988, Continental Express Flight #2286 crashed on approach to the Durango, CO, airport; the crew and several of the passengers were killed.

The NTSB ruled that the probable cause of the accident was error on the part of the first officer flying the approach in conjunction with "ineffective monitoring" by the captain due to his use of cocaine before the accident. Published reports do not mention the time that elapsed between death and autopsy, but specimens obtained at autopsy, analyzed at two different laboratories, showed BE levels of 22 and 26 ng/mL (Anon., 1989). Assuming that at one time the captain had a plasma cocaine level of 1000 ng/mL, most of which was converted to BE (Griesemer et al., 1983), then more than 30 hours must have elapsed between initial ingestion and the time samples were taken at autopsy. Even if the initial level had been several thousand nanograms (consistent with intravenous use or "crack" smoking, which seems not to have been the case in this instance), at least 24 hours would have passed between the time he used the drug and the time of the accident. Because it is now clear that postmortem redistribution can cause cocaine blood concentrations to increase after death, the captain's levels may have been even lower (Hearn et al., 1991). And, because the amount of cocaine actually detected in the pilot was not enough to have produced measurable physiological effects anyway, attributing significance to very low cocaine levels is not considered to be a good idea.

Cocaine can be recovered from most of the currency in circulation (Oyler et al., 1996) and can also be detected in the sweat and hair of the children of drug abusers, even those in rehabilitation! In one study, 85% of the children living with cocaine-using parents had detectable levels of cocaine in their hair (Smith and Kidwell, 1996). Whether the positive tests were a result of inhaled cocaine being deposited within the hair or were a result of environmental cocaine deposited on the hair has not been determined.

Volatilized cocaine, just like cigarette smoke, can be passively absorbed. The process has been described in children and can even produce transient necrologic syndromes (Bateman and Heagaraty, 1989). Whether or not such exposure can lead to serious consequences is not clear, but it certainly can lead to positive urine, blood, and hair tests. If parents use cocaine, then it will be in the home environment and, no matter what their wishes, it will end up in their children.

In general, the courts have tended to rule that the presence of detectable amounts of cocaine, or cocaine metabolite, is proof of willful child endangerment. One of the most frequently cited studies in this regard described 16 dead children who had cocaine or cocaine metabolite in their blood. Scene investigations documented that shortly before death these infants had been exposed to "crack" smoke. Most of the infants were under three months of age, none had revealing autopsy findings, and their mean cocaine blood level was 76 ng/mL, just barely over the level required to produce any measurable physiologic effects (Mirchandani et al., 1991). On the basis of this evidence alone, and in the absence of any plausible mechanism, sudden infant death syndrome (SIDS) would appear to be the more likely diagnosis in these particular cases, especially given the absence of pathologic findings and the evidence, outlined above, that low levels of cocaine could have had their origin in the children's environment.

In fact, low levels of cocaine detected in a fetus do not even constitute evidence of maternal cocaine use. Side-stream intake of volatilized cocaine can occur in innocent mothers (Cone et al., 1995), and if the mother is exposed to this vapor then cocaine and

its metabolite could appear in the infant, although the mother herself was not a voluntary cocaine user. Thus, the identification of cocaine in an infant is not necessarily proof of abuse by the mother. Similar considerations apply to breast milk. There is evidence that cocaine becomes concentrated in breast milk (Bailey, 1998) but unless there is a maternal admission of drug use, its presence could be explained by environmental exposure.

Because so much cocaine is in the environment and because the possibilities of accidental contamination are so real, NIDA has promulgated regulations for drug testing that include "cutoffs." For BE, the cutoff is 150 ng/mL; levels below that are reported as negative. Of course, these "cutoffs" were formulated with living patients in mind, but the reasoning is still valid. In the absence of any other information, cocaine or cocaine metabolite levels of less than 50 ng/mL are of only historic interest and should not be taken as proof of recent ingestion. Even when levels are higher than 50 ng/mL, postmortem blood cocaine measurements must be interpreted with great care. Cocaine blood concentrations only rise after death (Hearn et al., 1991) and, depending on how and where the specimen is collected, the rise may be very considerable.

1.8.7 Cocaine–prescription drug interactions

Because cocaine is mainly used in illicit settings and not all that widely used surgically, formal studies of cocaine–prescription drug interactions have rarely been undertaken. However, some interactions of importance have been identified. Cocaine users who are treated with disulfiram develop significantly higher plasma cocaine concentrations when they are taking disulfiram than when they are not. They also develop higher systolic and diastolic blood pressure and higher mean heart rates (McCance-Katz et al., 1998). Whether this interaction is clinically significant is not known. Similar considerations apply to documented interactions with amitriptyline, procanamide, and quinidine, all of which inhibit human plasma butrylcholinesterase. Clinical measurements are lacking, but *in vitro* studies have shown that the breakdown of cocaine is slower in the presence of drugs that inhibit butrylcholinesterase (Bailey, 1999a,b,c). The lack of clinical reports may be explained, at least in part, by the declining use of drugs such as quinidine. An issue of perhaps greater concern would be the interaction between cocaine and vasoactive compounds, such as ephedrine (both an α- and a β-adrenergic agonist) and yohimbine (a selective α-2-antagonist which readily enters the central nervous system [CNS] and elevates blood pressure). Even though ephedrine and yohimbine are contained in some of the dietary supplements that are said to enhance virility, and even though cocaine is certainly used as a sexual stimulant, no adverse reactions related to combinations of herbal supplements with cocaine have been reported.

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1.9 Cocaine tissue disposition

Drug users empirically select a method and route of drug administration that delivers the most drug to the brain (Quinn et al., 1997). Inhalation and smoking are the routes of administration that allow the most rapid delivery of drug to the brain, while intravenous injection maximizes the bioavailability of an administered drug. Experimental studies have identified low-affinity cocaine receptors in the heart, lungs, gut, kidney, and testes (Calligaro and Elderfrawi, 1987; Jatlow et al., 1991). Distribution of C^{11}-labeled cocaine has been studied in humans using positron emission tomography (PET) scanning (Volkow et al., 1992; Abi-Dargham et al., 1997; Fowler et al., 1999), and the results generally parallel the results seen in isotopic studies done in animals (Collins et al., 1999). Extrapolation from these values to the interpretation of postmortem measurements requires a great deal of faith.

As Prouty and Anderson (1990) were the first to observe, drug concentrations measured during life may bear little or no relation to drug levels measured after death. The problem is especially great for basic drugs, which includes the most popular drugs of abuse. Postmortem cocaine blood levels vary, depending on which blood vessel they are obtained from (Logan et al., 1997). They may be considerably higher or lower than they were at the time of death (Sylvester et al., 1998). Concentrations measured in other tissues are likely to increase after death, but the magnitude of the change depends on the postmortem interval, the means of collection, the temperature at which the cadaver was stored, the position in which it was lying, and whether cardiopulmonary resuscitation (CPR) had been performed (Moriya and Hashimoto, 1997, 1998; Langford and Pounder, 1997). Even the portion of the organ sampled can affect the final result (Pounder et al., 1997).

In the case of blood specimens, if the collection site is not specified, drawing legitimate inferences about either the time of death or the role of cocaine is difficult. All that can be legitimately concluded is whether or not cocaine was used prior to death. The situation is even worse in the case of other tissues and, except for the presence or absence of drug,

little else can be inferred. There is, for example, general agreement, that postmortem measurements should be made in blood from the femoral vessels. But, unless the proximal vessels are ligated first, any attempt at aspiration from the femoral vein is likely to yield blood that arose from the liver, where concentration would be expected to be much higher.

In animals and humans, concentrations of cocaine and cocaethylene are highest in the brain, followed by liver and femoral muscle; however, there is enormous intra-individual variation (see Figure 1.9.1) (Moriya and Hashimoto, 1996b). After death, cocaine disappears from blood and liver quite quickly, but it can be detected in brain and muscle for some time. The same phenomenon has been observed in *in vitro* studies, suggesting that brain and femoral muscle may be the most suitable tissue for postmortem analysis (Moriya and Hashimoto, 1996a,b).

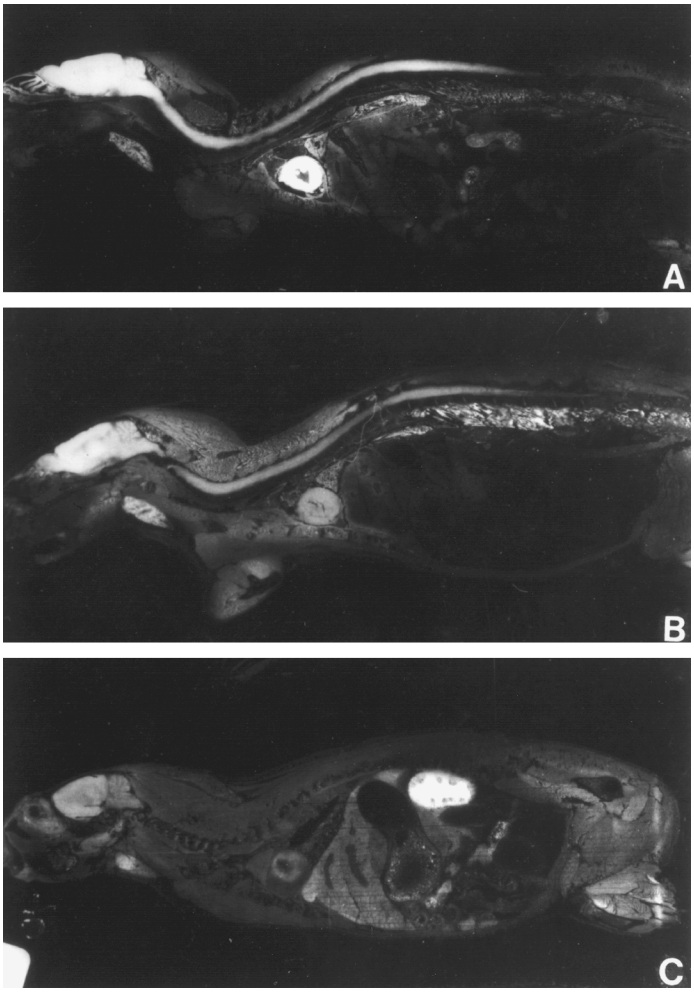

Figure 1.9.1 **Cocaine tissue distribution.** Sagittal sections of a rat injected with C^{14}-labeled cocaine. Sections B and C are from animals pretreated with drugs blocking cocaine uptake. Section A shows intense uptake in the heart, brain, spinal cord, and salivary glands. (From Som, P. et al., *Life Science*, 55(17), 1375–1382, 1994. With permission.)

1.9.1 Adrenals

Rapid, intense adrenal uptake is seen in the rat, presumably a result of binding to the norepinephrine transporter. Uptake by rat adrenal gland is second only to uptake within the brain and spinal cord (Som et al., 1994). In human tracer studies, the adrenal glands take up more of an intravenous tracer dose than the liver. In humans, peak uptake occurs 10 minutes after injection. Within the adrenal, the half-life of the labeled cocaine is 20 minutes (Volkow et al., 1992). No autopsy measurements have been reported, but the relatively slow rate at which the cocaine is washed out makes it probable that significant amounts of cocaine could be found at autopsy.

1.9.2 Brain

Brain may be the best matrix for postmortem cocaine determinations. Throughout the body, cocaine blood concentrations change significantly, but unpredictably, after death, and levels measured at autopsy may bear little relationship to levels at the time of death (Spiehler and Reed, 1985). However, cocaine appears to be more stable in the lipid-rich environment of the brain, and there is reason to believe that cocaine brain levels more accurately reflect concentrations at the time of death than do measurements made in blood or any other tissue (Hernandez et al., 1994).

Because cocaine is so lipophilic, it freely crosses the blood–brain barrier (Misra et al., 1975; Nayak et al., 1976), as does cocaethylene (Hearn et al., 1991b). Receptors with varying affinities for cocaine are found throughout the brain. The region with the highest density of cocaine receptors, which is also the region containing the receptors with the greatest affinity for cocaine, is the stratum. However, when cocaine is taken in behaviorally active doses, uptake occurs in other, lower affinity sites (Volkow et al., 1995). Lower levels of activity are found in the frontal and occipital cortices (Calligaro and Elderfrawi, 1987). In experimental animals and in autopsied cases of cocaine-related deaths in humans, the concentration of cocaine found in the brain is four to ten times higher than in the plasma when measured from 0.5 to 2 hours after drug administration (Spiehler and Reed 1985; Reith et al., 1988). Benzoylecgonine, the principal metabolite of cocaine, crosses the blood–brain barrier only with great difficulty (Misra et al., 1975).

In animal studies, peak cocaine concentrations in the brain are four times higher than in the blood (Nayak et al., 1976). In an autopsy study of 37 patients dying of cocaine toxicity, the mean blood cocaine concentration was 4.6 mg/L (range 0.04–31 mg/L), while the mean BE level was 0.88 mg/L (range 0–7.4 mg/L). The mean concentration of cocaine found in the brain was 13.3 mg/kg (range 0.17–31 mg/kg), and that of benzoylecgonine was 2.9 mg/kg (range 0.1–22 mg/kg). In most cases, the blood–brain ratio was close to four. In a second study of 14 deaths, where cocaine was only an incidental finding (instances of murder, accidental death, etc.), the average blood–brain ratio was only 2.5 (Spiehler and Reed, 1985). Unmetabolized cocaine can be detected in the cerebrospinal fluid (CSF) for at least 24 hours after use (Rowbotham et al., 1990).

Another advantage of brain concentration measurements derives from a unique feature of cocaine metabolism; cocaine rapidly crosses the blood–brain barrier and BE does not (Rowbotham et al., 1990). Because BE does not cross the blood–brain barrier, levels of BE in the brain are lower than in the blood for up to 2 hours after ingestion. Not only does postmortem analysis of brain tissue give a good indication of levels at the time of death, but brain levels can also be indicators of chronic abuse, because extensive prior use is the only way to explain how a decedent could have more BE in the brain

than in the blood or, for that matter, why a decedent would have more BE than cocaine in the brain. This relationship occasionally allows for some very valuable forensic inferences. For example, an individual with a brain cocaine concentration of 8 mg/kg of cocaine and .5 mg/kg of BE must have taken the drug just before death. Conversely, patients with excited delirium are usually found to have only modest cocaine concentrations, but high concentrations of BE, a result of "binging," having ingested large amounts of drug over several days (Karch et al., 1998). Cocaine is stable in frozen brain for months (Spiehler and Reed, 1985) and can be recovered, along with its metabolites using solid-phase extraction techniques (Bogusz et al., 1998; Hall et al., 1999; Paul et al., 1999; Jenkins and Goldberger, 1997).

Despite a paucity of information about brain concentrations in the fetus, the results of animal studies (DeVane et al., 1991; Binienda et al., 1993; Downs, et al., 1996) and a handful of human reports suggest that brain concentrations are lower in the fetus than in the mother. In a case reported by Mittleman et al. (1989), the maternal-to-fetal brain cocaine ratio was 6.5:1. A study of fetal demise, including 47 cocaine-related cases where both blood and brain cocaine levels were measured, found that mean blood concentrations of cocaine were 800 ng/mL, while the mean brain concentration of cocaine was 1100 ng/mg (Critchley et al., 1988; Morild and Stajic, 1990). At present, the data are insufficient to be sure, but preliminary investigations suggest that cocaethylene levels in the brain are generally equal to cocaine levels (Hearn et al., 1991a).

1.9.3 Hair

Disagreement exists as to the route (or routes) by which cocaine is incorporated into hair, but the process certainly occurs. There is evidence for passive diffusion from blood into the hair follicle, but hair is coated with sebum, which may also contain drug, and the possibility of external contamination exists (Blank and Kidwell, 1993; Huestis and Cone, 1998). Whether or not the color of hair or the race of the individual has any affect on the avidity with which hair binds cocaine is a matter of debate, but mounting evidence suggests that it does (Kidwell et al., 2000; Kintz et al., 2000), although the results of other experiments suggest it does not (Hoffman, 1999; Kelly et al., 2000).

When deuterium-labeled cocaine was given to human volunteers, the parent drug, cocaine, was the predominant analyte detected in hair, just the opposite situation to blood, where BE is the major analyte. The estimated threshold dose for detection was estimated to be 25–35 mg of drug administered intravenously, and a single dose of cocaine could be detected for two to six months, although there was very large intra-individual variation in the amount of cocaine detected in the hair, with non-Caucasians generally exhibiting much higher concentrations than Caucasians, even though both racial groups had received the same amount of cocaine (Nakahara and Kikura, 1994; Henderson et al., 1996).

All of the other cocaine metabolites can be detected in hair samples, but the parent compound predominates. In cases of opiate abuse, heroin ingestion can be proved conclusively by demonstrating the presence of the unique heroin metabolite, 6-monoacetylmorphine. Unfortunately, that is not possible when testing for cocaine, because there are no unique metabolites that cannot also be produced externally. Cocaethylene can be produced *in vitro*, for example, when cocaine has been smuggled in bottles of alcoholic beverages (Casale and Moore, 1994).

Hair cocaine concentrations in active users range from 1 to 5 ng/mg of hair, or even higher (Henderson et al., 1996). Once cocaine is deposited in hair it is stable indefinitely,

a fact that can be of considerable importance should questions about drug use arise after death. The question can be easily answered by exhumation. Cocaine has been detected in the hair of mummified Peruvian coca chewers who died more than 1000 years ago (Springfield et al., 1993). As a practical matter, hair storage requires very little space, and some medical examiners now routinely collect and store samples, analyzing them only should the need arise at a later date.

1.9.4 Heart

Positron emission tomography (PET) scanning studies of humans show a high uptake of cocaine in the heart. Within 2 to 3 minutes after injection, 2.5% of the administered dose appears in the heart and is then cleared rapidly over the next 10 minutes. When pharmacologic doses of cocaine are given to baboons, the pattern of uptake and washout is similar to that seen in humans. However, inhibition of the norepinephrine transporter persists for some time after the cocaine is gone (Fowler et al., 1994; Volkow et al., 1996). Although the half-life of cocaine in the baboon heart is 2.5–9 minutes, 78 minutes after an injection of cocaine re-uptake of norepinephrine was only 48% of normal. This finding suggests that toxic levels of norepinephrine may persist in the heart for some time after the cocaine has been cleared. It may explain the typical patterns of catecholamine-induced necrosis seen in the hearts of some abusers.

In spite of the relatively high uptake by the heart, the rapid rate at which cocaine is cleared makes it unlikely that high levels will be detected at autopsy. This is borne out by the few measurements that have been reported. In a case described by Poklis et al. (1985), where death occurred after an intravenous dose of undetermined size, the concentration of cocaine was 6000 ng/mg in the heart while the cocaine concentration in the blood was only 1800 ng/mL. Unfortunately, the report does not state how many hours had lapsed between the time of death and the time of autopsy. How much cocaine actually gets to the heart is a matter of some importance. Large doses of cocaine are only lethal to experimental animals when they are given via a route that guarantees that high concentrations of cocaine actually reach the heart. If the cocaine passes through the liver first, only minimal effects are observed (Jones and Tackett, 1991).

1.9.5 Kidneys

In human radioactive uptake studies, renal uptake is higher than cardiac uptake but still considerably less than hepatic uptake. Uptake occurs in the renal cortex only. As in the heart, peak uptake occurs at 2 to 3 minutes, and after 10 minutes half of the dose has been cleared (Volkow et al., 1992). Few autopsy measurements of renal cocaine levels have been reported. The values that have been observed ranged from 1 to 28 mg/kg (Price, 1974; Lundberg et al., 1977; DiMaio and Garriott, 1978; Poklis et al., 1985), but comparing the results is difficult because, in most cases, the time elapsed from death to autopsy is not mentioned.

1.9.6 Liver

Hepatic cocaine receptors are present in higher concentrations and have greater affinity for cocaine than those located in the brain (Calligaro and Elderfrawi, 1987). In Volkow's PET studies, hepatic accumulation of drug was very high, although the rate of uptake was much slower than for most of the other organs. Peak uptake occurred 10–15 minutes after intravenous injection. More than 20% of a given dose reached the liver and the

levels remained stable for more than 40 minutes. The findings of these dynamic studies are generally in agreement with autopsy studies that have also shown high levels in the liver.

In the autopsy study reported by Spiehler and Reed (1985), the mean hepatic cocaine level in patients dying of cocaine toxicity was 6.7 mg/L, and the BE concentration was 21.3 mg/L. An earlier retrospective study of 15 cases gathered from several centers yielded slightly different results. More cocaine was detected in the blood than in the liver, with a blood/liver ratio of 1.4 (Finkle and McCloskey, 1977). High concentrations of BE are hardly surprising given that the major metabolic pathways of cocaine metabolism involve plasma and hepatic esterase activity. Cocaethylene is also synthesized in the liver, and hepatic cocaethylene levels are much higher than hepatic cocaine levels (Hearn et al., 1991a). Whether or not this concentration difference explains why cocaethylene appears to be more hepatotoxic than cocaine (Odeleye et al., 1992) or if cocaethylene is actually more toxic remains to be seen.

Hepatic oxidation of the nitrogen atom in the tropane ring also occurs. The resulting products are *N*-hydroxynorcocaine and the free radical norcocaine nitroxide. Norcocaine can also be found as a contaminant in illicit cocaine (Kumar, 1991). Norcocaine found in illicit samples is there as a byproduct of the refining process. When potassium permanganate is added to crude cocaine mixtures, norcocaine can be formed. Norcocaine is believed to be responsible for the hepatotoxicity observed when cocaine is given to experimental animals (Thompson et al., 1979). Mice pretreated with phenobarbital, whose P-450 microsomal systems have been activated, develop a specific type of hepatic necrosis (Kloss et al., 1984).

Norcocaine can be detected in humans, but only in very small amounts. In addition to the norcocaine that may contaminate a sample, norcocaine can also be formed in the human body, although hepatic oxidation is not a preferred route of metabolism. Human volunteers given both cocaine and alcohol will produce more norcocaine than controls given cocaine alone. An explanation for this phenomenon is still wanting. It has been suggested that, given enough alcohol, blood pH will drop slightly and plasma cholinesterase will become less efficient, leaving more cocaine to circulate through the liver. No matter how the norcocaine gets into the body, its relationship to hepatic injury in cocaine users is unclear (Inaba et al., 1978). In humans, lesions histologically similar to those seen in mice have been described but are quite rare (Freeman and Harbison, 1981; Marks and Chapple, 1986; Perino et al., 1987; Powell et al., 1991; Falk et al., 1995).

1.9.7 Skin and nails

Basic drugs, including those that are not thought of as being very lipid soluble, accumulate in the epidermis, dermis, and subcutaneous fat. Even the stratum corneum, the outermost layer of the skin consisting entirely of keratinocytes that have lost their nuclei, binds drugs. Cocaine, for example, reaches the skin either through the circulation or via external contamination. In a controlled study of cocaine and heroin users housed in a locked ward, cocaine and BE remained present in most stratum corneum specimens collected over a three-week "washout" period, when the volunteers were not receiving drugs. When drugs were given, low concentrations quickly appeared in the stratum corneum and remained there for at least two weeks (Joseph et al., 1998). In other studies, cocaine, BE, THC (or 11-*nor*-delta-9-tetrahydrocannabinol, THC-COOH) — applied directly to the skin, remained detectable there for up to three days and were not removed by simple cleansing with isopropanol (Kidwell et al., 1998).

Table 1.9.7.1 Values from a Typical Cocaine-Related Death

	Adipose (ng/g)	Skin (ng/g)	Blood (ng/g)
Cocaine	220	259	341
Cocaethylene	348	188	209
Benzoylecgonine	111	N.T.	2903
Ecgonine methyl ester	Present	Negative	Present

Source: Data adapted from Levisky, J. et al., *Forensic Sci. Int.*, 110, pp. 35–46, 2000.

Basic drugs can also be extracted from the underlying dermis. The dermis is composed of fibrous, vascularized connective tissue; hair follicles; and sweat and sebaceous glands. The number of sweat and sebaceous glands, and the output of sweat and sebum found in the dermis, vary by location. The hands are the most richly supplied, but sweat glands in any location are capable of excreting drug-containing sweat and sebum onto any part of the skin. In autopsy studies, drug concentrations measured in the dermis were comparable to the concentrations measured in blood (Levisky et al., 2000). Values from a typical cocaine-related death are shown in Table 1.9.7.1.

The adipose layer, beneath the dermis, consists of lobules of fat separated by fibrous connective tissue. Lipophilic drugs including diazepam, nordiazepam, meprobamate, and alprazolam have all been detected both in skin and adipose tissue. In the case of heavy marijuana smokers, THC has been shown to remain detectable in fat for up to 28 days after smoking (Johansson et al., 1989). In the case of other drugs, the detection time may be even longer. Measurable amounts of the drug terbinafine can be found in plasma, serum, sebum, hair, nails, dermis/epidermis, and stratum corneum for more than six weeks (Faergemann et al., 1991).

Special considerations apply to the fetus. Human newborns rely on catecholamine-mediated liberation of energy from brown fat stores. The brown fat of experimental rats avidly takes up cocaine. The high uptake is probably explained by the fact that nuchal brown fat is richly supplied with sympathetic nerve terminals (Som et al., 1994). The children of cocaine-using mothers no doubt have detectable levels of cocaine in their fat stores, but measurements have not been reported. Although the actual mechanism is not completely understood, leptin, which is produced in several organs in addition to white adipose tissue, brown fat, the placenta, and fetal tissues (such as heart and bone/cartilage), almost certainly plays a role. It is known, however, that the production of leptin by white fat is at least partly controlled by inhibitory β-adrenoceptor agonists that bind to β-3-adrenoceptors. Cocaine- and amphetamine-regulated transcripts (CARTs) are integral to the process (Trayhurn et al., 1999).

Fingernails and toenails contain keratin and melanin that is basically indistinguishable from keratin found in hair. The results of preliminary studies suggest that nail drug testing may prove to be a more sensitive postmortem detector of cocaine use than either urine or blood. When fingernail and toenail specimens obtained from 18 suspected cocaine users were extracted in methanol purified by solid-phase extraction, nail analysis revealed a marked increase in the detection of cocaine use. As detected by nail analysis, cocaine or one of its metabolites was present in 14 (82.3%) subjects, but only five (27.7%) were found positive by conventional postmortem drug analysis. As is the case with hair and sweat, cocaine itself is the main analyte detected, but smaller quantities of BE were found in all the positive nail specimens. Other metabolites, including anhydroecgonine methyl ester,

ecgonine methyl ester, cocaethylene, norcocaine, and norbenzoylecgonine were inconsistently present. The ratio of cocaine to BE ranged from 2–10:1 (Garside et al., 1998).

In a related study, the toenails of 46 decedents were tested for cocaine, BE, norcocaine, and cocaethylene. Concentrations of cocaine and BE ranged from 0.20 to 140.17 (n = 20) and 0.30 to 315.44 ng/mg (n = 21), respectively. Norcocaine concentrations of 6.78 and 0.66 ng/mg and cocaethylene concentrations of 2.60 and 0.73 ng/mg were detected in two specimens (Engelhart et al., 1998). Cocaine can also be detected in the finger- and toenails of infants and children. One case report described finding cocaine in the nails of a three-month-old with SIDS (Skopp and Potsch, 1997).

1.9.8 Biofluids

1.9.8.1 Amniotic fluid

In one study, cocaine and its metabolites were measured in amniotic fluid and umbilical cord tissue, at birth, in 32 women who admitted to ongoing cocaine use. In the amniotic fluid, the main analyte detected was BE, which was detected in 28.1 and 18.5% of the amniotic fluid and umbilical cord tissue specimens, respectively. Ecgonine methyl ester and *m*-hydroxybenzoylecgonine were also measurable in amniotic fluid specimens, while umbilical cord tissue specimens were found to contain mainly EME, norcocaine, and *m*-hydroxybenzoylecgonine (Winecker et al., 1997). In the only case report published to date, cocaine and BE were quantitated in amniotic fluid, umbilical cord blood, and neonatal urine obtained at the time of delivery. Benzoylecgonine levels were 290 ng/mL and cocaine levels were 70 ng/mL. Levels of BE were much higher in the child's urine, although cocaine levels were roughly similar. Neither cocaine nor BE was detected in umbilical cord blood (Jain et al., 1993).

1.9.8.2 Breast milk

Cocaine can be transferred to infants via mothers' milk (Chasnoff et al., 1987), but the kinetics in humans has not been studied in detail, and the relevance of experimental models, at least in terms of cocaine handling, has not been proven. In experimental animals such as the rat, cocaine levels in the milk may reach higher concentrations than in the mother's liver or brain. In one experimental study, cocaine levels in rat milk were eight times higher than those seen in blood levels. This may have to do with the high lipid content of the milk (Wiggins et al., 1989), or it may be explained by protein binding. In human milk, both cocaine and cocaethylene are bound mainly to albumin, with only weak and nonspecific binding to lipid. Up to 55% of cocaine and up to 61% of cocaethylene found in milk is protein bound. It has been speculated that protein binding and the lower pH of milk than serum (6.9 vs. 7.4) may enhance the mammary secretion of cocaine and cocaethylene into the milk, exposing the child when it nurses (Bailey, 1998).

The consequences of such exposure, if it occurs, have not been established and will be difficult to prove. Women who use cocaine during their pregnancy also use ethanol, cigarettes, and other drugs, all of which may be excreted in the milk as well. Indeed, one case report describes finding nicotine, codeine, and oxycodeine along with cocaethylene in the milk of one admitted cocaine user, and no drug in the milk of another woman who was also an admitted drug user (Dickson et al., 1994). Nursing mothers have been charged with assault, endangerment, and even manslaughter for the administration of drug-tainted milk, but in none of the cases that have come to trial has the mother, or her milk, ever been tested for the offending drug (Ariagno et al., 1995).

1.9.8.3 *Fetal gastric aspirates*

The developing fetus swallows amniotic fluid, and cocaine delivered across the placenta appears in this fluid. Concentrations of cocaine measured in gastric aspirates taken from the newborn may contain unpredictable amounts of cocaine or cocaine metabolite. Such measurements appear to be no more useful than measurements of drug concentrations in meconium, blood, or hair (O'Connor et al., 1996; Kim, 1998).

1.9.8.4 *Saliva*

Saliva contains very little protein, so unbound drugs in the plasma appear in almost the same concentrations in both plasma and saliva. Because cocaine is weakly basic and saliva is normally more acidic than plasma, the concentration of ionized cocaine in saliva may be as much as five times higher than plasma cocaine concentrations. For the same reasons, concentrations of BE are two to three times higher in plasma than in saliva (Thompson et al., 1987; Schramm et al., 1992). When human volunteers are given intravenous cocaine, saliva cocaine levels correlate well with plasma levels. Levels in both saliva and blood correlate equally well with behavioral and physiological effects. The half-life of cocaine in both fluids is the same, about 35 minutes. Five hours after a 40-mg intravenous bolus of cocaine, levels in both saliva and blood are near the limits of detection (29 ng/mL for saliva and 8 ng/mL for plasma). Accordingly, cocaine detected in saliva is a good sign of very recent use (Cone and Menchen, 1988; Ferko et al., 1990).

Cocaine is the predominant analyte in saliva but, because BE and EME both have much longer half-lives (2.3 to 6.5 hours) than cocaine, both of the metabolites will accumulate in saliva with repeated dosing. The relative proportions and absolute concentrations of cocaine and its metabolites are highly dependent on how the saliva is collected. Stimulated saliva (specimens collected after the donor has been given a piece of sour candy) tends to contain much less drug than nonstimulated samples (Kato et al., 1993). The results of animal studies suggest that cocaethylene also appears in saliva, and saliva cocaethylene levels also correlate well with plasma cocaethylene levels, but studies in humans are lacking (Barbieri et al., 1994).

The same cautions apply to the interpretation of low cocaine levels in the saliva as those for blood. Chronic cocaine users may have persistent low levels of cocaine even when they have abstained for several days or more. The presence of low levels in the saliva is certainly consistent with past cocaine use, but it is not necessarily diagnostic of recent ingestion. During cocaine withdrawal, lipophilic storage sites in the brain continue to release cocaine. Small amounts of cocaine can appear in saliva and urine for weeks. Rats given 20 mg/kg twice a day for two weeks have measurable cocaine levels in their fat for as long as four weeks after the drug has been discontinued (Nayak et al., 1976). The same is true in the human. Chronic users monitored during withdrawal continue to excrete unmetabolized cocaine, detectable by radioimmunoassay (RIA), for 10 days or more after their last dose (Cone and Weddington, 1989). While most drugs of abuse, including cocaine, can be detected in saliva, the relatively short window of detection and problems with oral contamination and drug concentration make saliva a less desirable means for drug testing. In the case of alcohol, however, saliva can be used to estimate blood levels with considerable certainty (Kidwell et al., 1998; Skopp and Potsch, 1999).

1.9.8.5 *Spinal fluid*

Measurements of spinal fluid may prove useful, especially since cocaine crosses the blood–brain barrier so readily. There have been no systematic studies in humans, but one case report suggests that unmetabolized cocaine can be detected in the CSF for at least 24

hours (Rowbotham et al., 1990), and the process has been studied in an experimental model. Cocaine hydrochloride, in doses of 0.5, 1.0, 2.0, and 4.0 mg/kg, was administered i.v. to male Sprague-Dawley rats. After the cocaine had been given, samples of blood and cerebrospinal fluid were collected from the cisterna magna, and peripheral blood samples were obtained at the same time. After the 1-mg/kg dose, cocaine disappearance from the plasma exhibited first-order kinetics with a half-life of 18.11 ± 3.22 minutes. Cocaine and BE were found in the CSF after all four doses and, as might be expected, BE concentration increased along with the increased cocaine dosage. The CSF-to-plasma ratios for cocaine were quite similar to each other over the dosage range of cocaine that was administered. The same relationship was not observed for BE. Instead, the CSF-to-plasma ratios for BE decreased as the concentrations of BE increased in plasma and CSF (Barbieri et al., 1992).

1.9.8.6 Urine

Cocaine is eliminated almost entirely by biotransformation with a renal clearance of less than 30 mL/minute (Chow et al., 1985). The primary analytes in the urine are cocaine and BE. In a study of otherwise healthy drug addicts in treatment, the median concentrations of cocaine and BE equivalents were 235 and 14,900 ng/mL, respectively, but in many instances the maximum concentrations were many times higher (112,025 ng/mL of cocaine and 1,101,190 ng/mL of BE) (Preston et al., 1998). However, great intra-individual variation exists, and the route by which cocaine is taken has an effect on the proportion of metabolites produced. In a recent controlled study, single bioequivalent doses of cocaine were administered by intravenous, intranasal, and smoked routes to six volunteers, and all urine was collected for three days. Peak cocaine concentrations occurred in the first specimen collected and thereafter fell to 1 ng/mL (the limit of detection) within 24 hours. Benzoylecgonine was the most common metabolite (39, 30, and 16%, after intravenous, intranasal, and smoked routes, respectively). Other metabolites detected in much smaller amounts were EME and six minor cocaine metabolites (norcocaine, benzoylnorecgonine, *m*-hydroxycocaine, *p*-hydroxycocaine, *m*-hydroxybenzoylecgonine, and *p*-hydroxybenzoylecgonine). Taken together, the minor metabolites accounted for as much as 18% of the original dose when it had been given intravenously, and as little as 8% when it had been smoked as "crack" (Cone et al., 1998).

In cases of cocaine-related sudden death, urinary cocaine concentrations may well exceed concentrations of the metabolite (Ramcharitar et al., 1995; Karch et al., 1998). Most, but certainly not all, commercial screening tests are designed to detect the cocaine metabolite BE and not cocaine itself. Some cross-reactivity may exist, but antibody-based screening tests generally do not detect cocaine or other metabolites such as EME in the urine, even if they are present, which explains the false general impression that cocaine does not appear to any significant degree in the urine. Actually, detection of cocaine in the urine is a sign of recent ingestion, especially in occasional users. The absence of cocaine, on the other hand, is only evidence that the drug has not been taken within the last few hours (Jatlow, 1988). The window of detection for BE in the urine can be altered by a number of factors, including chronicity of use, mode of administration, urine volume, and urine pH. In one study, the mean half-life for BE in the urine was 6.8 ± 0.4 hours (Cone et al., 1989).

The half-life of BE is relatively long, on the order of 6 hours, and the metabolite may appear in the urine for days. Thus, the presence of BE is solid proof of past use, but the timing of the past use cannot be inferred from the urinalysis alone.

Hospitalized patients undergoing detoxification continue to excrete metabolite for weeks after their last dose of cocaine (Weiss and Gawin, 1988; Cone and Weddington, 1989; Burke et al., 1990). The same caveats that apply to saliva and blood testing also apply

to urine. It should also be apparent that no conclusions can be drawn about the degree of an individual's impairment, if any, at the time of urine testing.

The presence of metabolite indicates only that the drug was used in the past, and similar considerations apply to the newborn as well. The half-life elimination of cocaine and BE in the newborn has been determined. The half-life of BE during the first day of life, based on blood data in 13 subjects, was found to be 16 hours (95% confidence interval [CI], 12.8 to 21.4 hours). The half-life of BE during the first week of life, based on urine data in 16 subjects, was 11.2 hours (95% CI, 10.1 to 11.8 hours) (Dempsey et al., 1998).

It goes without saying that there is no fixed relationship between blood cocaine or cocaine metabolite concentrations and the amount that appears in the urine. The blood/urine ratio may be much greater or much less than 1, and the concentrations measured in the urine may vary greatly depending on the individual's state of hydration and renal function. In workplace drug testing, the amount of drug in the urine is often normalized to the creatinine content of the urine, which may also be a good practice for postmortem measurements. Neither blood concentration nor the existence of toxicity or impairment can be inferred from urine concentrations. Attempts to do so have been characterized as "pure folly" (Jones, 1998).

1.9.8.7 Vitreous humor

In swine given very large doses of cocaine intravenously (10 mg/kg) and euthanized five minutes later, the vitreous cocaine concentrations were much lower than the blood concentrations. But, after eight hours had elapsed, vitreous cocaine concentrations had risen by more than 300% percent and were comparable to concentrations measured in femoral blood (McKinney et al., 1995). Until recently, human studies were limited to a handful of anecdotal reports. Cocaine concentrations in blood, vitreous, and liver were measured in a 28-year-old woman who died shortly after an intravenous injection. When the blood cocaine was 750 ng/mL, the concentration in the vitreous was 380 ng/mL, and in the liver 130 ng/mL (Lundberg et al., 1977). DiMaio and Garriott (1978) described another case where the blood level was 370 ng/mL while the vitreous level was 210 ng/mL. Hearn et al. (1991a) measured vitreous cocaine concentrations in one eye just after death, and then measured concentrations in the other eye 18 hours later. The cocaine level, which was 1.0 mg/L just after death, rose to 3.5 mg/L after 18 hours. Benzoylecgonine levels also rose from 1.1 to 1.7 mg/L.

In the only large series ever to be published, cocaine, benzoylecgonine, ethanol, and cocaethylene concentrations were measured in 62 medical examiner cases. Mean concentrations of cocaine, cocaethylene, and ethanol measured in vitreous were not significantly different from mean concentrations of the same drugs in blood: 0.613 mg/L (standard deviation [SD] 0.994) vs. 0.489 mg/L (SD 1.204) for cocaine; 0.027 mg/L (SD 0.59) vs. 0.022 mg/L (SD 0.055) for cocaethylene; and 0.092 g/dL (SD 0.12) vs. 0.058 g/dL (SD 0.091) for ethanol. But, there were significant differences between BE concentrations in the two matrices; they were much lower in the vitreous than in the blood: 0.989 mg/L (SD 1.597) vs. 1.941 mg/L (SD 2.9). The usefulness of such measurements is limited by the very large variations recorded in terms of magnitude and also direction of the change in the two fluids. Correlations between blood and vitreous for cocaethylene are particularly poor (Mackey-Bojack et al., 2000).

1.9.8.8 Sweat

Cocaine and its metabolites are excreted in sweat, but usually the amount of parent compound is well in excess of the amount of metabolites. In controlled studies, cocaine first appears in sweat within one to two hours of administration (Huestis and Cone, 1998),

and concentrations of up to 100 ng/mL of cocaine have been detected in sweat after a single, 2-mg/kg dose (Henderson, 1993). Because it is simple to use, most forensic sweat testing is done using the PharmCheck™ sweat patch, or variations on the same design, and results are expressed as the amount of drug per patch. Results are, in good part, dependent upon where in the body the specimen is collected, as the number and type of sweat glands throughout the body are not uniform. Peak cocaine concentrations in volunteers given increasing doses of cocaine ranged from 33 to 3579 ng/patch, with peak concentrations generally occurring 4.5 to 24 hours after dosing. In the patch studies, cocaine could be detected for at least 48 hours after ingestion (Huestis et al., 1999).

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1.10 Cocaine's effects on catecholamine and the heart

1.10.1 General considerations

Cocaine and all of the other abused stimulants disrupt catecholamine metabolism. Cocaine abusers have elevated circulating levels of catecholamines. This has been demonstrated both in experimental animals and in humans (Gunne and Jonsson, 1964; Chiueh and Kopin, 1978; Schwartz et al., 1988; Dixon et al., 1989a,b; Kiritsy-Roy et al., 1990; Conlee et al., 1991; Trouve et al., 1991; Dixon et al., 1993; Melon et al., 1997; Mahlakaarto et al., 1998). Even the infants born of substance-abusing mothers have evidence of abnormal sympathetic function (Ward et al., 1991).

Unlike the medical complications associated with opiate abuse, which are almost always infectious, or secondary to the presence of drug contaminants, many of the pathologic changes reported in conjunction with cocaine use appear to be catecholamine mediated. Compelling evidence indicates that blood pressure elevations associated with cocaine use are centrally mediated, and that the elevation is independent of any effect that cocaine exerts on peripheral catecholamine uptake (Schindler et al., 1992). There is also evidence that cocaine induces epinephrine release from the adrenals, which very likely exacerbates the situation (Chiueh and Kopin, 1978).

Catecholamine effects on the cardiovascular system are mediated by specific receptors. A family of subtypes has been identified, but the receptors of principal concern are the α_1-adrenergic receptors which are mainly located on blood vessels, and β_1-adrenergic receptors located in the heart. These receptors are coupled to phospholipase-C via a G protein. When the receptor is activated, phosphoinositol is cleaved into inositol phosphate and diacylglycerol. Separation of the two fragments releases free calcium into the cytosol and causes the blood vessels to contract. The α_2-adrenergic receptors are found on blood

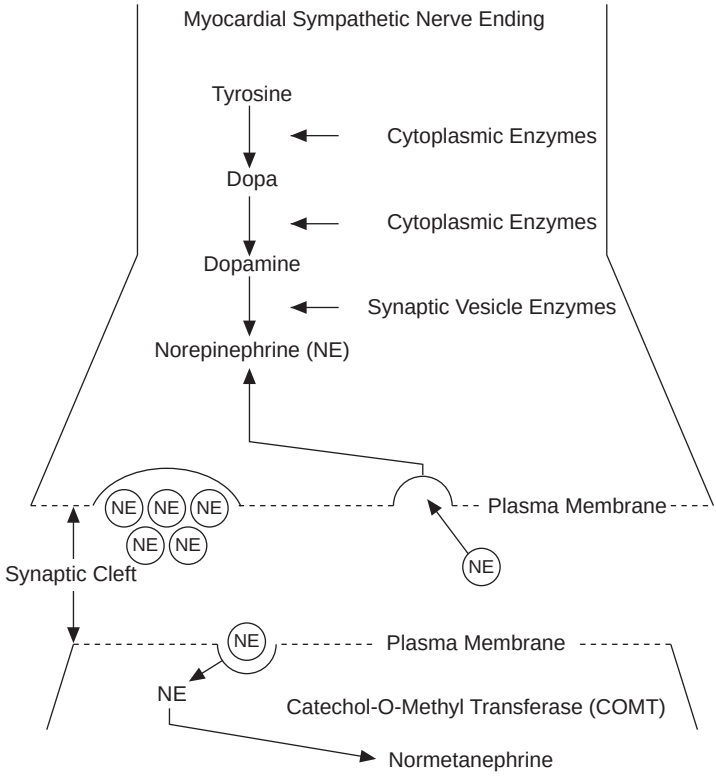

Figure 1.10.1.1 **Synthesis and fate of norepinephrine.** Norepinephrine is produced within the sympathetic nerves that supply the heart. The heart handles norepinephrine differently than other parts of the body do; instead of the heart breaking norepinephrine down, the actions of norepinephrine in the heart are terminated mainly by re-uptake.

vessels and neurons. When receptors on vessels are stimulated, adenyl cyclase is inhibited, intracellular levels of cyclic adenosine monophosphate (cAMP) drop, and vasoconstriction results. Stimulation of the α_2-adrenergic receptors located on nerves inhibits the release of norepinephrine from postganglionic nerve endings, thus decreasing sympathetic flow.

Human β receptors belong to a group of receptors known as the seven-transmembrane receptors (because the structure of the receptor traverses the membrane seven times). Genes for these receptors are located on human chromosome five. They are classified into three main groups: β_1, β_2, and β_3. β_2 receptors are mainly found in the respiratory tract, particularly in the airway smooth muscle. cAMP, which is formed when a β agonist binds to a β_2 receptor, causes airway relaxation, which is why this group of compounds is so widely used to treat asthma (Johnson, 1998). Ephedrine binds to the β_2 receptor which is why, until the 1930s, it was a mainstay in the treatment of bronchial asthma.

The principal catecholamine of the heart is norepinephrine (Figure 1.10.1.1). Within the local circulation of the heart, norepinephrine functions as a neurotransmitter. Norepinephrine is released into the synaptic cleft each time an impulse is transmitted. Impulse transmission stops when norepinephrine is pumped back into the presynaptic nerve ending. In the heart, only 30% of norepinephrine is metabolized by catechol-*o*-methyl

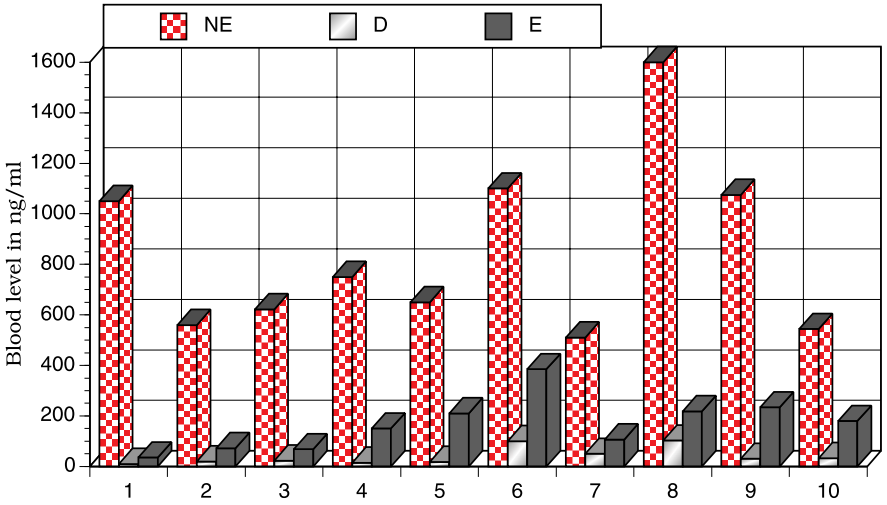

Figure 1.10.1.2 **Elevated catecholamine levels in cocaine users with chest pain.** Catecholamine levels were measured in symptomatic crack smokers. The large, checked columns represent norepinephrine levels, which are markedly elevated. Modest elevations in epinephrine could be seen (dotted columns), but not in dopamine. These levels are comparable to those seen in patients with pheochromocytoma.

transferase (Goldstein et al., 1988); the rest is actively pumped back into the presynaptic terminal. Cocaine prevents the re-uptake of norepinephrine, and unmetabolized norepinephrine overflows into the systemic circulation. The effects of cocaine on norepinephrine re-uptake last much longer than would be expected, based upon the 1-hour half-life of cocaine in naïve users. In studies on dogs using positron tomography, norepinephrine re-uptake was still inhibited more than 2.5 hours after intravenous cocaine injection (Melon et al., 1994). Once norepinephrine enters the circulation, it acts as a circulating hormone (α_1, α_2, and β_1), not as a neurotransmitter. Epinephrine and norepinephrine bind to both α and β receptors but differ in their relative affinities. Thus, both are full agonists for α_1 and β_1 receptors, but epinephrine elicits a much greater response at β_2 receptors.

Cocaine is avidly taken up by, and has a direct effect on, the adrenals (Volkow et al., 1992). In rats, cocaine causes the increased release of both epinephrine and norepinephrine (Gunne and Jonsson, 1964; Chiueh and Kopin, 1978). The same is true of squirrel monkeys (Trouve et al., 1990). For unknown reasons, this increase in circulating catecholamines does not lead to central nervous system catecholamine depletion. Rats, given repeated doses of cocaine, show constant brain levels of catecholamines in the face of increased urinary excretion (Chiueh and Kopin, 1978). In a prospective study of "crack" users with chest pain, elevations in both epinephrine and norepinephrine levels were observed (Figure 1.10.1.2). In 10 such patients, norepinephrine levels ranged from 345 to 1200 pg/mL (normal range 0–90 pg/mL) and epinephrine ranged from 135 to 300 pg/L (normal range 0–55 pg/L) (Karch, 1987).

The data on what happens to dopamine in the peripheral circulation are conflicting. In the study of "crack" smokers cited above, no changes in dopamine levels were observed. However, when measurements were made in 15 chronic cocaine users admitted to a rehabilitation program, all of the patients were found to have dramatic increases in plasma

dopamine sulfate levels (89,626 ± 121 pg/mL vs. 2356 pg/mL in controls). Even more interesting, a relationship was observed between elevation in plasma dopamine levels and the patients' estimates of the amount of cocaine being used (Faraj et al., 1994).

Catecholamine measurements in dogs given intravenous cocaine were comparable to the elevation seen in humans (Schwartz et al., 1988) as were elevations in exercising rats (Conlee et al., 1991). Elevated plasma norepinephrine concentrations have even been observed in infants born to cocaine-using mothers. When catecholamine concentrations were measured in the otherwise healthy children of cocaine-using mothers, venous norepinephrine levels were 1.8 times those of controls, while no differences in epinephrine or dopamine levels were found (Ward et al., 1991).

Very limited data suggest that cocaine users respond abnormally to elevated catecholamine concentrations. Chronic catecholamine excess is usually associated with downregulation of β receptors, but it appears that cocaine users do not downregulate. Several groups have made measurements of the adrenergic receptors found on lymphocytes (which mirror those in the heart) and have found no change in binding sites or receptor affinity for either α or β adrenoreceptors, in spite of elevated circulating levels of catecholamines (Costard-Jackle et al., 1989; Trouve et al., 1990; Conlee et al., 1991). This failure to downregulate has also been observed in infants born to substance-abusing mothers, in spite of the fact that they, too, have increased circulating levels of norepinephrine.

Stimulation of both α and β receptors promotes elevation of intracellular calcium. As a direct consequence of catecholamine stimulation, calcium enters the cell and additional calcium is released from sequestered stores within the endoplasmic reticulum. Once intracytosolic calcium has risen to about 100 times resting concentrations, the myofilaments contract. The cycle terminates when the calcium is pumped out of the cytosol and back into the endoplasmic reticulum. Alpha stimulation also elevates intracytosolic calcium. Inositol triphosphate facilitates the release of calcium from the endoplasmic reticulum, and diacylglycerol enhances production of protein kinase-C which interacts with calcium channels and β receptors. This combination of activities further increases the amount of free calcium in the cytoplasm. If too much calcium accumulates within the cell, toxic effects can occur. These effects may be manifested as altered membrane potentials and abnormal impulse conduction or even by the presence of visible lesions.

The situation is somewhat different in the case of the vascular smooth muscle which controls the caliber of blood vessels. Blood vessel tone depends both on the sympathetic nervous system and on the release of various chemicals from the endothelial cells lining the vessels. As with muscle in the heart, the vascular smooth muscle contraction–relaxation process occurs when the concentration of cytosolic Ca^{2+} rises. Depolarization waves open the slow calcium channels, permitting Ca^{2+} to enter in small quantities which then triggers the release of much larger amounts of calcium from the endoplasmic reticulum. The entrance of calcium into the cytosol is controlled by: (1) calcium channel voltage, which is controlled indirectly by changes in the potassium channels (CK^{+}), and (2) by the activity of Na^{+}/K^{+}-ATPase pump (Ramon de Berrazueta, 1999).

Release of Ca^{2+} from intracellular stores of the sarcoplasmic reticulum involves two separate channels. One is ryanodine sensitive, the other is the inositol 1,4,5-triphosphate receptor. Endothelial cell dysfunction is accompanied by a decrease in the production and/or the release of nitric oxide and the increased production of factors that favor contraction, including the abnormal accumulation of calcium within the cell. Mounting evidence indicates that cocaine use results in endothelial dysfunction (Havranek et al., 1996; Mo et al., 1998).

1.10.2 *Mechanisms of catecholamine toxicity*

Persistently elevated concentrations of circulating catecholamines lead to the occurrence of undesirable effects. Increased α-adrenergic stimulation of coronary vascular smooth muscle causes vasoconstriction and ischemia (Mathias, 1986; Ascher et al., 1988). The simultaneous stimulation of both α and β receptors also means that cocaine-induced vasoconstriction is accompanied by increased oxygen demand. In individuals with undiagnosed pre-existing coronary artery disease, myocardial infarction may be explained by this combination of simultaneous α and β adrenergic stimulation. An individual with an undiagnosed, asymptomatic, 70% left anterior descending lesion could become symptomatic or even experience a fatal arrhythmia just by virtue of the increased demand created by simultaneous α and β stimulation.

At the molecular level, acutely elevated concentrations of epinephrine and norepinephrine cause myocardial dysfunction (Bosso et al., 1994; Powers et al., 1994) and alter membrane potentials favoring the occurrence of malignant ventricular arrhythmias. This sequence was first suggested more than 50 years ago (Bozler, 1943). In experimental models, sympathetic nerve stimulation is a potent trigger for a variety of cardiac arrhythmias, including ventricular tachycardia (Du et al., 1999). In human clinical studies, it is clear that epinephrine administration increases the probability that ventricular fibrillation can be induced and decreases the probability of spontaneous defibrillation (Tovar et al., 1998). In patients prone to sustained ventricular tachycardia, even mental stress can alter the cycle length and the amount of energy required to terminate ventricular tachycardia, even when there is no evidence of ischemia (primary heart muscle disease or scarring from a previous infarct greatly increases the likelihood of lethal arrhythmias). In other words, mental stress may lead to sudden death through the facilitation of lethal ventricular arrhythmias (Lampert et al., 2000).

Catecholamine can cause gross morphologic changes, the most obvious being myocardial hypertrophy. Even in the absence of cocaine use, myocardial hypertrophy is associated with structural changes that increase the risk for arrhythmia and sudden death (Frohlich, 1999). Some of these structural changes are clearly related to catecholamine toxicity, while others may not be. Each of these mechanisms will be discussed separately.

1.10.3 *Histopathology of catecholamine toxicity*

The specific morphologic changes induced by catecholamine excess are essentially the same as those associated with cocaine and methamphetamine (Bravetta and Invernizzi, 1922; Karch and Billingham, 1986; Karch, 1987a; Tazelaar et al., 1987; Karch et al., 1999). The changes associated with cocaine and catecholamine toxicity are, in turn, the same as the morphologic changes associated with intracellular calcium overload. It follows that, depending on the experimental design, the morphologic changes induced by cocaine and methamphetamine, like the changes associated with experimental catecholamine toxicity, or even pheochromocytoma, can be prevented by calcium channel blockade (Nahas et al., 1985). It is important to remember that calcium overload is not synonymous with catecholamine toxicity. Anything that disrupts membrane integrity, including ischemia, can result in calcium overload (Rona, 1985).

Catecholamines cause recognizable histologic changes within the myocardium (Szakacs and Cannon, 1958; Szakacs et al., 1959). The most widely recognized change is the injury known as contraction band necrosis (CBN). This lesion has both pathologic and forensic significance. CBN is sometimes also called coagulative myocytolysis and some-

Table 1.10.3.1 Conditions Associated with Contraction Band Necrosis

Reperfusion	Norepinephrine
Steroid therapy	Cobalt poisoning
Electrocution	Starvation
Defibrillation	Myocardial infarction
Drowning	Free-radical injuries
Cocaine	Brain death
Amphetamine	Phenylpropanolamine
Epinephrine	Intracerebral hemorrhage
Isoproteronol	

Source: From Karch, S. B. and Billingham, M. E., *Hum. Pathol.*, 17, 9–13, 1986. With permission.

times myofibrillar degeneration. Whatever the nomenclature, it is a nonspecific finding. It can be seen in a variety of apparently unrelated disorders. The most common setting for CBN is in the zone bordering an area of reperfused myocardium salvaged with angioplasty (Bouchardy and Majno, 1974; Michael et al., 1995; Monticello et al., 1996), but CBN also occurs in the hearts of patients who have been subjected to multiple defibrillation attempts (Karch and Billingham, 1984). It is a common finding in cases of intracerebral hemorrhage, drowning (Lunt and Rose, 1987), pheochromocytoma, and other conditions associated with catecholamine excess (Table 1.10.3.1) (Karch and Billingham, 1986). CBN is frequently observed in cases of sudden cardiac death.

The term *contraction band necrosis* was introduced by Caulfield and Kilonsky in 1959 (Caulfield and Kilonsky, 1959), but the lesion had actually been described in the heart of a cocaine user in 1922 by Bravetta and Invernizzi (their paper and original illustrations are cited by Maier in his 1926 monograph; Maier, 1926). Szakacs was the first to systematically characterize the effects of catecholamines on myocardial structure, and he was the first to note the unique distribution of these lesions. Areas of CBN tend to occur "without any apparent preferential distribution" (Szakacs and Cannon, 1958; Szakacs et al., 1959). What Szakacs was referring to were the severely damaged cells often found nestled between totally normal cells. If the damage to the cell had been due to ischemia, then one would expect all of the cells in a specific area to show signs of injury. Szakacs made a second important observation. He realized that the changes seen after chronic catecholamine administration were identical to those seen in patients with pheochromocytoma (Karch and Billingham, 1986).

The reason that the same lesion is seen in such diverse conditions is that the underlying mechanism is always the same: calcium overload (Figure 1.10.3.1). Calcium enters the cells when calcium channels are opened by catecholamine stimulation. When there is myocardial ischemia, a loss of cell membrane integrity can lead to the same result, and the cell floods with calcium. Whatever the mechanism of entry, a continuum of morphologic alterations can be seen; these may range from hypereosinophilia to total disruption of the cell. As Szakacs discovered, the lesions are characterized as much by their location as by their appearance. They bear no apparent relationship to blood supply. Contraction bands may be found in myocytes adjacent to normal capillaries. They can, and do, occur in the absence of significant coronary artery disease.

Unlike the pattern seen in ischemic infarction, where the myofibrillar apparatus remains visible and in register, in CBN the sarcomeres are hypercontracted and distorted (Figure 1.10.3.2). The contractile apparatus may not even be visible. Milder forms of the

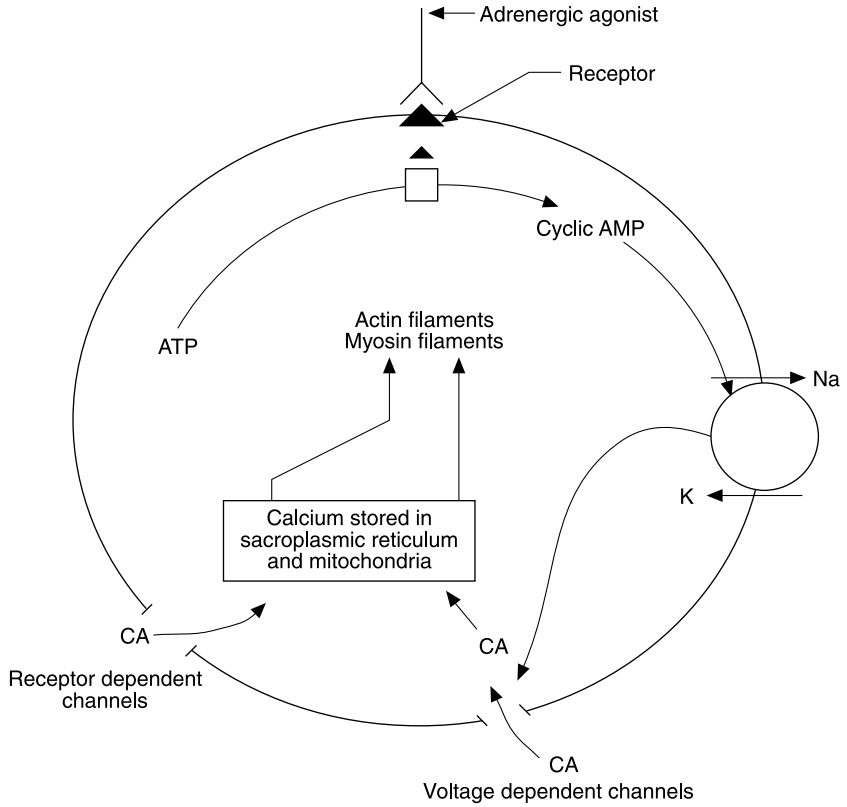

Figure 1.10.3.1 **Sequence of events leading to cardiac myocyte contraction.** Norepinephrine binds at both α and β receptor sites but has much greater affinity for the α receptor. Calcium enters via voltage-dependent channels (known as "slow channels") and through other calcium channels that open when norepinephrine binds to a receptor. Calcium is also released from storage sites within the myocyte. Once the level of calcium within the cell has risen 100-fold, myofilaments are able to contract. If cytosolic calcium levels become too high, irreversible damage occurs to the myofilaments, a condition known as contraction band necrosis.

lesion consist of eosinophilic transverse bands separated by areas containing fine eosinophilic granules. With electron microscopy, it is apparent that the myofilaments are completely out of register and the mitochondria translocated. The dense bands visible with light microscopy are seen as amorphous gray material. This material is all that remains of both the thick and thin filaments. This exact change has been observed in the hearts of rats chronically treated with cocaine (Trouve et al., 1991). Z-band remnants, the hallmark of dilated, congestive cardiomyopathy, are generally not seen; however, if the process were ongoing and particularly severe, then the presence of Z-band remnants would not be particularly surprising. In severe instances, as in open-heart defibrillation, the sarcomeres look as if they have been torn apart, and dehiscence of the intercalated disks can occur (Karch and Billingham, 1984).

Initially, and probably for at least 12 hours, inflammatory cells are not in evidence. Occasionally, a mononuclear infiltrate may be seen. Eventually, the injured cells are resorbed and replaced with fibrous tissue. The pattern is classically seen in patients (and experimental animals) with pheochromocytoma. Illustrating the progression of lesions in

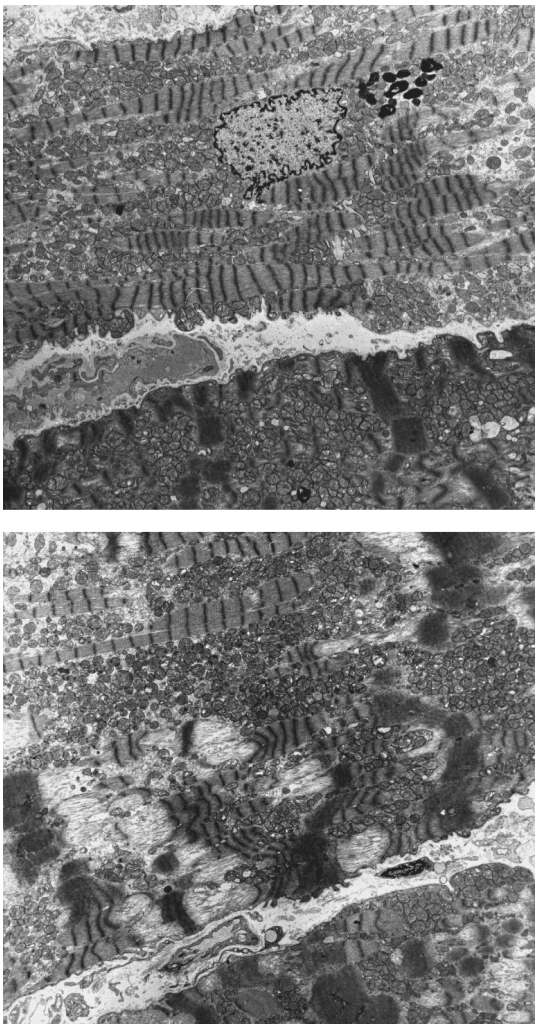

Figure 1.10.3.2 **Effects of catecholamines on cardiac myocytes.** The electron micrograph on top shows normal human myocardium. The myofilaments are in register; the mitochondria are of uniform size and are neatly packed between the filaments. The bottom micrograph illustrates the changes seen in contraction band necrosis. The dark electron-dense material is all that remains of the myofilaments; the mitochondria are swollen and translocated. (Original magnification 4320×, top and bottom.) (Micrographs courtesy of Dr. Margaret Billingham and Marilyn Masek, Stanford University School of Medicine.)

humans is quite difficult, but lesions corresponding to each stage in the evolution of catecholamine injury have been reported. The resultant fibrosis, which is often quite prominent in the hearts of cocaine users, may supply the substrate for lethal arrhythmias (Merx et al., 1977; Strain et al., 1983). The catecholamine levels required to produce necrosis have been determined, largely as a result of research in the field of heart transplantation. Until adequate preservation techniques were introduced, hearts from donors maintained with pressor therapy frequently failed after surgery. In the course of research designed to explain the failure, experimenters found that a surge of catecholamine accompanies brain

death, and that this surge is associated with the presence of contraction band necrosis (Novitzky et al., 1987).

In the baboon model of brain death, catecholamine elevations comparable to those seen in some cocaine users are observed (Worstman et al., 1984; Novitzky et al., 1987). In experimental models of brain death, cardiac lesions can be prevented by denervation or beta blockade. The occurrence of myocardial contraction bands must, in some way, be related to β receptor number, density, and regulation. These parameters, in turn, depend on whether any drugs have been taken, which ones they were, and the duration of use. The impact of cocaine and chronic catecholamine excess on receptor physiology still remains, for the most part, unstudied. The limited number of studies that have addressed this question have all reached the same conclusion. In the heart, at least, there is no indication of β receptor downregulation in cocaine users (Conlee et al., 1991; Nahas et al., 1991; Trouve et al., 1991; Vitullo et al., 1993). This failure of downregulation distinguishes cocaine abuse from all other chronic hyperadrenergic states.

The β and α receptors on lymphocytes and platelets downregulate in the presence of catecholamine excess, and one would expect the same result whatever the reason for the catecholamine elevation. It may well be that some alteration in signal transduction has occurred between the receptors and adenyl cyclase, although that possibility remains to be investigated. It has been shown that tyrosine hydroxylase activity is increased by cocaine administration (Taylor and Ho, 1977; Masserano et al., 1996). That observation is consistent with the notion that increased catecholamine synthesis is occurring in an attempt to keep up with increased catecholamine turnover. Evidence from other fields suggests that when this happens, postsynaptic calcium channel receptors will downregulate in an attempt to prevent calcium overload (Lefkowitz et al., 1984).

1.10.4 Contraction band necrosis and sudden death

Contraction band necrosis is a marker for sudden death, whatever the cause. The incidence of CBN in various autopsy studies is over 80% (Reichenbach and Moss, 1975; Baroldi and Mariano, 1979; Cebelin and Hirsch, 1980). Some believe that the quantitative assessment of CBN can provide useful additional information in cases of sudden death where the cause is not immediately obvious but myocardial infarction is suspected (Hopster et al., 1996).

In stimulant-related deaths, the incidence of CBN may be even higher (Rajis and Falconer, 1979; Tazelaar et al., 1987). Contraction band necrosis heals by fibrosis, and postmortem studies of addicts in general, and stimulant users in particular, confirm the presence of reparative microfocal fibrosis (Rajis and Falconer, 1979; Oehmichen et al., 1990; Pedal and Oehmichen, 1990). This picture is not always as clear as might be desired. The process of myocardial hypertrophy, which in cocaine users may be a function of increased pressure load, volume overload, or some direct action of cocaine on myocardial early genes (Besse et al., 1997), also leads to the deposition of collagen and scarring (Laviades and Varo, 1998; Rossi, 1998; Varo et al., 1999). Whether the two different types of scarring can be separated is difficult to say and may not, in any case, be relevant.

The role of CBN in cocaine-associated sudden death was established in a fairly large retrospective study (Tazelaar, 1987). Contraction band lesions were found to be significantly more common ($p < 0.001$) in cocaine users than in a group of controls dying of sedative–hypnotic overdose. Contraction band lesions were found in 93% of the cocaine group but in less than 10% of the controls. In addition, more that 25% of the cocaine users also had myocardial fibrosis, sometimes to quite striking degrees (Tazelaar et al., 1987).

Contraction band necrosis and microfocal fibrosis have been observed in other autopsy studies of cocaine users (Simpson and Edwards, 1986; Roh and Hamele-Bena, 1990; McKelway et al., 1990) and in experimental animals treated with cocaine (Knuepfer et al., 1993; Gardin et al., 1994; Keller and Todd, 1994). Contraction band necrosis has even been observed in tissue cultures of myocardium exposed to cocaine (Welder et al., 1993).

At least two published studies (Virmani et al., 1988; Fineschi et al., 1997) have failed to confirm an increased frequency of CBN in cocaine users, but because the frequency of CBN in the control group of the first study was so much lower than what is accepted as normal for the general population, the significance of these two studies is difficult to assess. There may have been some differences in the anatomic criteria used to diagnose CBN, as many other case reports specifically mention the finding of CBN in cases of sudden cardiac death (Kloner et al., 1992; Gardin et al., 1994; Keller and Todd, 1994; Osawa et al., 1994).

Contraction band necrosis never occurs as a fixation artifact (Karch and Billingham, 1986). The presence of such lesions always indicates some underlying abnormality, usually catecholamine excess. By themselves, contraction bands constitute only a presumptive indicators for cocaine use, especially if they are seen in biopsy specimens. Biopsy studies of symptomatic users have shown prominent contraction band necrosis (Peng et al., 1989), but some evidence of contraction bands is almost always seen in biopsy specimens (Adomian et al., 1978). Stronger inferences can be drawn if there are other supporting findings. For instance, if microfocal fibrosis is present, the differential diagnosis then becomes quite limited. Very few conditions produce CBN with microfocal fibrosis. In fact, the only real alternative diagnosis is pheochromocytoma, which should not be all that difficult to rule out.

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1.11 External markers of cocaine abuse

Certain external markers for cocaine abuse may be of clinical value. None of these changes is particularly common, as they are only seen with intense and compulsively repeated use. The absence of these external signs has little, if any, significance, but their presence provides confirmation that the individual has been a chronic user for some time.

1.11.1 *Perforated nasal septum*

Septal perforation is the best known external manifestation of cocaine abuse. The first cases were described in the early 1900s, shortly after the practice of snorting cocaine became popular (Hutant, 1910; Maier, 1926). The presence of this lesion, however, is not pathognomonic. Perforations of the nasal septum can also result from chronic abuse of nose drops containing vasoconstrictors (Vilensky, 1982).

Septal perforation occurs as a consequence of cocaine's ability to constrict blood vessels, which is one of the reasons it remains popular with ear, nose, and throat surgeons — it controls bleeding. With chronic use of intranasal cocaine, septal cartilage becomes deprived of its blood supply and breaks down (see Figure 1.11.1.1) (Kridel et al., 1998). Other, more severe complications have also been reported. These include nasolacrimal duct obstruction with orbital cellulitis (Alexandrakis et al., 1999), severe avascular necrosis of all of the nasal chambers (Braverman et al., 1999), and even perforation of the palate (Sastry et al., 1997). A type of central facial necrosis — necrosis of the nasal septum, maxillary sinus, ethmoidal sinus, sphenoidal sinus, and soft palate — also occurs (Caravaca et al., 1999) and is sometimes confused with Wegener's syndrome (Armstrong and Shikani, 1996; Helie and Fournier, 1997). Some of these cases may be the result of impacted cocaine providing a nidus for infection (Tierney and Stadelmann, 1999). In some instances, the reaction may be extreme enough to simulate angiosarcoma. A recent case report described an exuberant ulcerative angiomatoid nasal lesion in a cocaine abuser. Microscopic examination showed polymorphous endothelial cells with occasional mitoses, arranged in a lobular pattern with infiltrative-looking areas. Extensive areas of thrombosis with focal recanalization were also seen, but intravascular proliferation was not observed (Alameda et al., 2000).

1.11.2 *"Crack thumb"*

"Crack thumb" was first described in 1990, and is a "repetitive-use" type of injury. "Crack" smokers often use disposable cigarette lighters to heat their "crack" pipes. They may do this many times a day, and a callus can result from repeated contact of the thumb with the serrated wheel that ignites the lighter. The callus is usually located on the ulnar aspect of the thumb (Larkin, 1990). Constant handling of a heated "crack" pipe can lead to superficial burns on the palmar aspect of the hands. The same type of injury happens in "ice" smokers. A typical case is illustrated in Figure 1.11.2.1.

1.11.3 *Cocaine "tracks"*

The adulterants most commonly found in cocaine are water soluble. Their repeated injection tends not to produce the chronic inflammatory reactions and the type of granulomas associated with opiate abuse. Recent injection sites appear as salmon-colored bruises, sometimes with a clear central zone about the needle puncture site (Wetli, 1987). Typical lesions are illustrated in Figure 1.11.3.1. As lesions become older, they turn blue and yellow, eventually disappearing without leaving any scar.

Slowly healing cutaneous ulcers are also seen. The base of the ulcer may be red to gray, and the margins of the ulcers will have a pearly white appearance consistent with epidermal overgrowth (Yaffee, 1968). In experimental animals, healing of lesions is relatively rapid and complete. The histopathologic effects of subcutaneous cocaine injection

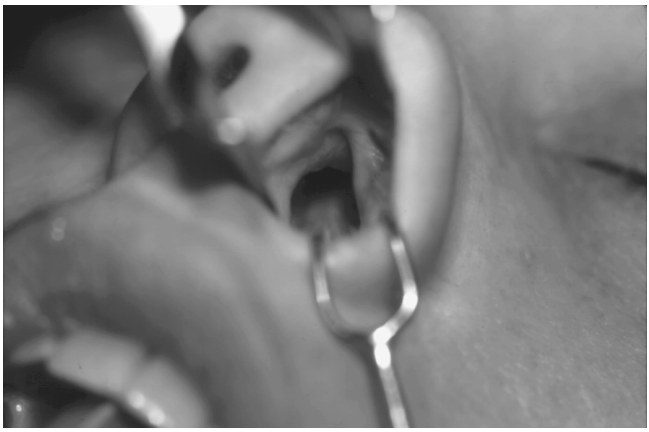

Figure 1.11.1.1 **Perforated nasal septum.** This lesion was first reported in conjunction with cocaine use in 1904. It is not absolutely diagnostic for cocaine abuse, as the same defect can be produced by the chronic use of vasoconstrictive nose drops. The first cases of cocaine-related septal perforation were reported just after the turn of the century. (Photograph courtesy of Dr. Russel Kridel, University of Texas Health Sciences Center, Houston.)

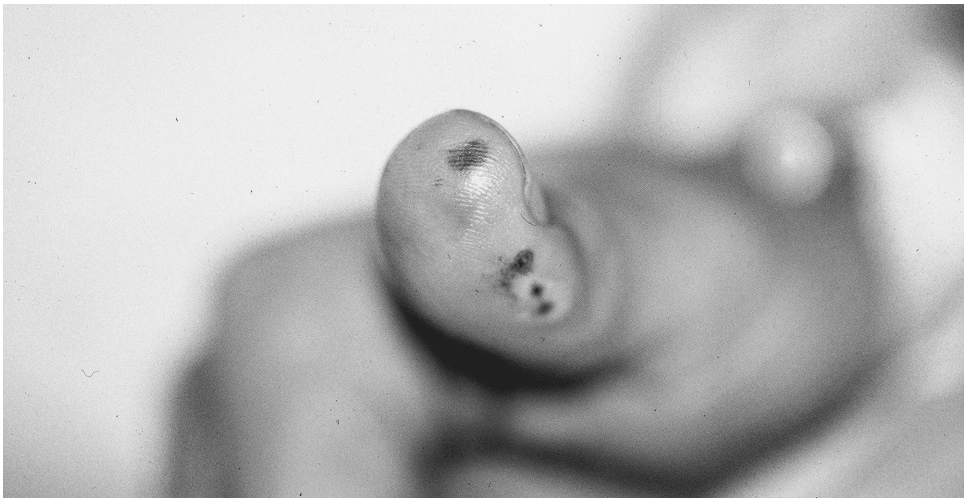

Figure 1.11.2.1 **Crack thumb.** A repetitive use injury from using disposable butane lighters to heat crack pipes. (Photograph courtesy of Dr. Kari Blaho, University of Tennessee, Memphis.)

have been studied on a limited scale (Bruckner et al., 1982). In one study, subcutaneous injections of 0.1–2.0% cocaine solutions were found to cause blanching and hemorrhage. However, other workers have found no histologic damage, even after rats were repeatedly injected with large subcutaneous doses (32 mg/kg twice a day) of cocaine over a 2-week period (Durazzo et al., 1994). If changes do occur, it is not because of cocaine-induced vasoconstriction and ischemia. Epinephrine is a more powerful vasoconstrictor than cocaine, and it does not produce similar lesions.

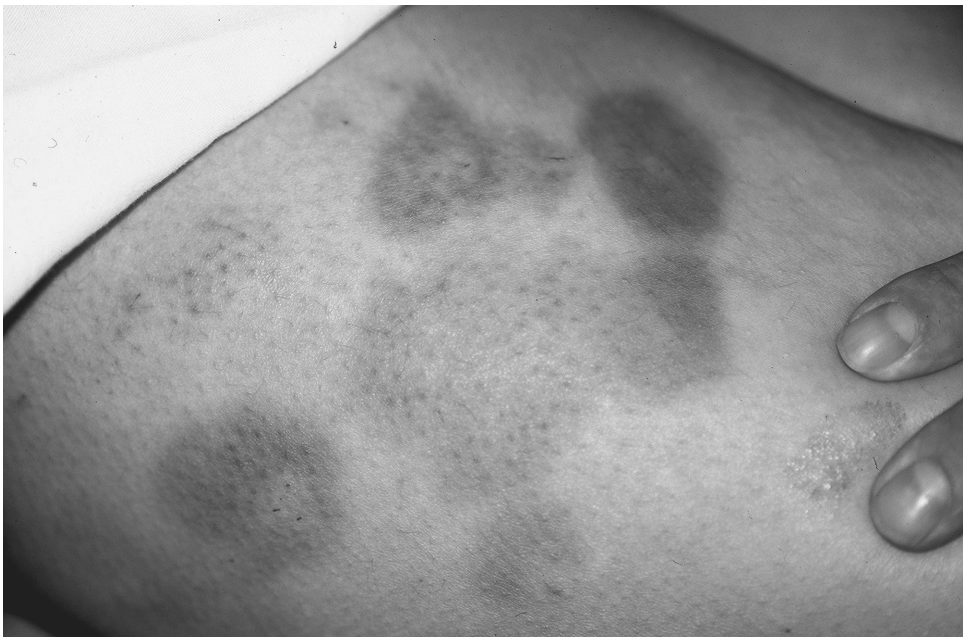

Figure 1.11.3.1 **Cocaine injection sites.** Injection with cocaine causes a distinctive salmon-colored bruise, sometimes with a clear zone around the needle puncture. (Photograph courtesy of Dr. Kari Blaho, University of Tennessee, Memphis.)

1.11.4 "Crack" keratitis

The corneas of "crack" smokers may inadvertently become anesthetized. When the smoker rubs his eyes, too much pressure may be applied and a sizable piece of the cornea may be rubbed off. This type of corneal abrasion has been referred to as "crack eye" (Figure 1.11.4.1) (Ravin and Ravin, 1979; Zagelbaum et al., 1991; Colatrella and Daniel, 1999). The same mechanism may lead to keratitis with corneal ulcer formation and infection (Strominger et al., 1990; Parmar et al., 1999). The results of some studies suggest that abnormalities of cell-mediated immunity develop in chronic cocaine users and these abnormalities may favor corneal infection (Watzl and Watson, 1990). Other local anesthetics used in the eye, such as proparacaine and tetracaine, exert mild antibiotic effects (Mullin and Rubinfeld, 1997).

1.11.5 Dental erosions and oral lesions

Chronic intranasal cocaine users may have erosions on the enamel of the upper front teeth. Erosions result when the teeth are bathed with acid cocaine hydrochloride that has trickled down from the sinuses and the posterior oropharynx (Krutchkoff et al., 1990). Rapid gingival recession and dental erosion secondary to local cocaine application have also been reported (Kapila and Kashani, 1997). Whitish lesions of the oral mucosa are said to be common in "crack" smokers (Parry et al., 1996), and leukoplakia is a recognized consequence of coca leaf chewing (Hamner and Villegas, 1969). HIV-infected patients who also use cocaine may manifest atypical ulcers of the mouth that may be difficult to identify (Mitchell-Lewis et al., 1994).

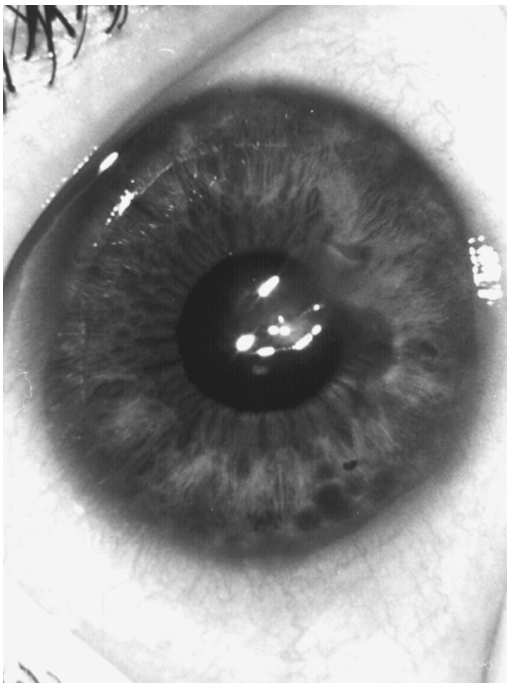

Figure 1.11.4.1 **Crack keratitis.** Volatilized cocaine anesthetizes the cornea so that abusers cannot feel how hard they are rubbing their eyes. Evidence indicates that crack smokers may be less able to resist corneal infection, and infected ulcers with corneal clouding may be the result. (From *Am. J. Ophthalmol.,* 111(3), 247–248, 1991. With permission. Photograph courtesy of Dr. Peter S. Hersh, Chairman, Department of Ophthalmology, Bronx-Lebanon Hospital, New York.)

1.11.6 "Crack hands"

This finding has much in common with "crack thumb." Examination of chronic "crack" smokers may disclose blackened, hyperkeratotic lesions on the palmar aspect of the hands. The pipes used to smoke cocaine can become quite hot, and chronic users are likely to sustain multiple small burns (Feeney and Briggs, 1992).

1.11.7 Evidence of terminal seizures

Another occasionally observed external marker is a bite mark on the lips and tongue. A minority of cocaine users may experience seizure activity as a terminal event (Wetli, 1987). However, because seizures do not always occur, even in conjunction with massive overdose, and because many other agents can cause terminal seizure activity, the usefulness of this sign is somewhat limited.

1.11.8 Marks and mutilation

Wetli et al. (1997) described a series of 10 heroin "body packers." In two of the cases, the drug couriers died after reaching their destinations, and their accomplices made abdominal incisions to remove the drug packets. A similar case was reported from the U.K., where the back and buttocks of a deceased courier were marked with a number of

superficial lacerations, corresponding to the number of drug-containing packets that the deceased had swallowed, a sort of "living" invoice (Karch, 1999). Similar markings have not been reported in cocaine smuggled but certainly are possible.

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1.12 Toxicity by organ system

1.12.1 Skin

Subcutaneous drug injection (called "skin popping") is much more common among heroin than cocaine users, and cocaine users who elect this route generally experience fewer complications than heroin users. The adulterants found in cocaine are much more likely to be water soluble and therefore less likely to produce irritation. Occasionally, the practice can lead to subcutaneous access formation, sometimes accompanied by cellulitis, lymphangitis, and lymphadenopathy (Hoeger et al., 1996). Infection is generally the result of oral flora sensitive to multiple antibiotics, but surgery is often required (Thomas et al., 1995). Necrotizing fasciitis has occasionally been reported in cocaine users (Jacobson and Hirschman, 1982), but the connection between this disorder and illicit drug injection is much stronger for heroin than cocaine (Freeman et al., 1981, 1997).

Scleroderma is an uncommon disease. The estimated annual incidence is between four and 12 new cases per 1,000,000 per year. Scleroderma is three times more common in females, but when it occurs in young people it is 15 times more common in women than men (Poormoghim et al., 2000). The median age of onset for scleroderma is between 40 and 50. Less than a half dozen cases in the English literature have involved cocaine users, all of which involved men, with two only in their twenties (Trozak and Gould, 1984; Kerr, 1989; Kilaru et al., 1991; Attoussi et al., 1998). The most recently reported case occurred in a 46-year-old male who developed scleroderma renal crisis, a type of systemic sclerosis that is classically characterized by accelerated hypertension, rapidly progressive renal failure, and hypereninemia. The patient was a "heavy" cocaine user, and it may well be that his use of the drug in some way unmasked his underlying skin disease (Kilaru et al., 1991; Attoussi et al., 1998).

The principal abnormality in scleroderma is the deposition of pathologic amounts of normal collagen. The etiology of scleroderma is not understood. Various theories have implicated alterations in cellular immunity, fibroblast function, and small vessel disease (Gay et al., 1980). The final common pathway by which the disease is manifested is believed to be a small vessel disorder that eventually produces fibrosis of the affected organ (Follansbee et al., 1984). Cocaine abuse and scleroderma share certain common features. Vascular abnormalities are common in both, particularly in the heart (Bulkley et al., 1976). In classic scleroderma, the heart becomes fibrotic and contraction band

necrosis is frequently seen (Follansbee et al., 1984, 1993). The presence of myocardial fibrosis predisposes both groups to conduction defects and arrhythmias. Both groups are prone to heart failure and sudden death (Ferri et al., 1998). The morphologic changes in the hearts of both groups are similar enough to raise the possibility that catecholamine toxicity is common to both.

Other similarities exist. Both cocaine users and patients with scleroderma may develop isolated cerebral vasculitis. It is an uncommon complication of both disorders, but it has been observed in both, even in the absence of systemic vasculitis. In the two biopsy-proven cases of cocaine-associated vasculitis, the vessels were infiltrated with lymphocytes. In the one case of scleroderma-associated vasculitis, the biopsy was nondiagnostic (Pathak and Gabor, 1991; Blanche et al., 1996; Andonopoulos et al., 1998).

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1.12.2 *Cardiovascular system, general overview*

Cocaine causes vascular disease, and the brunt of the injury is borne by the heart (Figure 1.12.2.1). In general, there is little to distinguish cocaine-induced vascular disease from naturally occurring vascular disease, and no single abnormality is absolutely diagnostic for cocaine. However, in some instances the pattern of histologic changes can be diagnostic. In the myocardium, the changes associated with catecholamine toxicity are distinctive but are seen with methamphetamine as well. Changes in the coronary arteries and in the microcirculation are more problematic.

Myocardial infarction is a relatively frequent complication of cocaine use, but more than 20 years into the second great cocaine pandemic there still is a paucity of autopsy data. It is clear that cocaine users, even those without other risk factors, experience a large, though transient, increase in the risk of acute myocardial infarction immediately after using cocaine (Mittleman et al., 1999). Just what the pathophysiological changes produced by cocaine are is difficult to say. A great deal of attention has been focused on the sympathomimetic effects of the drug and coronary artery spasm, but other mechanisms, including vasculitis, accelerated atherosclerosis, pre-existing fixed lesions of the epicardial arteries, and disease of the microvasculature are all possible contributors.

In various reported series, the incidence of fixed lesions, presumably atheromatous but possibly thrombotic, has been anywhere from 0% (Virmani et al., 1987) to well over 50% (Virmani et al., 1987; Minor et al., 1991). Only a handful of published reports have included autopsy findings (Young and Glauber, 1947; Kossowsky and Lyon, 1984; Nanji and Filpenko, 1984; Isner et al., 1986; Simpson and Edwards, 1986; Stenberg et al., 1989; Karch et al., 1995, 1998). Occasionally angiographic findings have been described (Kossowsky and Lyon, 1984; Cregler and Mark, 1985; Howard et al., 1985; Wilkins et al., 1985; Pasternack et al., 1986; Rollingher et al., 1986; Weiss, 1986; Rod and Zucker, 1987; Zimmerman et al., 1987; Ascher et al., 1988; Jackson, 1997; Williams and Stewart, 1997; Yao et al., 1997; Wilbert-

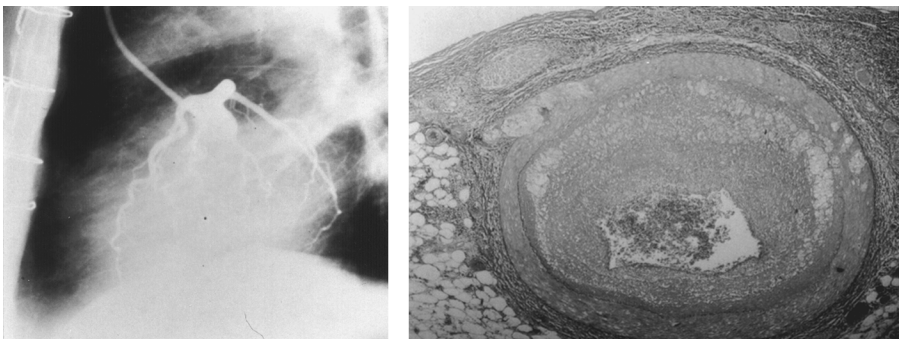

Figure 1.12.2.1a **Coronary artery disease in cocaine users.** The coronary arteries of cocaine users may undergo the same type of intimal hyperplasia as seen in transplant recipients. Because this sort of lesion concentrically involves the entire length of the involved vessel, obstructions may not be apparent unless earlier studies are available for comparison. The normal-appearing study on the left was obtained just two weeks before the patient died of myocardial infarction. On the right is a cross section of the left anterior descending coronary artery (LAD) from the same patient. Concentric intimal hyperplasia has almost entirely obstructed the lumen. (H & E stain.) (Courtesy of Margaret Billingham, Stanford University School of Medicine.)

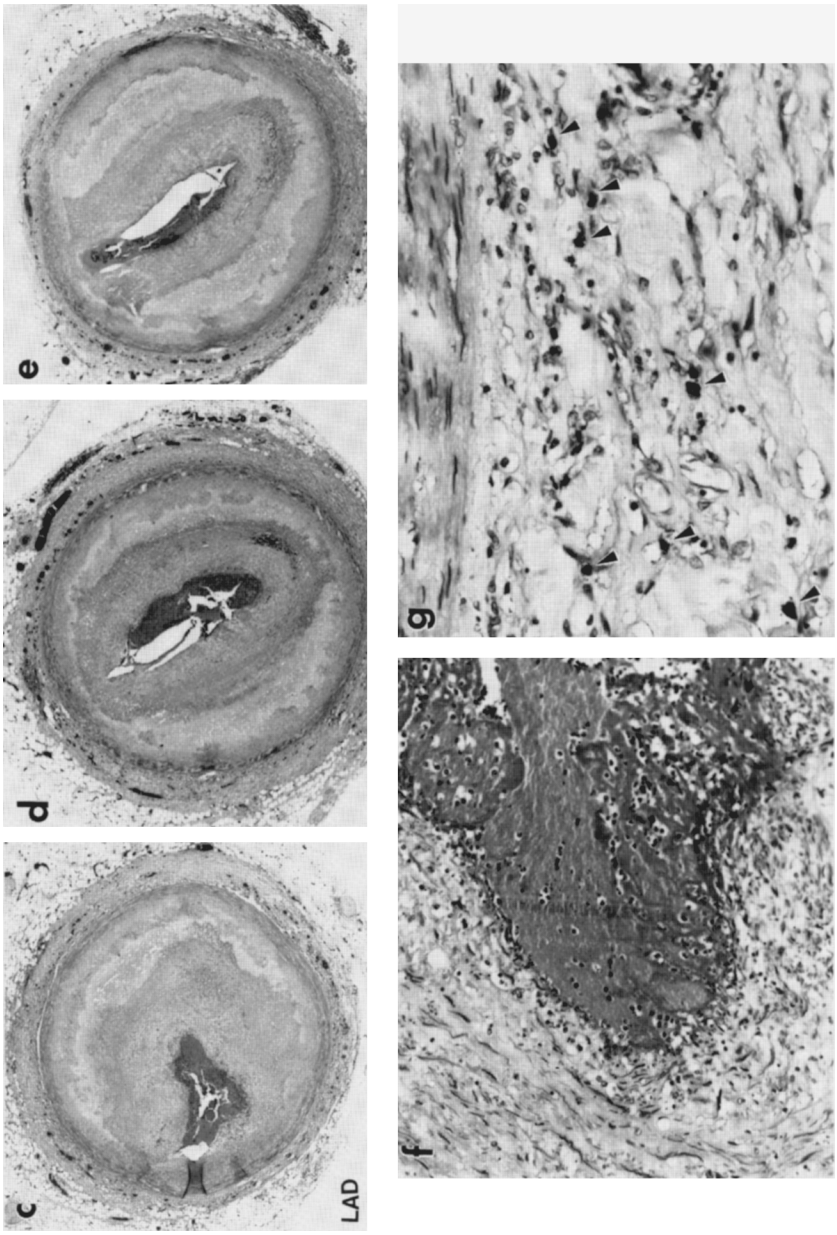

Figure 1.12.2.1b **Adventitial mast cells in cocaine users.** Compared to age- and sex-matched controls, more mast cells are present in the adventitia of the coronary arteries of cocaine users, and the degree of luminal narrowing correlates well with the number of mast cells present. On the left are three cross sections of severely diseased LAD from a chronic cocaine user. On the right are higher power views of the adventitia in this vessel. Toluidine blue staining demonstrates the presence of numerous mast cells. (Original magnification 150×.) (Courtesy of Dr. Rene Virmani, Department of Cardiovascular Pathology, Armed Forces Institute of Pathology, Bethesda, MD.)

Lampen et al., 1998; Williams et al., 1998; Pavon-Jimenez et al., 1999; Schar and Jenzer, 1999). Approximately half of the individual case reports describe lesions; the rest do not.

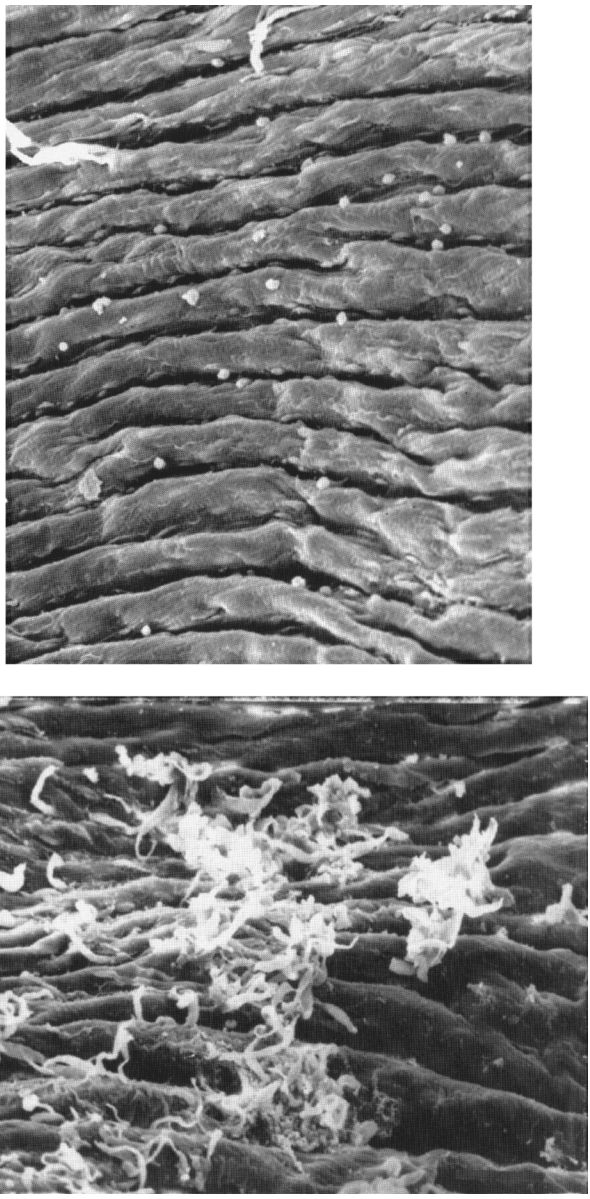

Figure 1.12.2.1c **Effects of cocaine on endothelium.** Both scanning micrographs are of a canine coronary artery. The photograph on top is from a control animal (original magnification 312×). The lower photograph is from a dog that received 1 mg/kg/day of cocaine for 4 weeks; sloughing of endothelial cells is evident (original magnification 520×). (Courtesy of Dr. Randall L. Tackett, Department of Pharmacology and Toxicology, University of Georgia, Athens.)

1.12.2.1 Nonatheromatous coronary artery disease

Cocaine users occasionally have coronary artery lesions resembling those seen in the hearts of transplant patients suffering from chronic rejection. The first such case was described in 1986 (Simpson and Edwards, 1986), when a 21-year-old construction worker was found to have multivessel blockage due entirely to intimal hyperplasia. There was no sign of collagen

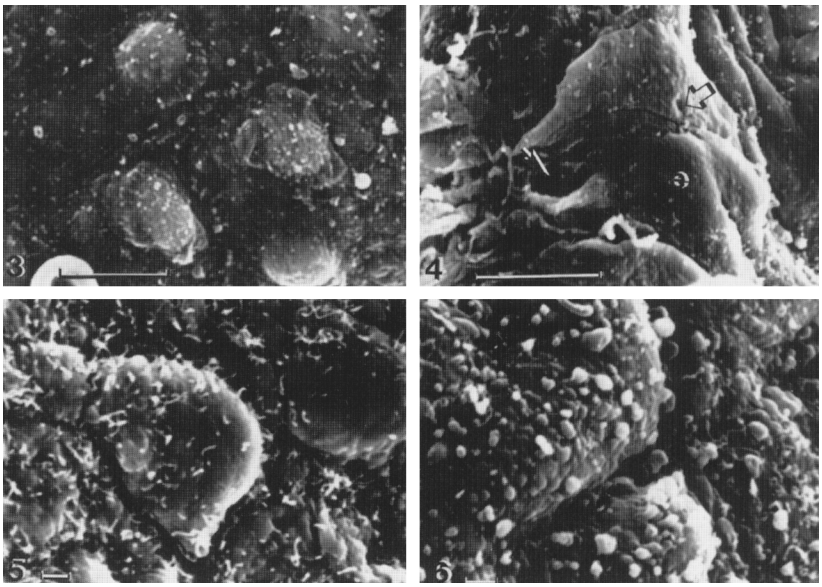

Figure 1.12.2.1d **Transplacental cardiotoxicity.** Whether or not cocaine exerts cardiotoxic effects in humans remains an open question. In animal models, toxicity is easily demonstrated. This pair of scanning micrographs shows endothelial sloughing in hamster neonatal right atrium. The figure on the left is a scanning micrograph of control right atria; the one on the right is from a neonate whose mother received cocaine on the 6th, 7th, and 9th days of gestation. The endothelium is abnormally flattened and no longer completely covers the underlying myocytes. Both scans are at the same magnification (scale bar = 10 mm). (Courtesy of Dr. Jacques Gilloteaux, Department of Anatomy, College of Medicine, Northeastern Ohio Universities, Akron.)

or elastin deposition. This type of lesion is routinely seen in transplanted organs, and also occurs in some connective tissue disorders (Dawkins et al., 1985). Similar alterations have been observed in the hearts of other cocaine users (Roh and Hamele-Bena, 1990).

The authors of the original report postulated that recurrent episodes of coronary artery spasm might lead to endothelial injury with platelet aggregation and release of smooth muscle growth factor which would, in turn, result in obstructive intimal hyperplasia. While this mechanism still remains a possibility, the results of more recent laboratory studies suggest that it is activation of the complement system that is responsible. Cocaine use causes increased local complement production, possibly via the production of reactive oxygen species. An immunologic etiology is also favored by the observation that, in isolated, perfused rabbit hearts, cocaine significantly increased myocardial C1q, C1r, C8, and C9 mRNA expression, increased mRNA transcription for C3 complement, and increased production of membrane attack complex (MAC) formation in the myocardium (Tanhehco et al., 2000). Whether the same situation obtains in humans has not been determined, nor is it known whether complement-related endothelial damage can produce the sort of intimal hyperplasia that is occasionally seen in cocaine users.

Exactly the same lesions can be produced in coronary arteries by catecholamine treatment. Chronic exposure to high concentrations of catecholamines results in endothelial damage and intimal hyperplasia (Szakacs et al., 1959). Dogs infused with norepinephrine at 1–1.5 μg/min/kg consistently develop fibrinoid necrosis, followed by intimal hyperplasia. The appearance of these lesions is indistinguishable from the pattern occasionally seen

in cocaine abusers. Similar lesions have been identified in patients who die after receiving prolonged infusions of vasopressors and in patients dying of pheochromocytoma. To a greater or lesser degree, all of the vessels in the body appear to be vulnerable to this type of injury. Intimal hyperplasia of the small vessels in the gastrointestinal tract may result in bowel infarction and perforation. Bowel infarction and perforation have also been seen in cocaine users (Nalbandian et al., 1985; Mizrahi et al., 1988; Endress and King, 1990; Freudenberger et al., 1990; Garfia et al., 1990; Nathan and Hernandez, 1990; Brown et al., 1994; Hoang et al., 1998).

Whatever the underlying mechanism, chronic cocaine use also causes changes in the smaller coronary vessels, highly reminiscent of the changes seen in hypertensive individuals, i.e., a decrease in the lumen of arteriole, as a direct consequence of either vasoconstriction or wall thickening, along with the deposition of an abnormal amount of collagen within the ventricular wall (Gavin et al., 1998; Frohlich, 1999). The acute administration of cocaine raises both pulse and blood pressure, so it is hardly surprising that endomyocardial biopsies from 11 cocaine users with symptoms of myocardial ischemia demonstrated marked medial thickening of small intramyocardial arteries (20–40 μm) in seven of the 11 patients (Majid et al., 1990). Thickening of the media and intimal hyperplasia have also been seen in the nasal submucosal vessels of chronic cocaine addicts (Chow et al., 1990), suggesting that in susceptible individuals similar changes occur throughout the body.

1.12.2.2 Atheromatous coronary artery disease

Cocaine itself is atherogenic (Escabedo et al., 1992; Karch et al., 1995). In one study, over 60% of the patients with cocaine-associated sudden death had moderate to severe coronary atherosclerosis (the patients had a mean age of 47). In such a young age group, a much lower percentage of significant lesions would be expected (Dressler et al., 1990). Other autopsy studies have also noted the increased incidence of significant atherosclerotic lesions (Virmani et al., 1988; Farb et al., 1990; Karch et al., 1995, 1998).

When the coronary arteries of cocaine abusers dying of thrombosis were compared to those of cocaine users without thrombosis and to cases of sudden death not associated with cocaine use, the average age for the cocaine-thrombosis group was only 29 years, and the degree of luminal narrowing was much higher than would be expected in this age group. In the patients with thrombosis, moderate to severe coronary atherosclerosis was seen, as were increased numbers of adventitial mast cells (Figure 1.12.2.1b) (Kolodgie et al., 1991). One feature that distinguished the cocaine group was the fact that, even though thrombi were present in vessels that had extensive atherosclerosis, there was no plaque rupture or hemorrhage, as would normally be seen in atherosclerotic lesions not associated with cocaine use. This observation has not been repeated by others.

The role of histamine in atherosclerosis is controversial (Born, 1991), but there is good evidence that histamine-containing mast cells may be implicated in the pathogenesis of human coronary vasospasm. The presence of increased numbers of histamine-rich mast cells has been noted in atherosclerotic coronary vessels, even in non-drug-using populations. Histamine is not the only vasoactive compound contained in mast cells. Prostaglandin D2 and leukotrienes C4 and D4 have also been demonstrated (Maseri et al., 1978). Another factor contributing to accelerate atheroma formation may be catecholamine excess. It has been shown that arterial wall uptake of LDL cholesterol is accelerated in the presence of epinephrine and norepinephrine (Born, 1991). Because most cocaine users are polydrug abusers who also smoke cigarettes, no one can say with certainty which toxic agent is responsible for the process.

It is also evident that, if underlying fixed lesions are present, cocaine use can make those lesions symptomatic. Intranasal cocaine (2 mg/kg body weight) increases arterial pressure and the rate–pressure product. At the same time that the rate–pressure product is rising, coronary sinus blood flow significantly decreases (Lange et al., 1990). As a result, cocaine increases myocardial work and oxygen demand while at the same time decreasing blood flow. If asymptomatic lesions are already present, the extra work load imposed by the cocaine can lead to infarction, even without coronary spasm. Increased oxygen demand in the presence of pre-existing lesions can be sufficient to cause infarction.

Failure to demonstrate lesions angiographically does not necessarily mean that they are not there. Studies have shown that angiography usually underestimates the severity of lesions, especially when they are in the 50–75% range and when multivessel disease is present (Gruberg et al., 1999). The discrepancy is mostly explained by the false assumption, made by many, that segments of artery adjacent to a stenosis are normal. In fact, compensatory dilation of the vessel usually occurs in response to the accumulation of lesser degrees of plaque. The opposite situation obtains when the obstruction is due to intimal hyperplasia. That process tends to involve vessels along the entire length in a concentric fashion. The lesions may not be noticed on angiography unless earlier films are available for comparison (Karch and Billingham, 1988). An arteriogram that looks normal may actually be missing serious underlying heart disease. It may very well be that the frequency of these lesions is significantly underestimated.

1.12.2.3 Coronary artery spasm

Clinical studies show that cocaine-mediated coronary artery constriction occurs in humans. In one study, 2 mg/kg of cocaine was given intranasally to 45 patients undergoing cardiac catheterization. The dose given did not cause chest pain, but it did reduce the diameter of the left coronary artery by at least 8–12% (Lange et al., 1989a,b). In related studies, it was found that vasoconstriction is more intense in atherosclerotic vessels (Flores, 1990). It has also been shown that cocaine and cigarettes act synergistically on diseased arterial segments to produce even greater degrees of vasoconstriction (19% for cigarettes and cocaine combined vs. 9% after cocaine and 5% after cigarette smoking) (Moliterno et al., 1994). Just the opposite happens when cocaine is combined with alcohol. When patients evaluated for chest pain were given ethanol and cocaine in combination, significant increases in myocardial oxygen demand occurred. However, there was also a concomitant increase in measured epicardial coronary artery diameter, suggesting that there was no net decrease in myocardial oxygen supply (Pirwitz et al., 1995).

Unless spasm occurs at the site of pre-existing coronary artery narrowing, it would seem unlikely that spasm alone could account for very many episodes of infarction in cocaine users. In humans, anything less than a 75% cross-sectional coronary obstruction is unlikely to produce symptoms, so constriction of an epicardial vessel amounting to only 10–12% should be asymptomatic unless, of course, severe atherosclerotic disease is already present. And, in fact, doses of 1.2 mg/kg of cocaine administered intravenously to 20 human volunteers (resulting in mean cocaine levels of 709 ng/mL vs. levels of only 120 ng/mL in the Lange et al. studies cited above) produced only nonspecific T- and R-wave changes with no changes in the left ventricular ejection fraction or wall motion score index (Eisenberg et al., 1995).

1.12.2.4 Microvascular disease and decreased flow reserve

Within the last few years it has become increasingly apparent that myocardial perfusion may be decreased, even in the absence of occlusive epicardial disease — atherosclerotic

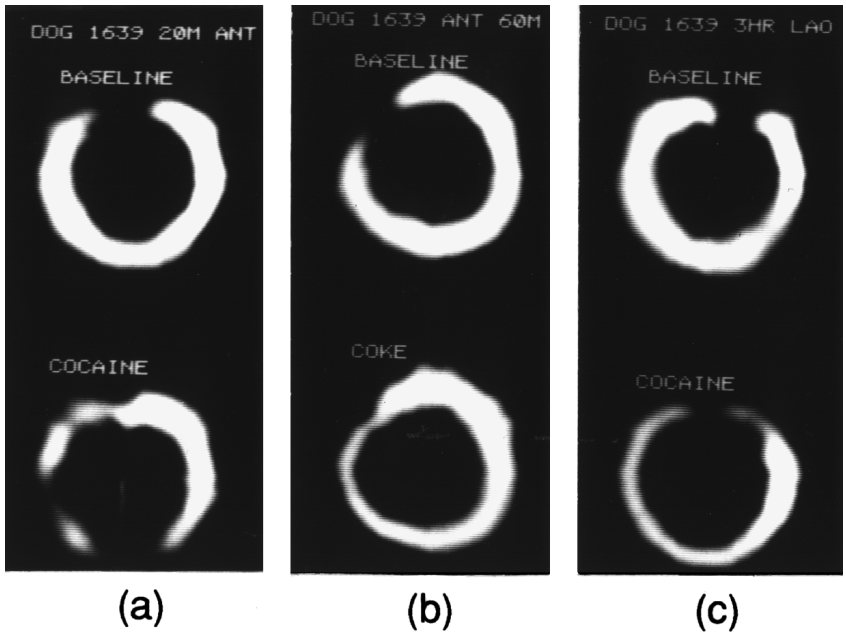

Figure 1.12.2.3 **Decreased myocardial perfusion after treatment with cocaine.** Scans are from three different dogs given cocaine intravenously, then injected with 2–4 mCi ^{201}Ti-chloride. Significant decreases in septal and apical perfusion were evident within 5 minutes. Evidence for decreased cardiac output can be seen. (From Oster, Z. H. et al., *J. Nucl. Med.*, 32, 1569, 1991. With permission.)

or otherwise. The degree of cross-sectional narrowing of the large epicardial vessels, as assessed by angiography, intravascular ultrasound, or even by direct measurement at autopsy, cannot be relied upon to provide an accurate assessment of myocardial perfusion. Thickening of the media of the smaller, intramyocardial arteries has already been demonstrated in cocaine users and can lead to coronary insufficiency (Figures 1.12.2.4.1 and 1.12.2.4.2).

The degree of insufficiency can only be measured during life, and a number of new hemodynamic indices have been devised for just that purpose. The most useful of these indices is known as the fractional flow reserve (FFR). It is determined by placing an ultrasound flow probe into a coronary artery and measuring flow and resistance at baseline and after maximal vasodilation (Kern, 2000). The difference between the two measurements allows for an accurate assessment of perfusion (Frohlich, 1999). Such measurements have not been seen in cocaine abusers, in spite of their known propensity for disease of the small intracardiac vessels.

Cocaine elevates blood pressure, and the hearts of chronic cocaine users display many of the same features seen in hypertensive heart disease; in addition to myocyte hypertrophy, hypertrophy of the media of the coronary resistance vessels is also seen. In the hypertensive, and presumably in cocaine users, the result is diminished oxygen supply to the myocardium and the occurrence of secondary lesions, such as myocardial fibrosis and perivascular collagen deposition, all of which lead to diminished flow reserve (Picano et al., 1990; Ikeda et al., 2000). A significant decrease in flow reserve could explain some of the very large number of emergency room visits by cocaine-using young men who present with chest pain but with little or no obvious evidence of ischemia.

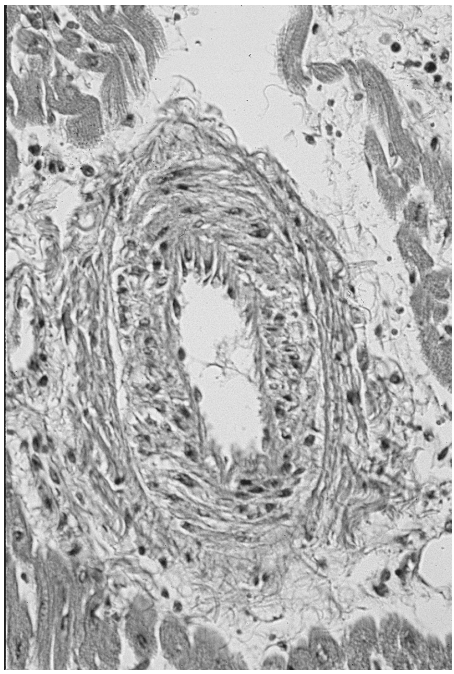

Figure 1.12.2.4.1 **Small vessel disease.** As illustrated here and in Figure 1.12.2.4.2, small vessel disease is a frequent finding in the hearts of stimulant abusers. Note the luminal narrowing and perivascular fibrosis. Disease of such small vessels would not be visible with routine angiographic studies but would, nonetheless, result in myocardial ischemia, and could account for some cases of sudden cardiac death among stimulant abusers.

1.12.2.5 Centrally mediated vascular disease

The sympathetic axis plays an important role in the vascular adjustments to cocaine use. Cocaine-related pressor effects (and, therefore, cocaine-related vasoconstriction) are mediated by norepinephrine released from neurons of the sympathetic nervous system. Other changes, such as heart rate, are mediated by release of epinephrine from the adrenal medulla (Tella et al., 1993). In intact organisms, the net effects of cocaine are closely linked to the underlying level of sympathetic adrenergic activity (Perreault et al., 1991).

The first suggestion that there was a relationship between coronary vasospasm and alterations in adrenergic function came from studies of Prinzmetal's angina. In that disorder, repolarization abnormalities (Q–T prolongation) precede episodes of spasm (Ricci et al., 1979; Roberts et al., 1982). It is well known that Q–T interval prolongation may be secondary to increased sympathetic discharge. In animal studies, unilateral stellate ganglion stimulation causes selective coronary spasm, Q–T prolongation, and a marked increase in coronary artery resistance. These changes can all be prevented with adrenergic blockade (Randall et al., 1972), and all of these changes can be produced by giving cocaine.

Both PR and Q–T prolongation are easily induced in animals infused with cocaine (Beckman et al., 1991). Torsades de pointes (reciprocating ventricular tachycardia associated with Q–T interval prolongation) has been reported in cocaine-intoxicated patients (Khan et al., 1999; Gamouras et al., 2000). In a group of 45 hospitalized cocaine users, those with chest pain had much longer Q–T intervals than those for noncardiac complaints, and lethal ventricular arrhythmias occurred in three of the individuals (Gamouras et al., 2000).

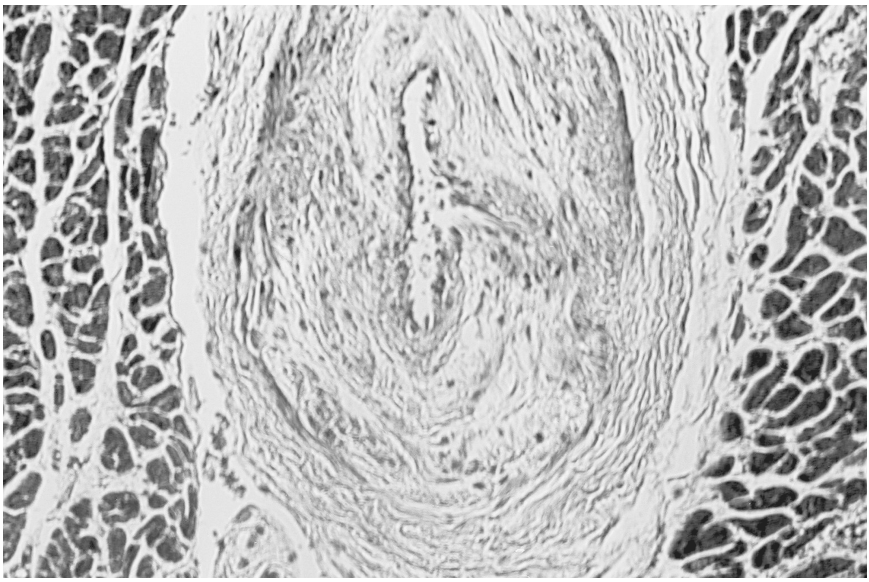

Figure 1.12.2.4.2 **Small vessel disease.** Methods now exist for the invasive measurement of myocardial flow reserve. These techniques make it possible to diagnose this abnormality even in living drug abusers. (See Figure 1.12.2.4.1.) This profoundly narrowed small vessel is from the heart of a chronic cocaine abuser.

Factor and Cho (1985) have identified what they believe are contraction bands in the media of coronary arteries, and other studies have confirmed the findings in cases of brain death (Novitzky et al., 1984). Lesions appear in the media as discrete zones of hypereosinophilia, usually in widened cells with rarefaction of the cytoplasm on either side of the eosinophilia area. It has been suggested that this morphologic finding is a marker for both coronary artery spasm and sudden death. Similar lesions have been produced in the coronary arteries of animals infused with catecholamines (Joris and Majno, 1981).

Even if contraction band necrosis cannot be identified, other studies have shown that the sustained contraction of the smooth muscle cells in arterial walls is associated with specific morphological changes, remodeling of the vessel wall structure, decreased external wall diameter, and thickening of individual muscle bundles, resulting in a thickened media and decreased luminal cross section (Lin et al., 1998). Experience suggests that if enough sections of myocardium are studied, such changes can usually be detected in cocaine-related deaths.

1.12.2.6 Myocardial hypertrophy

Chronic cocaine users have enlarged hearts. This places them at a greatly increased risk for sudden cardiac death, even when no cocaine is present in their bodies. In the most recent study of the subject, Spanish researchers followed 480 consecutive patients with left ventricular hypertrophy, dividing them into groups based on maximal wall thickness. The risk of sudden death increased progressively and in direct relation to wall thickness ($p = 0.001$), ranging from 0/1000 person–years (95% CI, 0 to 14.4) for a wall thickness of 15 mm or less to 18.2/1000 person–years (95% CI, 7.3 to 37.6) for a wall thickness of 30 mm or more, almost doubling from each wall-thickness subgroup to the next. The cumulative risk 20 years after the initial evaluation was close to zero for patients with a wall

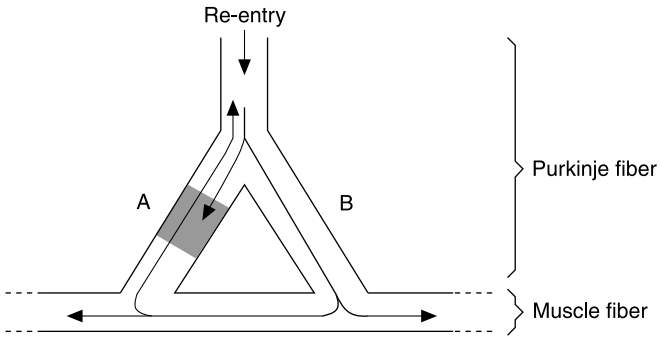

Figure 1.12.2.6.1 **Unidirectional heart block.** Zones of patchy myocardial fibrosis may provide the anatomic substrate for re-entry arrhythmia. The mechanism is thought to account for many cases of cardiac sudden death. (From *Textbook of Advanced Cardiac Life Support*, American Heart Association, Dallas, TX, 1987. With permission.)

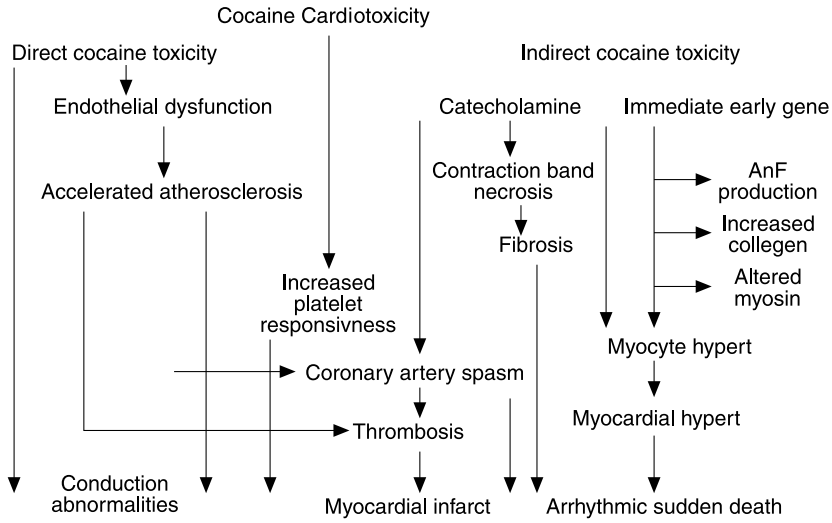

Figure 1.12.2.6.2 **Mechanisms of cocaine cardiotoxicity.** This flow chart has been constructed from both human and experimental data, and many of the mechanisms remain unclear. Toxicity may be the result of direct or indirect actions of cocaine on the heart. Direct effects include myocardial infarction and conduction abnormalities secondary to the local anesthetic effects of cocaine; however, the latter are only seen when massive amounts of cocaine are consumed. (From Kolodgie, F. D. et al., *Hum. Pathol.*, 26(6), 583–586, 1995. With permission.)

thickness of 19 mm or less, but almost 40% for wall thicknesses of 30 mm or more (Spirito et al., 2000) (see Figures 1.12.2.6.1 and 1.12.2.6.2).

Compared with controls, rats chronically treated with cocaine have larger left ventricles (Tseng et al., 1993; Besse et al., 1997), increased collagen content, higher levels of atrial naturetic hormone (Hargrave and Castle, 1995), and increased expression of the low ATPase myosin isoform V3 (Morris et al., 1994; Besse et al., 1997). Echocardiographic studies of asymptomatic cocaine users have yielded conflicting results. Several have found significant increases in left ventricular mass and posterior wall thickness (Brickner et al.,

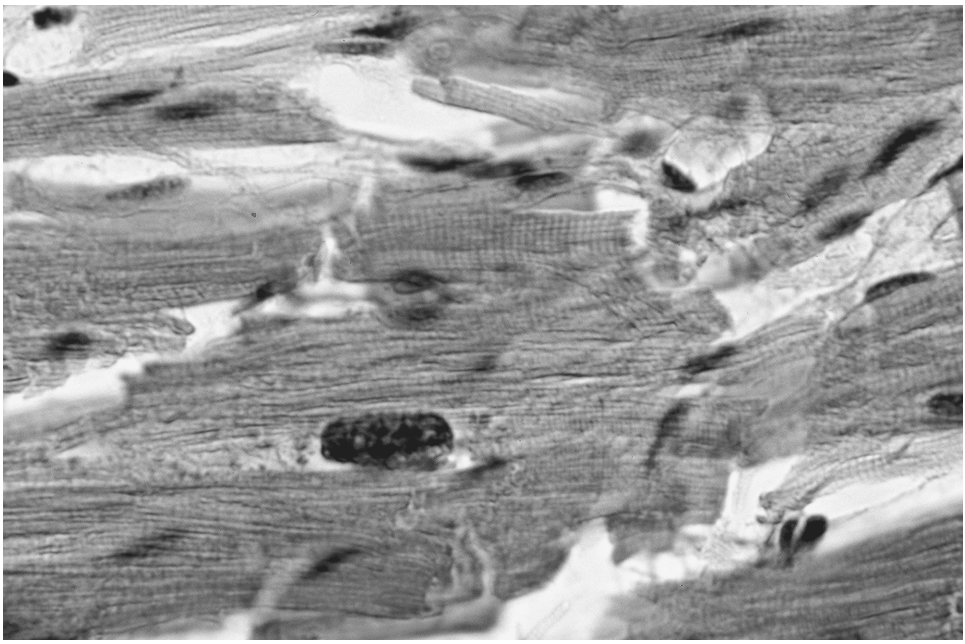

Figure 1.12.2.6.3 **Myocardial hypertrophy.** Modest, and occasionally massive, degrees of myocardial hypertrophy are common in cocaine and methamphetamine abusers. The nuclei in hypertrophic myocytes become elongated and squared. They are sometimes referred to as "boxcar" nuclei. A typical "boxcar" nucleus is illustrated in this section of myocardium from a cocaine user with sudden arrhythmic death. (H & E stain.)

1991; Om et al., 1993), but others have not (Eisenberg et al., 1995; Hoegerman et al., 1995). The conflicting results are probably explained by the sensitivity of the techniques used. In most cocaine users, the increase in heart size is less than 10% (Karch et al., 1995, 1998). It is an open question as to whether or not echocardiography can reliably detect increases in heart size amounting to less than 50 g.

Myocardial hypertrophy in cocaine users has also been confirmed in studies comparing electrocardiograms of age- and sex-matched controls to those of asymptomatic cocaine users in rehabilitation, and to symptomatic cocaine users with chest pain (Nademanee, 1992; Chakko et al., 1994). More importantly, increased heart size has also been confirmed by direct measurements made at autopsy (Figure 1.12.2.6.3) (Escabedo et al., 1992; Karch et al., 1995, 1998). Heart weights of asymptomatic, cocaine-using trauma fatalities were found to be 10% heavier than those of controls, even though the heart weights of both groups fell within ranges generally considered to be normal.

The mechanism by which cocaine induces myocyte hypertrophy is not known. Many different chemical and mechanical signals can make myocytes enlarge (Figure 1.12.2.6.4). The enlargement may be the result of some direct effect of cocaine on myocardial cells, or it may be a reaction to some extrinsic stimuli, such as drug-induced hypertension. Most of the stimuli associated with myocardial hypertrophy cause activation of a G protein and either adenyl cyclase or phospholipase-C. Activation of either leads to activation of the genes needed to make the proteins necessary for cell growth (Francis et al., 1993). The myocardial hypertrophy that occurs after infarction is accompanied by activation of early expression genes such as c-*fos*, c-*jun*, and c-*myc*. However, that is not the case in cocaine

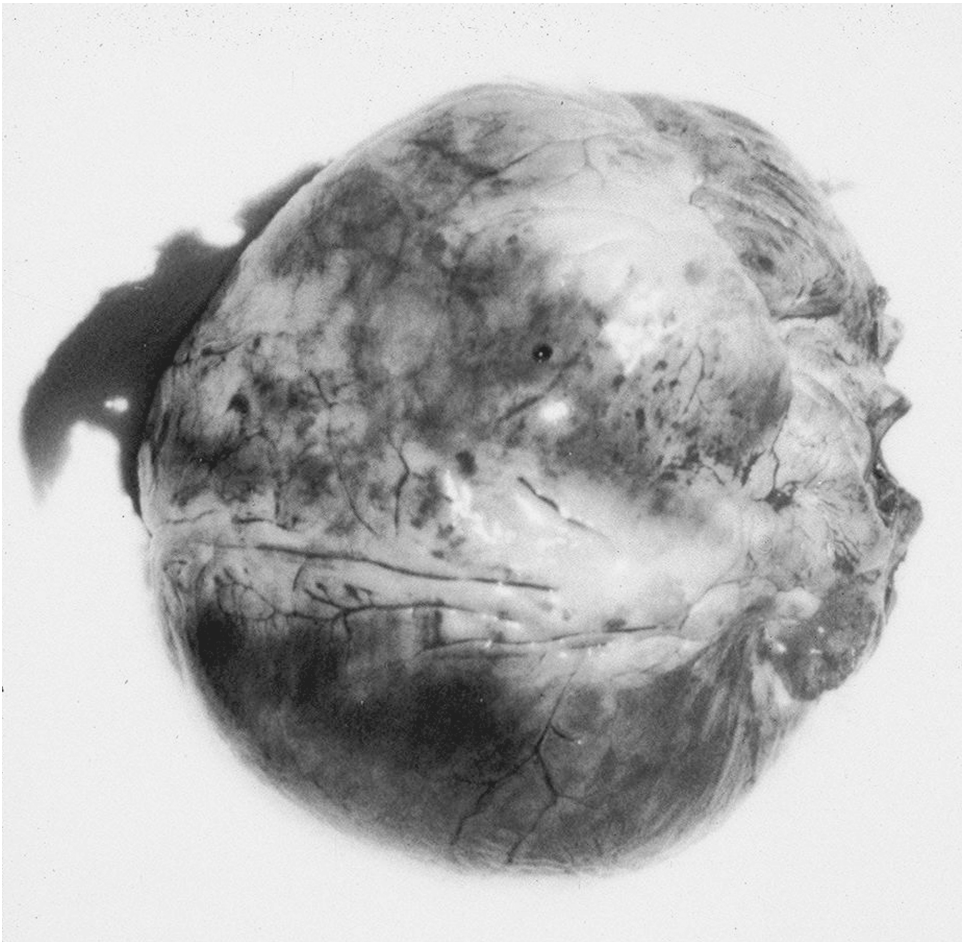

Figure 1.12.2.6.4 **Myocardial hypertrophy.** The occasional cocaine user is found to have massive myocardial hypertrophy, sometimes referred to as "cor bovinum." The heart shown here weighed over 1200 gm. The decedent succumbed during his second episode of excited delirium. (Courtesy of Dr. Kari Blaho, University of Tennessee, Memphis.)

users, or at least not the case in rats with cocaine-associated myocardial hypertrophy (Besse et al., 1997), even though the expression of these early genes is well documented in experimental animal brains. The picture is further confused by the observation that in experimental brain death, which is accompanied by a massive surge of catecholamines, levels of messenger RNA encoding for skeletal and cardiac α actins and heat shock protein increase significantly within four hours of injury (Yeh et al., 1999). Data from humans are lacking.

Sustained hypertension occurs in experimental animals treated with cocaine (Poon and van den Buuse, 1998; Mo et al., 1999) but is less predictable in humans, partly because of the development of tolerance to at least some of cocaine's cardiovascular effects (Fischman and Schuster, 1981; Ambrosio et al., 1996; Mendelson et al., 1998; Tella et al., 1999). If hypertension is the cause for left ventricular hypertrophy, then other signaling mechanisms may be involved. These would include the production of stress-response protein

kinases (SAPKs), the p38 kinases and calcineurin. Any of these molecules could activate transcription factors, which could, in turn, initiate hypertrophy (Force et al., 1999). In fact, the hearts of cocaine users resemble those of the hypertensives in many respects, with enlarged myocytes, increased collagen deposition, perivascular fibrosis, and medial hypertrophy in the smaller arterioles (Tazelaar et al., 1987; Karch and Billingham, 1988; Gavin et al., 1998).

Alternatively, the high prevalence of myocardial fibrosis in cocaine- and methamphetamine-related deaths could represent previous episodes of ischemia. Examination of hearts from patients who die after repeated episodes of unstable angina pectoris have shown that one-half have focal ischemic lesions and half areas of intense contraction band necrosis. Even the apparent histologic age of the lesions correlated well with the time frame of the patients' symptoms (Dominitz et al., 1996). However, the anatomic distribution of the fibrotic areas seen in the cocaine users could also be explained by the healing process that occurs after recurrent bouts of contraction band necrosis (Karch and Billingham, 1986).

Myocardial hypertrophy often goes undiagnosed during life, particularly in patients who are significantly overweight (body mass index > 30). Obesity limits the sensitivity of the ECG voltage criteria used to make the diagnosis of left ventricular enlargement. In particular, the older Sokolow–Lyon voltage criteria significantly underestimate the size of the left ventricle (Okin et al., 2000). The importance of accurately assessing left ventricular mass during life is difficult to overstate (particularly in the obese hypertensive, cocaine users or not), as heart size is an independent risk factor for sudden cardiac death (Kannel et al., 1969; Kozakova et al., 1997; Frohlich, 1999; Messerli, 1999). As the heart enlarges, perfusion of individual myocytes decreases, as does coronary flow reserve (Kozakova et al., 1997), causing decreased endocardial perfusion (Chen et al., 1994), especially during situations where there is a high demand for oxygen.

Flow and perfusion abnormalities may arise because of the inadequate growth of coronary arterioles or a reduction in luminal diameter, or as a consequence of medial hypertrophy within the resistance vessels leading to the diminished oxygenation of individual myocardial fibers. When myocardial hypertrophy occurs, angiogenesis lags behind myocyte growth and is less robust in the old than in the young. One consequence of this mismatch is that, even without medial hypertrophy of the resistance vessels, the center of the lumen of the vessel is farther away from the muscle fiber it is intended to supply (Gavin et al., 1998). Studies have shown that a hypertrophied heart is less efficient at utilizing oxygen than nonhypertrophied myocardium (Laine et al., 1999). As a result, the myocytes in the area are relatively under-perfused at all times. During exercise, the degree of under-perfusion may become critical (Gavin et al., 1998). Interestingly, these changes only occur when myocardial enlargement is due to pressure overload. When the heart enlarges as a consequence of exercise training, angiogenesis keeps pace with myocyte hypertrophy and no complications arise (Tomanek, 1994).

Under normal circumstances, coronary flow can increase by as much as 80%, but if the resistance vessels are abnormal, the flow reserve may be much smaller (Lerakis et al., 1999). Even if the large epicardial vessel appears normal or manifests only minimal disease, life-threatening decreases in coronary flow reserve are still possible and may well account for the sudden death of cocaine users who violently exert themselves — either in some sort of athletic competition or, even more likely, when forcibly restrained by police. Given the fact that some degree of myocardial hypertrophy is always evident in decedents with excited delirium, relative hypoperfusion is likely to be the cause of death in many of these cases (Vogt et al., 1990).

In cases of pressure overload, but not in cases where myocardial hypertrophy is a consequence of exercise (Chen et al., 1994), progressive accumulation of interstitial collagen fibers, particularly in the left ventricle, is also seen. With time, this accumulation will lead to decreases in normal systolic (ejection fraction) and diastolic function (incomplete relaxation, high filling pressures) (Rossi 1998). The risk for arrhythmia also increases because of the underlying silent ischemia or because myocardial fibrosis provides a substrate for re-entry arrhythmias, or both. The increase in collagen can be quantitated by measuring the amount of hydroxyproline in samples of the right and left ventricle (in the normal heart, collagen content is greater on the right side), but this measurement is never used clinically (Caspari et al., 1977, 1978).

A 10% increase in heart weight is likely to be unrecognized at autopsy; in life, without serial studies, an increase in heart weight of only 40–50 grams will not be disclosed by ultrasonography, nor would such a modest weight increase cause wall thickness to increase beyond generally accepted limits. Even if wall thicknesses were fastidiously measured at autopsy, which is not always the case, the increase would most likely be undetected. Weighing of the heart could disclose a large increase in weight, but because there is no universally accepted way to determine heart weight, differences in methodology are likely to obscure the presence of small increases.

Several different systems for determining normal heart weight are in use. Some pathologists use arbitrary cutoffs: 380 or 400 g for men and 350 g for women. Others consider heart weight to be normal provided the heart weighs less than 0.4% of the body weight (or 0.45% for women) (Ludwig, 1979). The most reliable approach is to use the Mayo Clinic nomogram relating heart weight to body weight (see Appendix). This nomogram is based on measurements made in 890 autopsies of individuals found to be free of heart disease (Kitzman et al., 1988). Hearts weighing significantly more than predicted by the nomogram are abnormal, even if the heart weighs less than the 400 g or 0.4% of body weight. The only problem with the nomogram is that the data used to derive it came from hospitalized patients. Even though their hearts were found to be normal, all of the patients had fatal diseases, which probably explains why the range of values observed was relatively wide. A new nomogram based on drug-free trauma patients is very much needed, but it may be some years in the making — most trauma fatalities have positive, not negative, drug screens!

1.12.2.7 Catecholamine cardiotoxicity

A handful of clinical reports suggest an association between dilated cardiomyopathy and long-term cocaine use. Most of these reports are not very informative, as they merely describe the occurrence of heart failure in polydrug abusers, although one pregnant abuser did have biopsy-proven sarcoid (Seballos et al., 1994). Without angiography or biopsies, the diagnosis must remain in question (Wiener et al., 1986; Chokshi et al., 1989; Duell, 1987; Wolfson, 1990; Mendelson and Chandler, 1992). The limited number of morphologic observations that have been published in the literature suggest that true cocaine cardiomyopathy is extremely uncommon, but when it occurs it is catecholamine mediated (Karch and Billingham, 1988; Peng et al., 1989; Henzlova et al., 1991).

The myocardial response to chronic catecholamine toxicity has been well characterized and is the same in humans and animals. Norepinephrine "myocarditis" was observed almost as soon as intravenous pressor agents were introduced (Szakacs and Cannon, 1958). Histologically, this type of necrosis is indistinguishable from what is seen in patients and animals with pheochromocytoma (Rosenbaum et al., 1987). Contraction band necrosis is the earliest recognizable lesion. Catecholamine-induced necrosis and ischemic necrosis

Table 1.12.2.7.1 Differences Between Ischemic and Catecholamine Necrosis

Ischemic Necrosis	Catecholamine Necrosis
Involves many cells in area supplied by a single vessel	Very focal; necrotic cell may be surrounded by normal cells
Myofilaments remain in register	Myofilaments are destroyed, forming eosinophilic clumps
Mitochondria remain neatly packed and are of uniform size	Mitochondria are translocated with distorted shapes

can be distinguished by their pattern of distribution (Table 1.12.2.7.1). In cases of ischemic injury, all the cells supplied by a given vessel will be affected. When the injury is due to catecholamine excess, individual necrotic myocytes are found interspersed between normal cells. Distribution is, in fact, one of the principal diagnostic features of catecholamine injury. Another feature that separates the two is the arrangement of the myofilaments. When the insult is ischemic, the myofilaments remain in register. When the damage is due to catecholamine excess, the filaments are disrupted.

Catecholamine necrosis does not have a "zone" of injury or any apparent relationship to blood supply. After 12 or more hours have elapsed, a mononuclear infiltrate, predominantly lymphocytic, may be seen. The necrotic myocytes are eventually re-absorbed and replaced by nonconduction fibrous tissue. The hallmark of both the acute and healed catecholamine lesions is that they are extremely focal. With repeat bouts of necrosis, the ventricle becomes increasingly fibrotic, leading to altered function and abnormal impulse propagation (Weber and Brilla, 1991; Weber, 1994).

One study describes findings in three patients with histories of cocaine abuse and end-stage chronic heart failure who underwent cardiac transplantation. The morphologic changes in the native hearts were noted to be distinctly different from those seen in other patients with the same clinical diagnosis. Fewer nuclear abnormalities and less myocyte hypertrophy were observed. The fibrosis was much more focal in distribution, and focal lymphocytic infiltrates were found (Karch and Billingham, 1988). Biopsy findings in a second group of seven patients, six with recent onset of congestion failure and one with chest pain, showed very similar changes. Myocyte necrosis was observed in five of the seven patients, and its distribution was identical to that seen when contraction band necrosis occurs as a result of catecholamine toxicity (Figures 1.12.2.7.1 to 1.12.2.7.3). Necrotic cells were found next to normal cells with no apparent relationship to blood supply. Focal interstitial fibrosis, of varying degrees of severity, was noted throughout. In two specimens, necrosis was associated with predominantly lymphocytic infiltrates and eosinophilia was not present (Peng et al., 1989). Similar changes have been described in chronic amphetamine abusers (Smith et al., 1976).

Contraction band necrosis is a prominent feature of all myocardial biopsies, regardless of the underlying cause. For that reason, contraction bands found in biopsy material are difficult to assess (Adomian et al., 1978; Karch and Billingham, 1986). Clinical experience suggests that the presence of nuclear pyknosis may be one way to distinguish pre-existing contraction band lesions from those produced by the biopsy process itself; however, that has never been proven in a controlled study. In some of the biopsies, Z-band remnants can be seen with electron microscopy. This particular finding is classically associated with dilated congestion cardiomyopathy, and is not generally associated with the type of necrosis

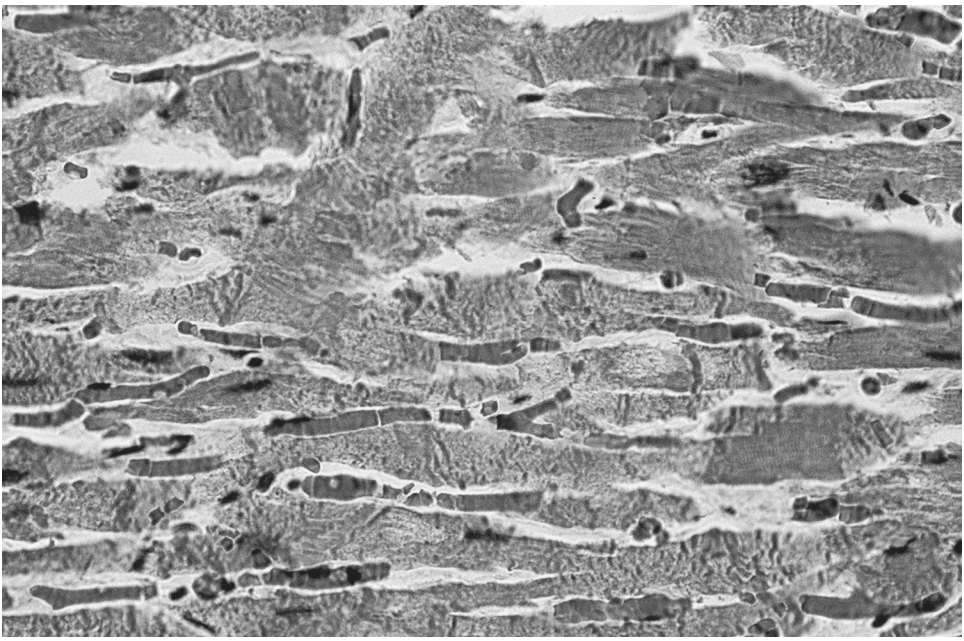

Figure 1.12.2.7.1 **Sudden arrhythmic death.** Contraction band necrosis in myocardium of cocaine user with sudden arrhythmic death (H & E stain). Decedent was aggressively resuscitated, which probably accounts for the areas of interstitial hemorrhage and may have made the process of contraction band necrosis more intense.

resulting from catecholamine toxicity. While it has not been observed in other patients with cocaine-related heart disease, it has been seen in patients with amphetamine toxicity (Smith et al., 1976). Its presence probably signifies only that necrosis was very severe.

Bravetta and Invernizzi (1922) were the first researchers to report finding cellular infiltrates in the heart of a cocaine user, and that was more than 70 years ago! Since then, the observations have been repeated many times. However, 64 years elapsed between the publication of the Bravetta and Invernizzi paper and the appearance of a paper by Isner et al. (1986) that reported finding eosinophilic infiltrates in an endomyocardial biopsy specimen from a 29-year-old man with cocaine-related cardiac symptoms.

1.12.2.8 HIV-related myocardial disease

Another possibility that must be considered when infiltrates are encountered in drug users' hearts is that they may have HIV. A variety of opportunistic infections occur, and, as more effective therapies have been introduced, survival times have lengthened and new complications of late-stage HIV infection have emerged. Almost any agent that can cause disseminated infection in patients with acquired immunodeficiency syndrome (AIDS) may involve myocardium, but clinical evidence of cardiac disease is usually overshadowed by manifestations in other organs, primarily the brain and lungs. Cardiac abnormalities are found at autopsy in two thirds of patients with AIDS. More than 150 reports of cardiac complications have been published (Milei et al., 1998).

Today, the probability is that any obvious infiltrate in the heart of an HIV-positive cocaine user represents an opportunistic infection and not a cocaine-related injury, although the number of individuals with lymphomatous involvement of the heart is also

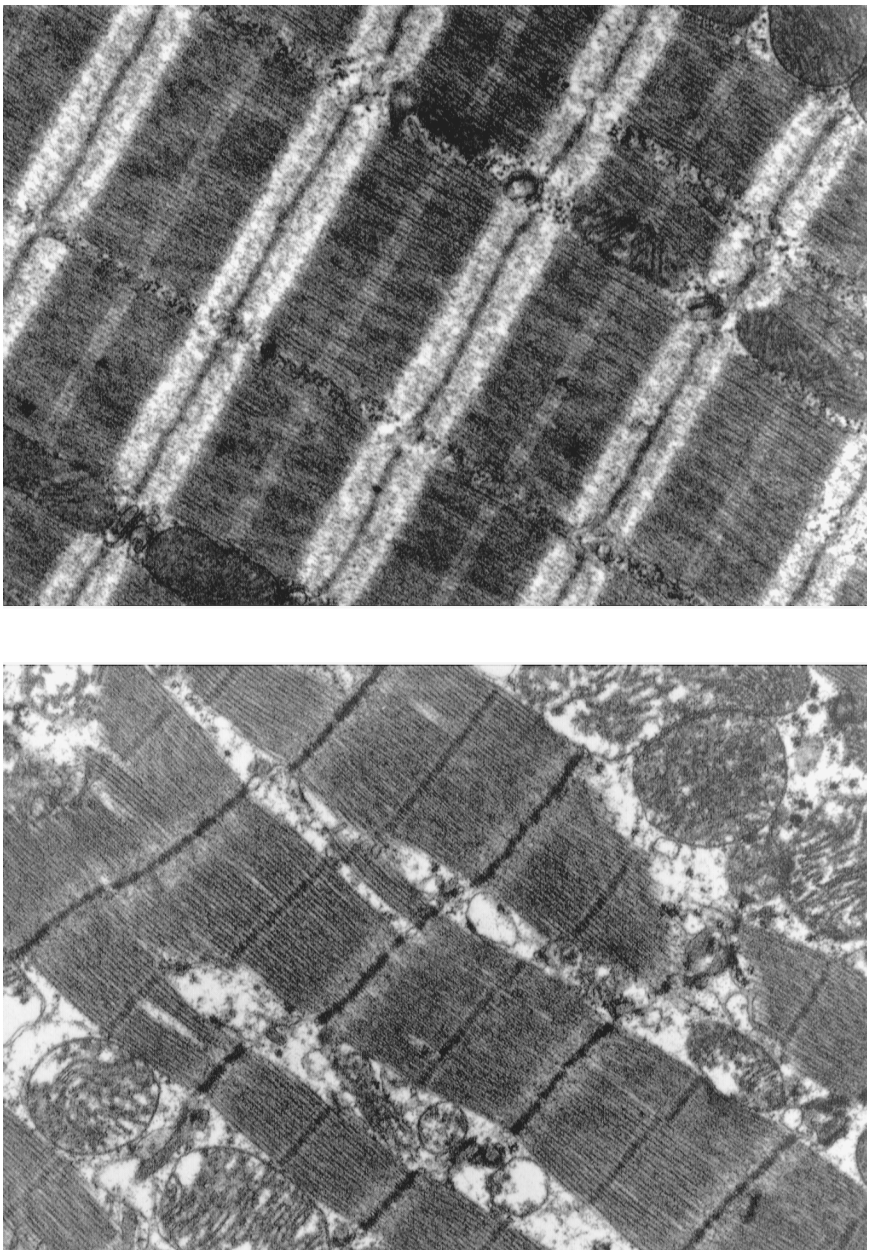

Figure 1.12.2.7.2 **Mitochondria disruption and myofibrillar damage.** The top figure is from a control rat; the bottom figure is from a rat infused with 40 mg/kg/day for 21 days. The mitochondria are swollen and translocated, and many of the myofilaments are degenerating. (Original magnification 7200×.) (Courtesy of Prof. M. Maillet, Hôpital Lariboisière, Paris.)

increasing (Sanna et al., 1998). Similar considerations apply to pericardial effusion. HIV-associated pericardial effusion is now the most common type of pericardial effusion seen in inner-city hospitals. The presence of an effusion in an HIV-infected patient, generally pericardial, predicts a poor prognosis (Chen et al., 1999).

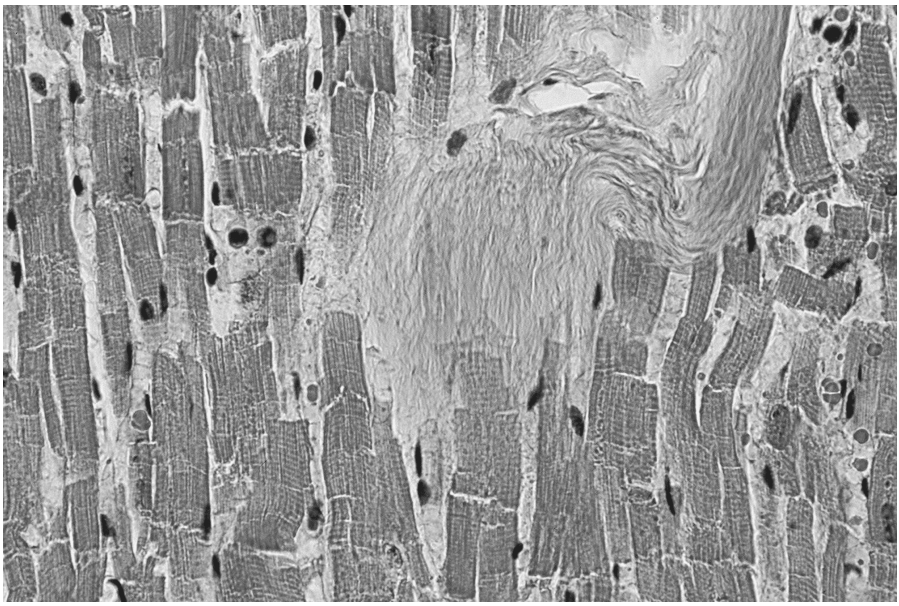

Figure 1.12.2.7.3a **Microfocal fibrosis.** Contraction band necrosis (CBN) can be distinguished from ischemic necrosis by its extremely focal nature; small numbers of damaged cells are surrounded by normal myocytes (H & E stain). If CBN is irreversible, the zones of necrosis are replaced by fibrous tissue which also have a microfocal distribution.

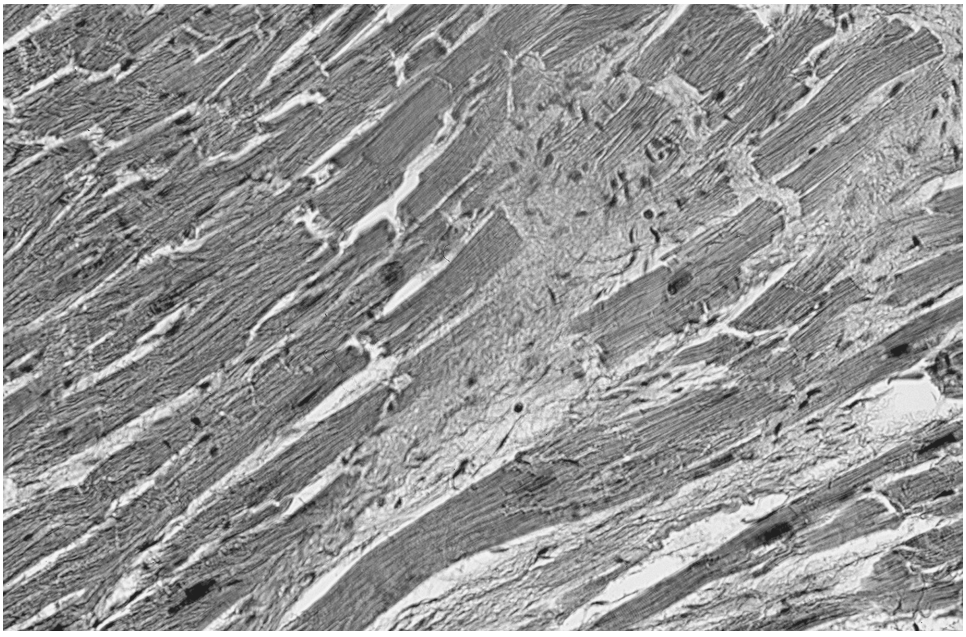

Figure 1.12.2.7.3b **Microfocal fibrosis.** Replacement of damaged CBN myocytes takes weeks or months, and lesions in various stages of evolution may be seen in chronic stimulant abusers. Neither CBN nor the resultant fibrosis is a specific finding. The occurrence of either abnormality simply indicates catecholamine toxicity.

The first report describing AIDS-related myocardial disease was published in 1985. An assortment of opportunistic agents was found in 10 of the 41 hearts studied (Commarosano and Lewis, 1985). In a second series of 82 patients dying of AIDS, 17% were found to have infectious agents in their hearts. The usual pathogens associated with decreased immune function, including toxoplasmosis, mycobacteria, histoplasmosis, *Cryptococcus*, cytomegalovirus, and pneumocystitis, have all been reported (Anderson et al., 1987, 1988). Several studies have reported a high occurrence rate for histologic changes consistent with inflammatory infiltrates, with myocardial cell necrosis demonstrable in from one third to one half of the autopsied cases (Anderson et al., 1987, 1988; Lafont et al., 1988). There is also evidence that the HIV virus itself invades the myocardium (Grody et al., 1990).

Kaposi's sarcoma, most often involving the pericardium, occurs (Anderson et al., 1987; Chyu et al., 1998), as does lymphomatous infiltration of the heart. In AIDS patients, both primary and secondary lymphomatous heart involvement are increasing in incidence. And, because the hematogenous route is the most common pattern of involvement, even extrathoracic lymphomas can present heart dissemination (Sanna et al., 1998). Thus, a high level of suspicion is indicated in lymphoma patients with cardiac symptoms.

A very high percentage of intravenous drug takers (the percentage varies by location) are infected with HIV and hepatitis C (Thomas, 2000). The risk of HIV transmission makes intravenous cocaine users unlikely candidates for organ donation. However, the outcome in patients who receive hearts from nonintravenous cocaine users (and it appears that fairly large numbers of donors fall into that category) is comparable to that observed in those receiving hearts from non-drug users (Freimark et al., 1994). A positive history for nonintravenous cocaine abuse should not disqualify possible donors.

1.12.2.9 Valvular heart disease

Intravenous drug users are at risk for endocarditis, and there is no reason to suppose that the subgroup of cocaine abusers is any different. Unfortunately, no autopsy data and no animal models are available to review. One clinical study reviewed the records of 115 intravenous drug abusers who were admitted to the hospital for evaluation of fever (Chambers and Mills, 1984). Endocarditis was proven in 20% of the drug abusers. When the subgroup was further analyzed, 80% of those with endocarditis were found to be intravenous cocaine users. Logistic regression analysis of the patients' histories demonstrated that cocaine use was the single variable most strongly predictive for endocarditis. History of cocaine use was, in fact, a better predictor than even the presence of a mitral or aortic murmur, the findings classically associated with endocarditis. More than 15 years later, these retrospective findings have never been confirmed by other clinical observations, and no one has managed to produce any valvular pathology in experimental animals. If a relationship between intravenous cocaine use and endocarditis exists, it may have to do with the fact that injected cocaine has a very short half-life. Maintaining a "high" takes repeated injections — many more injections than will be required by an opiate addict — increasing the probability of sepsis.

1.12.2.10 Aorta and peripheral vessels

Although most review articles mention cocaine abuse as a possible cause of aortic dissection (Figure 1.12.2.10.1), fewer than 20 individual case reports have been published since 1986 (Barth et al., 1986; Edwards and Rubin, 1987; Gadaleta et al., 1989; Bacharach et al., 1992; Cohle and Lie, 1992; Fisher and Holroyd, 1992; Om et al., 1992; Simons et al., 1992; Adkins et al., 1993; Cohle and Lie, 1993; McDermott et al., 1993; Sherzoy et al., 1994; Willens et al., 1994; Alspaugh, 1995; Chang and Rossi, 1995; Hohm, 1995; Rashid et al.,

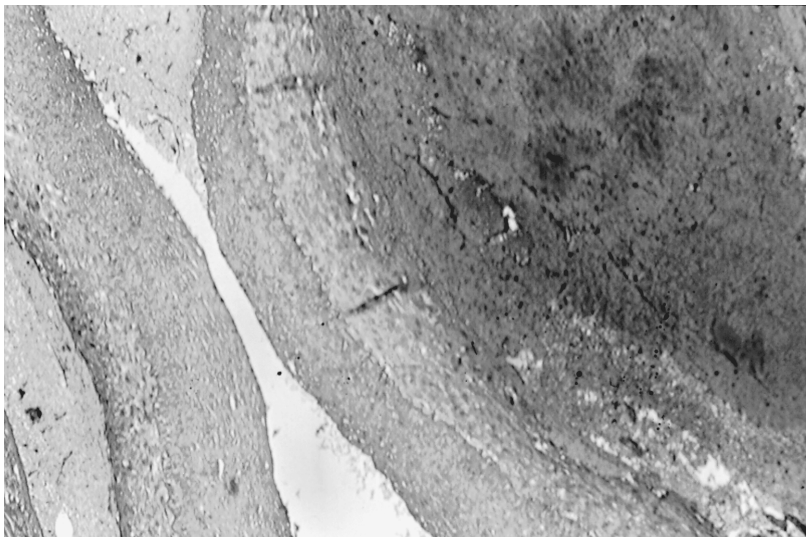

Figure 1.12.2.10.1 **Coronary artery dissection.** Dissection in the left anterior descending artery of a 38-year-old woman with a history of chronic cocaine abuse (H & E stain). Dissection is a rare complication of cocaine abuse and the underlying mechanism remains unknown.

1996; Baumgartner and Omari, 1997; Perron and Gibbs, 1997; Madu and Shala, 1999). Most have been type I dissections with the process extending from the ascending aorta to the iliac vessels. Only one of these individuals was found to have the typical pattern of medial degeneration associated with Marfan's syndrome, and even then, none of the other stigmata of the disorder were present (Cohle and Lie, 1993).

Two principal risk factors contribute to aortic dissection: aortic medial disease and hypertension. Cocaine use is certainly associated with at least one and possibly both of the disorders. Transient hypertension occurs in virtually all users, and some preliminary studies have shown damage to the media and elastic layers in the aortas of rats chronically treated with cocaine (Langner and Bement, 1991). A third, though seldom considered, predisposing factor is pregnancy, and dissection aneurysm has been described in pregnant cocaine users (Madu et al., 1999). Like coronary artery aneurysms, aortic aneurysms in pregnancy are thought to be the result of progesterone excess. The high concentrations of progesterone associated with pregnancy may lead to destruction of elastic fibers and fragmentation of reticular fibers in the wall of the aorta, ultimately resulting in loss of structural integrity (Madu et al., 1994).

Methamphetamine users appear to be at even greater risk for aneurysm than cocaine users. In one recent series of 84 acute aortic dissections, abused drugs were detected in 35 of the cases, and in seven of those, the abused drug was methamphetamine. After hypertension, methamphetamine use was the second most common risk factor for dissection (Swalwell and Davis, 1999).

Aortic dissection is initiated by transverse tears in the aortic wall. For dissection to occur, tears must extend through the intima and at least halfway through the media (Crawford et al., 1988). The case reported by Barth is interesting because the initiating tear was so extensive. A 45-year-old "crack" smoker, with a blood cocaine level of 9 mg/L, suddenly collapsed and could not be resuscitated. The heart weighed 500 grams. A circumferential tear through the intima and media was found in the ascending aorta 2 cm

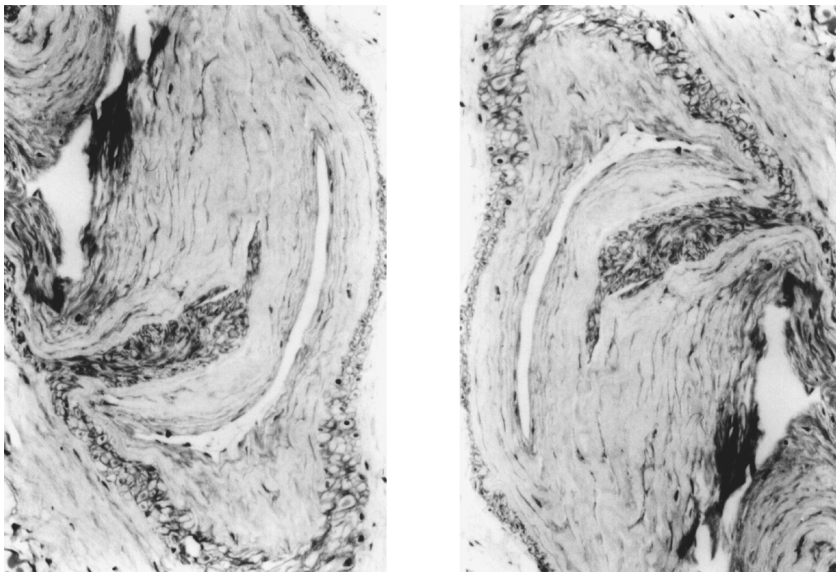

Figure 1.12.2.10.2 **Accelerated atherosclerosis is not confined to the coronary arteries.** This section of segmental artery, demonstrating severe intimal fibrosis and medial thickening, was obtained from a cocaine user with renal failure (PAS stain). (From Fogo, A. et al., *Am. J. Kidney Dis.*, 20(5), 513–515, 1992. With permission.)

above the sinotubular junction. No distal dissection was present, but medial extension proximally to the level of the aortic valve cusps, and adventitial hemorrhage around the aortic root extending into the proximal portion of the right and left coronary arteries (without compression) could be seen. Adventitial hemorrhage even extended down into the pulmonary arteries (Barth et al., 1986).

The most plausible explanation for these changes is hypertension-induced shearing injury to an aortic media that has, in some way, been weakened by chronic cocaine exposure, although in one case (Bacharach et al., 1992) aneurysmal dilatation was seen in conjunction with nonspecific aortitis. In that case, predominantly lymphoplasmacytic infiltrate in the media was interspersed with occasional scattered giant cells. Because this individual's serology was negative and there was nothing in the history to suggest Takayasu's disease or giant cell arteritis, it seems likely that cocaine was responsible for the process.

Several postmortem studies have found evidence for accelerated atherosclerosis (Figure 1.12.2.10.2), involving both the coronary arteries and the aorta itself (Kolodgie et al., 1991a, 1992), and it has been suggested that either production of endothelium-dependent vasorelaxation factor is impaired (Havranek et al., 1996) or autoregulation of prostanoid production is disrupted (Togna et al., 1996). Atherosclerotic changes in vessels other than coronary arteries, several involving the renal artery, have been reported (Fogo et al., 1992). Whether or not peripheral vessels respond to cocaine in the same fashion as coronary arteries is not known.

1.12.2.11 Eosinophilic myocarditis

The presence of eosinophilic infiltrates suggests a hypersensitivity phenomenon. Hypersensitivity myocarditis is distinguished from toxic myocarditis by a number of different

Table 1.12.2.11.1 Types of Cocaine Adulterants

A. Sugars	**D. Inert agents**
Dextrose	Inositol
Lactose	Corn starch
Mannitol	**E. Others**
Sucrose	Acetaminophen
B. Stimulants	Aminopyrine
Caffeine	Aspirin
Ephedrine	Ascorbic acid
Phenylpropanolamine	Boric acid
Phentermine	Diphenhydramine
C. Local anesthetics	Niacinamide
Lidocaine	Phenactin
Benzocaine	Quinine
Procaine	
Tetracaine	

Source: Based on information supplied by the Drug Enforcement Agency and Shannon, M., *Ann. Emerg. Med.*, 17(11), 1243–1247, 1988.

features: (1) the occurrence of eosinophilic myocarditis is not dose related, (2) the lesions are all of the same age, (3) hemorrhages are rare, and (4) myocyte necrosis is not present. The list of drugs causing hypersensitivity myocarditis is increasing (Billingham, 1985). When eosinophils have been observed in the myocardium of cocaine users, it has often been as an incidental finding, either at autopsy or in biopsy specimens obtained to evaluate chest pain, heart failure, or arrhythmia. Most of the time, the clinical manifestations of this disorder are so nonspecific that the diagnosis is rarely suspected during life (Taliercio et al., 1985).

None of the cocaine users with eosinophilic infiltrates have had signs of extra cardiac involvement such as polyarteritis nodosa or eosinophilic leukemia. In general, these patients do not match the picture classically associated with acute necrotizing myocarditis (Herzog et al., 1984) nor, with the exception of one case report, do they resemble patients with eosinophilic coronary arteritis (Churg–Strauss syndrome, also called allergic granulomatosis angiitis) (Orriols et al., 1996). The patient described in the one case report was a female "crack" smoker who first presented with relapsing fever, bronchoconstriction, arthralgias, and weight loss. She then went on to develop pulmonary infiltrates, arthritis, microhematuria, skin rash, and mononeuritis multiplex. Both skin and muscle biopsies showed eosinophilic angiitis.

Many agents can cause toxic myocarditis, and even though the purity of cocaine sold in the U.S. is increasing (generally >60%), a variety of adulterating agents is still likely to be encountered (Table 1.12.2.11.1). A review paper published in 1988 listed sugars (lactose, sucrose, mannitol) as the most common cocaine adulterants, followed by stimulant drugs (caffeine, amphetamines) and local anesthetic agents (Shannon, 1988). In Europe, and in many parts of the U.S., caffeine and lidocaine are the two agents most frequently encountered (Fucci and De Giovanni, 1998). However, most adult drug abusers are polydrug abusers, so even if they were all taking pure drug, proving whether a particular drug or an adulterant co-ingested with it was responsible for a particular finding would be a difficult undertaking.

After an initial flurry of reports in 1986 and 1987, recent mention of eosinophilic infiltrates has become uncommon. One explanation may be that most cocaine users are now "crack" smokers, and "crack," while it may contain large amounts of bicarbonate, is otherwise largely free of other chemical contaminants. Finally, it must be emphasized that the mere presence of cells in the myocardium does not necessarily mean that active myocarditis is present. The lymphocytic infiltrates seen in cocaine users are generally not accompanied by myocyte necrosis and, according to the Dallas criteria, infiltrates without necrosis do not prove myocarditis (Aretz et al., 1986). What these infiltrates represent is not clear, but similar infiltrates are also seen in experimental animals with catecholamine toxicity.

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1.12.2.12 Excited delirium and the neuroleptic malignant syndrome

1.12.2.12.1 Overview. Excited or agitated delirium was first reported more than 150 years ago by Lewis Bell, an American physician. The *American Journal of Insanity* published his lengthy paper describing the syndrome which was entitled "On a form of disease resembling some advanced stages of mania and fever, but so contra distinguished from any ordinarily observed or described combination of symptoms as to render it probable that it may be an overlooked and hitherto unrecorded malady." The patients described all died suddenly after experiencing a brief period of mania and fever (Bell, 1849). Fifty years after Bell's paper was published, similar reports began to appear in the popular press. These reports were deeply interwoven with elements of racist hysteria and were published in part by opponents of the prohibitionist movement who argued that if alcohol were no longer available then people would just start using other drugs.

The most notorious, and certainly the most racist, of these reports was actually penned by a physician writing for the *New York Times* (Williams, 1914). His article described a series of murders and violent crimes, allegedly committed by black men under the influence of cocaine. Williams claimed that cocaine made the men crazed and resistant to bullets because they had a "temporary immunity to shock." He attributed the new "menace" to the restriction of alcohol sales (Knopf, 1924). When prohibition ended, so did concerns about cocaine-related violence, and reports of new cases simply disappeared from the medical journals and newspapers. New case reports began to reappear in the early 1980s, at the beginning of the new cocaine pandemic. The first modern mention of cocaine-associated excited delirium was in 1985 (Wetli and Fishbain, 1985).

The syndrome is comprised of four components, which appear in sequence: hyperthermia, delirium with agitation, respiratory arrest, and death, although hyperthermia may be absent in some cases. As a rule, individuals succumbing to this disorder, if they are drug users and not schizophrenics, will be found to have low to modest cocaine blood levels. Their clinical course is entirely different from that seen in body packers with massive cocaine overdose (continuous seizures, respiratory depression, and death) (Figure 1.12.2.12.1.1). The incidence of this disorder is not tracked by any government agency, but there is little doubt that the number of cases has increased markedly since the late 1980s. Deaths from excited delirium now account for a significant number of deaths that occur while in police custody — both in the U.S. and in Europe (Karch and Stephens, 1999).

In the early stages of the syndrome which rarely last for more than a few hours, victims are hyperthermic, paranoid, grossly psychotic, and agitated. They often perform amazing feats of strength, usually while they are fleeing from imaginary threats. What happens next is not entirely clear. After a relatively short interval, agitation ceases and the patient becomes quiet. Death occurs shortly afterward. Many, but not all, have been restrained by police who fear injury to themselves or innocent bystanders. Victims who do not come to police attention are often found dead in their bathrooms, surrounded by wet towels

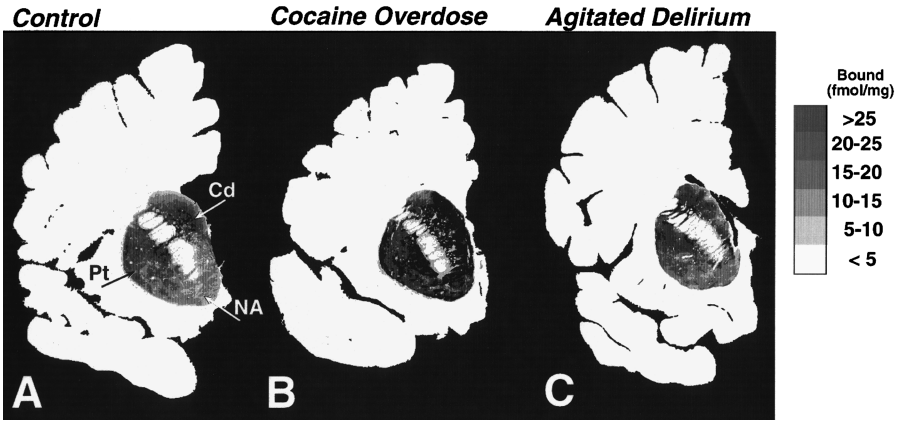

Figure 1.12.2.12.1 **Excited delirium.** Adaptive increases in the number of dopamine transporters can be seen in the brains of cocaine users dying of overdose but not in the brains of patients with excited delirium. Shown here are *in vitro* autoradiographic maps of [^{3}H]WIN 35,428 labeling of the dopamine transporter in coronal sections of the human brain from (A) a representative age-matched and drug-free subject, (B) cocaine overdose victim, and (C) cocaine-related excited delirium victim. An adaptive increase is evident in dopamine transporter density over the striatum in the cocaine overdose victim but not in the victim presenting with excited delirium. The dopamine transporter regulates synaptic concentrations of neurotransmitter, so the lack of compensatory upregulation may result in a dopamine overflow following a cocaine "binge." Repeated exposures may kindle the emergence of excited delirium syndrome. Gray-scale codes are presented at the right and are matched for the range of density values across the groups (black = high densities; gray = intermediate; light gray to white = low to background densities). Abbreviations: Cd, caudate; NA, nucleus accumbens; Pt, putamen.) (Courtesy of Debra Mash, University of Miami School of Medicine.)

and clothing, sometimes even with empty ice trays scattered about, all in a vain attempt to treat their fevers, which may be as high as 108°F.

Victims are much more likely to be men than women. They are also more likely to die in custody, and more likely to live for one hour after onset of symptoms. In Miami, men with excited delirium account for 10% of cocaine-related deaths. The syndrome is more common in summer, especially when the weather is warm and humid. Indeed, all types of cocaine-related deaths, not just excited delirium, seem to be more common when temperatures are elevated (Marzuk et al., 1998). Two thirds of the victims die on the scene or while being transported by paramedics to the hospital. The few who live long enough to be hospitalized succumb to disseminated intravascular coagulation, rhabdomyolysis, and renal failure. The patients reported from Miami had an average temperature of 104.8°F at the time of their first medical encounter (Ruttenber et al., 1997, 1999).

In 1985, Wetli described seven such cases. All had fairly stereotyped histories, such as the 33-year-old man who was found pounding on the door of a house he had moved out of some time previously (Wetli and Fishbain, 1985):

> He was shouting that he wanted to see his wife and daughter. The occupants informed him that nobody by that name resided there, yet he pursued his actions. Four bystanders finally restrained him and assisted police units upon their arrival. The subject was handcuffed and put into a police car, whereupon he began to kick out

the windows of the vehicle. The police subsequently restrained his ankles and attached the ankle restraints and handcuffs together. He was then transported to a local hospital. While en route, the police officers noted he became tranquil (about 45 minutes after the onset of the disturbance). Upon arrival at the hospital a few minutes later, the subject was discovered to be in a respiratory arrest. Resuscitative attempts were futile. A postmortem examination was performed 1 hour and 45 minutes later (about 3 hours after the onset of the disturbance), and a rectal temperature of 41°C (106°F) was recorded. He had needle marks typical of intravenous drug abuse and pulmonary and cerebral edema. Abrasions and contusions of the ankles and wrists were also evident from his struggling against the restraints. Toxicologic analysis of postmortem blood disclosed 52.3 mg/L of lidocaine and 0.8 mg/L of cocaine. No lidocaine was administered to the victim during resuscitative attempts.

1.12.2.12.2 Neurochemistry of excited delirium. The cellular and molecular changes resulting in this stereotyped set of symptoms are now reasonably well understood. Using ligand binding and autoradiographic methods, researchers have identified a series of neurochemical abnormalities in the brains of excited delirium victims, as well as the interactions between the mesolimbic areas of the brain, where dopamine is the principle neurotransmitter, and endogenous opioids (Mash and Staley, 1999). The abnormalities have to do with the number and type of dopamine receptors, the number of sites where cocaine can bind with brain tissue, and the ability of cocaine and dopamine to interact with κ-type opiate receptors located primarily in the amygdala, but also in the nucleus accumbens and other corticolimbic zones.

Dopamine receptors were initially classified into two main groups, but with advances in molecular biology, these main groups have been further subdivided into five different recognizable subtypes of receptors, although for practical purposes they are still considered as two groups: the "D1-like receptors" (dopamine receptors D1 and D5), and the "D2-like receptors" (dopamine receptors D2, D3, and D4) (Seeman and Van Tol, 1994). The situation is somewhat confusing, largely because of the nomenclature used to describe dopamine receptors. Most antipsychotic drugs block the D2 receptors in direct correlation to their clinical potency, except clozapine, which preferentially binds the D4 receptor. D1 and D2 receptors can interact with each other and enhance the actions of each other, possibly through subunits of G proteins. In schizophrenia, D2 and D3 receptor density is elevated by 10% while the D4 receptor density is elevated by 600%. It has been suggested that cocaine craving may be the result of marked D3 receptor elevation over the limbic sectors of the striatum (Strange, 1998; Mash and Staley, 1999).

Cocaine use alters the number of brain D1, D2, and D3 dopamine receptors (Seeman and Van Tol, 1994; Staley et al., 1994; Mash and Staley, 1999). When compared to the brains of drug-free trauma victims, the cocaine recognition sites on the striatal dopamine transporter are elevated in the brains of most cocaine users (i.e., the nonpsychotic ones). No such increase is seen in patients with excited delirium. The fact that psychotic cocaine users fail to demonstrate this compensatory increase means that they cannot clear excess dopamine from their synapses. At the same time, chronic cocaine abuse leads to striking decreases in the density of the D1 receptor subtype throughout the striatal reward centers, probably as a result of receptor downregulation (Staley and Mash, 1996). This type of downregulation is not seen in excited delirium.

The fact that cocaine users quickly become tolerant to the euphoriant effects of the drug is probably explained by the change in the number of dopamine binding sites. D2 receptors in nonpsychotic cocaine abusers are unchanged. However, in the psychotic subgroup, marked reductions in the number of D2 receptors in the hypothalamus have been observed. Because these receptors are known to mediate temperature control, decreased numbers of D2 receptors may explain the occurrence of malignant hyperthermia in the psychotic patients. With fewer D2 receptors available, D1-mediated temperature increases would be unopposed (Staley et al., 1994). Obviously, the occurrence of hyperthermia, and its severity, depend on the absolute decrease in D2 receptors; if it is not very great, then hyperthermia may or may not occur.

The significance of changes in the D3 receptor has only recently become apparent (Mash and Staley, 1999). Compared to drug-free controls, the brains of nonpsychotic cocaine users contain an increased number of D3 binding sites, with a one- to threefold increase measurable in the nucleus accumbens and in the ventromedial sectors of the caudate and putamen. Nucleus accumbens is a collection of brainstem neurons deeply implicated in the process of addiction to all drugs. Within this nucleus, cocaine exposure also causes increased production of D3 receptor mRNA.

By mechanisms yet to be determined, the increase in D3 receptors is in some way related to an increase in the number of κ-opioid receptors. Nonpsychotic cocaine users, when compared to drug-free controls, have twice the number of κ receptors in the nucleus accumbens and other corticolimbic areas. Unlike the nonpsychotic cocaine users, cocaine users who die of excited delirium have a selective upregulation of κ receptors in the amygdala (Staley et al., 1997; Mash and Staley, 1999). The observation almost certainly explains the paranoid nature of the psychotic episodes experienced by these patients. Although it would have been an unthinkable undertaking just a few years ago, PET scanning has been used to map the functional neuroanatomy of psychosis (Epstein et al., 1999).

The amygdala and other portions of the striatum play a very significant role in controlling our emotional response to external stimuli. Studies of schizophrenic patients, with or without hallucinations and paranoid delusions, have shown marked increases in mesolimbic activity, particularly when there is a perceived threat (Goodwin, 1996; Fudge et al., 1998). Of particular interest is the observation that, in drug-free patients with schizophrenia, projections from the amygdala to the frontal area of the brain may be involved. Decreased frontal lobe blood flow and glucose uptake are known concomitants of chronic cocaine abuse (Volkow et al., 1993).

Some of the neurochemical effects of cocaine seem to be gender related. Studies utilizing proton magnetic resonance spectroscopy have shown that the brains of cocaine users, when compared to those of non-drug-using controls, contain decreased amounts of *N*-acetyl compounds, an indicator of neuronal damage. Production of myoinositol, an indicator of glial activation, is increased. Both of these alterations are most prominent in the frontal lobes, and both changes are much more pronounced in men than in women. Whether these neurochemical alterations explain why nearly all excited delirium victims are men is not known (Chang et al., 1999).

As Bell first observed in the 1840s, excited delirium can occur in conjunction with many different medical disorders, not just cocaine or stimulant toxicity. It has been suggested that this constellation of symptoms is actually a variant of neuroleptic malignant syndrome (Kosten and Kleber, 1987, 1988). Neuroleptic malignant syndrome (NMS) is a highly lethal disorder seen in patients taking dopamine antagonists and in individuals who have been withdrawn from dopaminergic agents, such as bromocriptine and levodopa (Friedman et

al., 1985; Levinson, 1985). NMS is usually associated with muscle rigidity, though variants of the syndrome without rigidity are also recognized. Whether the same set of abnormalities underlie both excited delirium and NMS is unclear, but given that schizophrenic patients and patients suffering from bipolar disorder can also develop excited delirium, even when they are not taking dopaminergic agents, it seems likely that two different processes are at work (O'Halloran and Lewman, 1993).

1.12.2.12.3 Medico-legal considerations. Not uncommonly, patients with excited delirium find themselves "hog-tied," with their wrists and ankles bound together behind their backs while they lie prone (Reay et al., 1988, 1992; O'Halloran and Lewman, 1993; Reay, 1993; Pollanen et al., 1998; O'Halloran and Frank, 2000). Based on some early studies and anecdotal case reports, the cause for death in these individuals was said to be an entity called "positional asphyxia," a term originally used to describe what happens when alcoholics or otherwise infirm individuals fall into a confined space and are unaware that their respiratory status has been compromised and that their chests are not expanding adequately (DiMaio and DiMaio, 1989; Purdue, 2000).

In all such cases, autopsy will disclose marked congestion, cyanosis, and petechiae. However, the term is now applied to agitated psychotics, transported prone, who die suddenly, and in whom autopsy is said to be unrevealing (Reay et al., 1992). Or, as a 1995 publication from the U.S. Department of Justice puts it, "positional asphyxia" occurs as "a result of a body position that interferes with one's ability to breathe — as it occurs within a confrontational situation involving law enforcement officers" (Petty and McDonough, 1995). This same report goes on to state that such deaths are more likely to occur when there is either "cocaine-induced bizarre or frenzied behavior … or drugs and alcohol intoxication" or a "violent struggle extreme enough to require the officers to employ some type of restraint technique."

There is no question that intoxicated, massively obese individuals trapped in confined spaces may not be able to expand their own chests, and the term "positional asphyxia" is appropriately used in such cases. But, this new definition, as defined by the Justice Department, was formulated before the neurochemical changes in excited delirium had been characterized (Staley et al., 1994, 1997; Mash and Staley, 1999), before it was apparent that stimulant abusers have enlarged hearts (Karch et al., 1995), before it was widely recognized by pathologists that myocardial hypertrophy was an independent and potent risk predictor for sudden cardiac death (Frohlich, 1999; Zipes and Wellens, 1998), and before it was demonstrated that "hog-tying," at least of normal-sized individuals (body mass index [BMI] < 30), has no significant effect on respiratory function (Chan et al., 1997, 1998; Schmidt and Snowden, 1999; Elfawal, 2000), at least not those with normal hearts.

Failure to recognize these anatomic and histochemical changes, coupled with incomplete autopsies (no heart weights or heart weight not normalized) and minimal scene investigation, has led to a flood of litigation (Table 1.12.2.12.3.1). Much of the confusion stems from the failure of those involved to properly document what occurred. For example, paramedics, and even medical examiners, more often than not fail to record a victim's temperature, either at the scene or at the time of postmortem examination. If the temperature has not been recorded, proving that a decedent suffered from excited delirium becomes that much more difficult. Similarly, unless strangulation is specifically ruled out at autopsy, considerable liability may result. Meticulous neck dissection is required, and the findings need to be documented photographically. Efforts made during prehospital care require equally precise documentation. Attempts at endotracheal intubation and cardiopulmonary resuscitation may produce petechiae, contusion, and even damage to

Table 1.12.2.12.3.1 Protocol for Excited (Agitated) Delirium Deaths

1. *Training:* Establish protocols that:

   Do not use pepper spray when excited delirium is suspected. It will not subdue the individual, and will only create needless liability.
   Do not hog-tie the victim. If the heart is abnormal, doing so may hasten death.
   Make every effort to transport the patient by ambulance, not police car.
   Never transport an excited delirium patient unattended in a police van.
   Always take excited delirium victims to a hospital, never to a jail.
   Notify the medical examiner immediately of any excited-delirium-like death.
   Document that each officer has learned the protocol.

2. *Neurochemical testing:* Make arrangements with a local university or medical school to process the brain. The University of Miami brain endowment bank has done extensive research in this area and can always be consulted (1-800-UMBRAIN).

3. *Temperature:* Take and record the core temperature of the deceased at the scene. Take and record the ambient air temperature.

4. Interview all witnesses; verify the method of restraint and time to loss of consciousness.

5. If the deceased was transported by ambulance, review paramedic records for temperature and oxygen-saturation measurements.

6. If pepper spray was used, confiscate the unit and weigh it to estimate the amount remaining (as an indication of how much was used).

7. Autopsy protocol to be completed within 24 hours of death:

   a. Remove brain, place 1-cm slices on baking sheet, rinse with saline, freeze with dry ice, and ship to neurochemistry reference lab.

   b. Remove heart and fix prior to examination. Consider consultation with a university-based cardiac pathologist.

   c. Obtain urine, blood samples from right heart, and also brain tissue for toxicologic testing; record sites of sampling

8. Always remove the brain and thoracic organs *before* performing and photographing the neck dissection (prevents artifacts simulating neck trauma).

9. Consider asking family of decedent to designate a forensic pathologist to be present at time of autopsy.

the tracheal mucosa and strap muscles of the neck (Raven et al., 1999). Any one of these artifactual changes could mistakenly be attributed to the effects of neck compression or choke hold. If the resuscitative attempts go undocumented, false accusations of brutality may result.

The presence of petechiae is often cited as proof of death from "positional asphyxia" (Reay et al., 1992), but petechiae around the eyes are not infrequently seen in individuals with heart failure, for whom there is no question of drug abuse or strangulation having occurred (Rao and Wetli, 1988). Petechiae can, and do, occur as a result of resuscitative attempts (Maxeiner and Winklhofer, 1999; Raven et al., 1999), and they may not be apparent until some time has elapsed after death (Kondo et al., 1997; Burke et al., 1998). That being the case, photographic documentation of the absence of petechiae is just as important as documentation of their presence.

The mean cocaine concentration in 45 cases seen by the Miami–Dade County Medical Examiner was 1.32 mg/L (range .05–11.8 mg/L, $n = 34$), while the benzoylecgonine level was 3.78 mg/L (range .08–14.75 mg/L, $n = 38$). In these same deceased individuals, the mean brain cocaine concentration was 1.90 mg/kg (range .05–4 mg/kg, $n = 10$), while the mean benzoylecgonine concentration was 2.69 mg/kg (range .85–3.5 mg/kg, $n = 6$) (Wetli et al., 1996). By comparison, cocaine blood concentrations in a group of 51 trauma victims, where the presence of cocaine was an incidental finding, were not much lower than in victims of excited delirium (Karch et al., 1998).

Questions as to whether the death of these individuals is centrally mediated or a consequence of unrecognized heart disease, and whether either possibility is increased by the process of restraint remain unanswered. In experimental animals, the stress of restraint makes fatal outcomes more likely. Rats injected daily with moderate doses of cocaine (30 mg/kg) and then restrained are three times more likely to die from seizures than rats injected with the same amount of drug and allowed free access to their cages (Pudiak and Bozarth, 1994). However, because seizure activity in actual patients with this syndrome is extremely rare, the relevance of this experimental model is doubtful. It has also been suggested that the mechanism of death may involve a surge of catecholamines released by the stress response, acting upon a myocardium already sensitized by cocaine (Mirchandani et al., 1994).

This last explanation seems to be increasingly probable. As discussed in Section 1.12.2.6, myocardial hypertrophy, even in individuals who are not drug users, is associated with structural changes that increase the risk for arrhythmia and sudden death. Some of these structural changes are clearly related to catecholamine toxicity, while others are the result of myocardial hypertrophy, which can almost always be detected in chronic cocaine users (but only if the heart is weighed and compared to the standard nomogram). Surges in catecholamines produce myocyte damage (contraction band necrosis and damage to vessel walls) and, at the same time, lower the threshold for ventricular fibrillation. The microvasculature changes seen in the hearts of excited delirium patients are highly reminiscent of those seen in hypertensive individuals — a decrease in the lumen of arteriole, as a direct consequence of either vasoconstriction or wall thickening (O'Halloran and Lewman, 1993; Gavin et al., 1998), and these changes also favor ischemia, which lowers the fibrillatory threshold.

Whatever the cause, the syndrome is occurring with some regularity. And, because violent behavior is part of the syndrome, the police are almost inevitably involved, which means that patients with this disease often die in police custody or en route to the hospital (Mirchandani et al., 1994). In some jurisdictions, "Tasers" are used to subdue the violently agitated. This device produces an electrical charge sufficient to produce immobilization. Virtually all fatalities associated with "Taser" use have been patients with excited delirium (Kornblum and Reddy, 1991). It may be that the device activates a stress response similar to being "hog-tied." On the other hand, death and use of the "Taser" could have been purely coincidental.

Similar considerations apply to the pepper sprays used by some police departments. All of the adult deaths associated with pepper spray use have been in individuals with excited delirium, usually in cocaine users. In the absence of laryngeal edema, it is difficult to conceive of a mechanism, or any connection at all, other than that violently psychotic individuals are more likely to be exposed to pepper spray than people who are not psychotic. However, because of low cocaine blood levels at autopsy, because of general misunderstandings about cocaine blood concentrations and the probability of death, because of core temperatures generally not being taken, because of heart weights not being normalized, and because hearts are not examined microscopically, it is hardly surprising

that death is often attributed to use of a choke hold or pepper spray or hog-tying. The other alternative, attributing death to a trivial head injury (minor cerebral contusions or subdural hematomas), is still another obvious temptation best avoided (Mirchandani et al., 1994).

In some cities in the U.S., medical examiners have taken the sensible approach of contacting the deceased's family and asking them to retain their own pathologist to witness the autopsy. In the U.K., this is standard practice. But even the presence of an independent observer may not be enough to prevent litigation or to prevent individuals from confusing temporal proximity of an action, such as hog-tying, with causality. Aristotle identified this type of logical error more than 2000 years ago. One would hope that, in the interim, pathologists would have learned to avoid this mistake and base their decisions on factual analysis, not flawed reasoning.

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1.12.3 Pulmonary disease

Cocaine-related pulmonary disorders can be grouped into four categories: local inflammatory and infectious processes, barotrauma, parenchymal disease, and vascular adaptations. Most of the changes in the upper airway are a result of local inflammatory processes, but all four types of alterations may be seen in the lower portions of the airway.

The effects of cocaine on the upper airway are primarily local. The most common cocaine-induced disorder of the upper airway is perforation of the nasal septum. This disorder has been recognized for nearly 100 years (Maier, 1926). Much less common are chronic inflammatory processes involving the oropharynx. Occasionally, the inflammatory process may be so intense that it mimics limited Wegener's granulomatosis (Becker and Hill, 1988; Deutsch and Millard, 1989; Kuriloff and Kimmelman, 1989; Daggett et al., 1990; Allbery et al., 1995; Sevinsky et al., 1995; Armstrong and Shikani, 1996; Sittel and Eckel, 1998; Carter and Grossman, 2000).

A heterogeneous group of disorders, ranging from decreased diffusing capacity (Itkonen et al., 1984) and pneumomediastinum (Hunter et al., 1986) to bronchiolitis obliterans (Patel et al., 1987), pulmonary edema (Allred and Ewer, 1981), and even pulmonary hypertension, have all been attributed to cocaine use. It is not known with any certainty whether intravenous cocaine abuse carries with it the same increased risks for community-acquired pneumonia associated with intravenous heroin abuse, although there is some suggestion that it may (Baldwin et al., 1997). Results of ongoing clinical studies in cohorts of cigarette, marijuana, and cocaine smokers suggest that habitual cocaine smoking has minor, nonspecific effects on airway responsiveness (thought to be a marker for airway injury) and alveolar structure (Tashkin et al., 1992a,b; Fligiel et al., 1997). Much more severe disease is demonstrable in experimental animals, but the relevance to humans is not known.

Because intravenous cocaine abuse is less common than intravenous heroin abuse and because the contaminants in illicit cocaine are water soluble while those in heroin are not, the complications of intravenous abuse are seen less frequently in cocaine users, but they can occur (Dicpinigaitis et al., 1999). Intravenous cocaine abuse can result in infectious complications such as pneumonia, vascular complications such as foreign particle embolization, and mechanical complications such as pneumothorax. Perhaps the most important difference between intravenous heroin and cocaine abuse is that cocaine users inject themselves much more frequently. As a consequence, they are at a greater risk of developing infectious complications, including HIV infection.

1.12.3.1 *Local inflammation*

Chronic coca leaf chewers may develop stomatitis, glossitis, and buccal mucosal leukoderma (Hammer and Villegas, 1969). The practice of "snorting" probably did not begin until shortly before 1903, the year when the first cases of septal perforation were reported (Maier, 1926). Septal perforation is now a well-known complication of drug abuse (Pearman, 1979), but little is known about the histologic changes accompanying the process. One controlled autopsy study compared histological findings in septal mucosa from 20 individuals with proven histories of chronic nasal inhalation of cocaine, and 15 controls. As might be expected, chronic inflammatory disease was seen in the cocaine users. The glandular elements were in total disarray, and mononuclear cells, particularly lymphocytes, were seen surrounding arterioles and glands (Chow et al., 1990).

An unexpected finding in cocaine users was the presence of thickened submucosal arterioles. Intimal hyperplasia and fibrosis of these vessels was evident in the majority of cases. There was also increased perivascular deposition of collagen. The arterial findings were similar to, but not nearly so marked as, those that have been observed in the coronary arteries of cocaine users (Simpson and Edwards, 1986; Roh and Hamele-Bena, 1990), or in cases of catecholamine toxicity (Szakacs et al., 1959). Sampling septal mucosa at autopsy might prove quite useful in confirming a suspected diagnosis of cocaine toxicity, as the finding would suggest a pattern of chronic prior use; however, this observation has never translated into common practice. Even if sections of the septum are not obtained, the mucosa should be swabbed with saline, because cocaine may be recovered for some time, possibly days, after it was last used.

Besides the changes in the septum, upper respiratory tract necrosis, sometimes on a fairly massive scale, also occurs (Becker and Hill, 1988; Deutsch and Millard, 1989; Daggett et al., 1990; Allbery et al., 1995; Sevinsky et al., 1995). The etiology is thought to be ischemic, secondary to chronic cocaine-induced vasoconstriction, but it could also be secondary to contaminants in the inhaled cocaine. Biopsies of a posterior oropharyngeal ulcer in one patient showed only necrosis and a mixed inflammatory cell infiltrate, and there is nothing diagnostic about the tissue changes. The causative role of cocaine is usually confirmed by the resolution of the lesions with cocaine abstinence. In the living, computed tomography remains the preferred imaging modality for evaluating nasal masses that contain calcification, or that originate from bone or cartilage.

Pott's puffy tumor, an old name for subperiosteal abscess of the frontal bone associated with underlying frontal osteomyelitis, has rarely been reported in stimulant abusers. This complication of frontal sinus infection was once fairly common, but the introduction of antibiotic medications has made it something of a rarity. When it does occur in cocaine (Noskin and Kalish, 1991) or methamphetamine users (Banooni et al., 2000), the underlying mechanism presumably has something to do with recurrent vasospasm and ischemia of the underlying tissue favoring the spread of infection.

Some individuals sustain upper airway burns, caused by the inhalation of hot particulate matter from inadequately filtered "crack" pipes (Bezmalinovic et al., 1988; Snyderman et al., 1991; Reino and Lawson, 1993). Some of these patients experience severe stridor, but others may have uvular edema without apparent respiratory distress. No predictable pattern of symptoms suggests upper airway injury as a consequence of cocaine use (Reino and Lawson, 1993). More recently there have been reports of burns resulting from aspiration of the filter used in "crack" pipes. Many of the pipes used to smoke "crack" cocaine contain a small wire screen or mesh, sometimes made from Brillo™ or steel-wool scouring pads. These filters can be aspirated, resulting in unilateral superglotitis (McQueen et al., 1995) or damage to the posterior arytenoids (Moettus and Tandberg, 1998).

1.12.3.2 Barotrauma

The general classification of barotrauma includes disorders where increased intra-alveolar pressure or decreased interstitial pressure leads to rupture of an alveolus with leakage of air. Whether pneumothorax or pneumomediastinum occurs depends on the location of the alveolus. Increased intra-alveolar pressure is usually the result of coughing or performing the Valsalva maneuver, which "crack" smokers routinely do. There are, however, other possibilities. Pulmonary inflammation could weaken the alveolar wall and lead to leakage of air. Alternatively, vasoconstriction in the vessels adjacent to an alveoli could cause decreased interstitial pressure, leading to alveolar rupture without any great increase in intra-alveolar pressure (Macklin and Macklin, 1944; Deutsch and Millard, 1989; Seaman, 1990; Chan et al., 1997; Uva, 1997). In cocaine users, all of these possibilities should be considered.

Another possible cause for pneumo- and hemothorax is injection into central veins, although this practice is much more common in heroin abusers. Heroin tends to be adulterated with material that is not water soluble. Repeated injections of adulterated heroin can lead to sclerosis of peripheral veins. When that happens, the users are forced to inject central veins. The two most popular central sites are the great vessels in the neck ("pocket shot") (Lewis et al., 1980) and the vessels of the femoral triangle ("groin shot") (Pace et al., 1984). Injections are made into the general area of the supraclavicular fossa (Figure 1.12.3.2.1), either by the addict himself or by a hired "street doc." Because the lung apex is directly contiguous with the area, pneumothorax commonly results (Kurtzman, 1970; Merhar et al., 1981; Douglas and Levison, 1986).

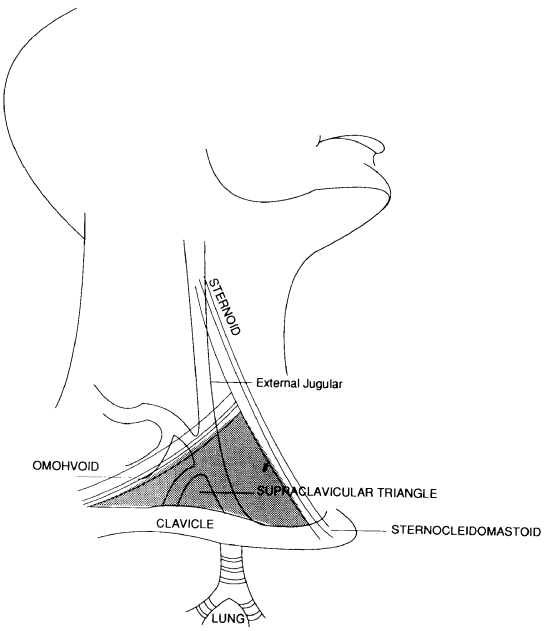

Figure 1.12.3.2.1 **The supraclavicular fossa.** As peripheral veins become sclerosed, chronic abusers resort to injecting themselves in the supraclavicular fossa and in the femoral triangle. The supraclavicular fossa overlies the great vessels and the apex of the lung. Pneumothorax and hemothorax are the predictable results.

Cocaine-associated pneumomediastinum occurs with some frequency (Shesser et al., 1981; Bush et al., 1984; Morris and Shuck, 1985; Aroesty et al., 1986; Hunter et al., 1986; Mir et al., 1986; Schweitzer, 1986; Luque et al., 1987; Salzman et al., 1987; Brody et al., 1988; Leitman et al., 1988; Savader et al., 1988; Christou et al., 1990; Sullivan and Pierson, 1997). Because pneumomediastinum is a benign condition and no fatal cases of pneumothorax have been reported, no autopsy studies have been done. Presumably, the mechanism has to do with the performance of a Valsalva maneuver by a deeply inhaling smoker. No cases have been reported after intravenous or intranasal use.

Surprisingly, barotrauma has not been proposed as the mechanism for the increasing number of cocaine-related strokes that have been reported (see Section 1.12.5.2), but it might offer just as good an explanation as cocaine-induced vasospasm. Air from ruptured alveoli may diffuse into pulmonary capillaries and veins, then pass through the left side of the heart and embolize via the systemic arteries to the brain. This possibility seems especially likely, now that the role of atrial septal defect in stroke is increasingly being recognized (Berthet et al., 2000). The diagnosis of barotrama as the cause of stroke would be particularly difficult to make. If the patient survives for more than a few hours, the air bubbles will have dissolved and typical morphologic changes (multiple small, well-circumscribed foci of cortical necrosis, sometimes associated with laminar necrosis) will not have had time to develop (Wolf et al., 1990).

1.12.3.3 Parenchymal disease

"Crack" smokers tend to have carbonaceous sputum and, not infrequently, emphysematous changes in their lungs. The pattern is readily apparent in microscopic sections, even before they are placed under the microscope; it is highly reminiscent of the pattern seen in "coal miner's lung." Sputum from these individuals is usually turbid, gray or even black, and considerably darker than sputum seen in heavy tobacco smokers dwelling in the same urban environment. Microscopic examination of sputum from "crack" smokers has disclosed excessive carbonaceous material in the cytoplasm of pulmonary alveolar macrophages and also in the extra cellular compartment of sputum smears (Figure 1.12.3.3.1) (Klinger et al., 1992; Greenebaum et al., 1993). Carbon-laden macrophages can also be found in the pleural fluid of "crack" smokers who develop malignancy or HIV-related pulmonary disease (Singh et al., 1995).

Pulmonary congestion and edema are common findings in drug-related deaths. Osler first wrote about morphine-induced pulmonary edema over 100 years ago (Osler, 1880), and turn-of-the-twentieth-century pathologists recognized a connection between pulmonary congestion and opiate-related deaths (Hamilton, 1894). Pulmonary congestion in cocaine-related deaths was also recognized at the turn of the twentieth century, but pulmonary edema in cocaine users can also be observed in nonfatal cases (Purdie, 1982; Cucco et al., 1987; Efferen et al., 1989; Hoffman and Goodman, 1989; Bakht et al., 1990; Kline and Hirasuana, 1990; Batlle and Wilcox, 1993; Raijmakers et al., 1994).

The etiology of cocaine-associated pulmonary edema is obscure; however, the relatively low protein content of the edema fluid (it does not froth like the edema fluid seen with heroin overdose) suggests that it is of cardiogenic, not neurogenic origin (Robin et al., 1989; Simon, 1993). Pulmonary edema in cocaine users could be just another manifestation of catecholamine toxicity of the lungs, or the heart, or both (Kurachek and Rockoff, 1985; Karch, 1989).

Cocaine itself and the catecholamine excess that occurs in association with cocaine use both decrease myocardial contractility (Strichartz, 1987; Perreault et al., 1989). If contractility is depressed enough to lower cardiac output, heart failure and pulmonary

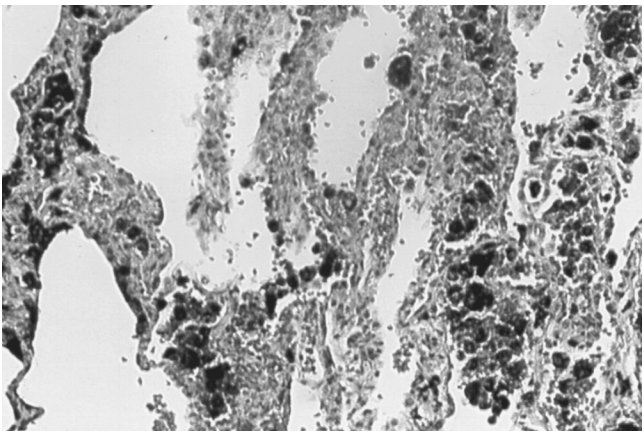

Figure 1.12.3.3.1 **Pulmonary anthracosis.** The lungs of crack smokers often are emphysematous and contain dense carbonaceous deposits. The changes can be apparent to the naked eye. Hemosiderin-laden macrophages are often present, probably reflecting recurrent bouts of focal hemorrhage. (San Francisco Medical Examiner Case No. 95-701.)

edema will develop. Another possible mechanism might be a direct effect of cocaine on the lungs. It has been suggested that the local anesthetic action of cocaine impairs the movement of sodium and fluid across the alveolar epithelium (Raijmakers et al., 1994). Parenteral administration of cocaine to rats results in lung damage with remarkable thickening in some inter-alveolar septa, along with interstitial hemorrhages, progressive thrombosis, and transformation of reticular and elastic fibers into diffusely fibrotic tissue. These findings are indicative of severe cocaine-induced microvascular disease (Barroso-Moguel et al., 1999). The typical alveolar changes seen in this animal model are seen in Figure 1.12.3.3.2.

The pattern of fibrosis seen in experimental models is also seen with some frequency in humans, but even more common is the presence of hemosiderin-laden macrophages. This change was first recognized in narcotic abusers (Siegel, 1972; Rajs et al., 1984; Strichartz, 1987), but similar macrophages are commonly seen in the subgroup abusing cocaine. Hemosiderin-laden cells are not seen in any particular relationship to recent hemorrhage, and their etiology is obscure. Siegel (1972) thought that hypoxia was in some way responsible. That theory has never been proven, but the possibility certainly exists that focal vasospasm, such as that demonstrated in the pulmonary bed of experimental animals, could result in localized ischemic changes. Whether the changes would be similar to those produced by generalized hypoxia, as seen in opiate abusers, is not clear.

Direct toxicity is another, unproven, possibility. Diffuse alveolar hemorrhage has been described, and clinical reports suggest that spontaneously resolving hemoptysis is not that uncommon among cocaine smokers (Murray et al., 1988; Forrester et al., 1990; Bouchi et al., 1992; Garcia-Rostan y Perez et al., 1997; Gallouj et al., 1999). Retrospective autopsy studies of cocaine users have disclosed hemorrhages and hemosiderin-laden macrophages in 27 to 58% of the patients (Murray et al., 1988; Bailey et al., 1994). Bailey et al. (1994) found evidence for acute or chronic hemorrhage in 71% of cases, even in the absence of any clinical history, suggesting massive hemoptysis, and concluded that relying on that particular clinical sign would lead to serious underestimation of how frequent alveolar hemorrhage actually was in crack smokers. On the other hand, longitudinal studies of

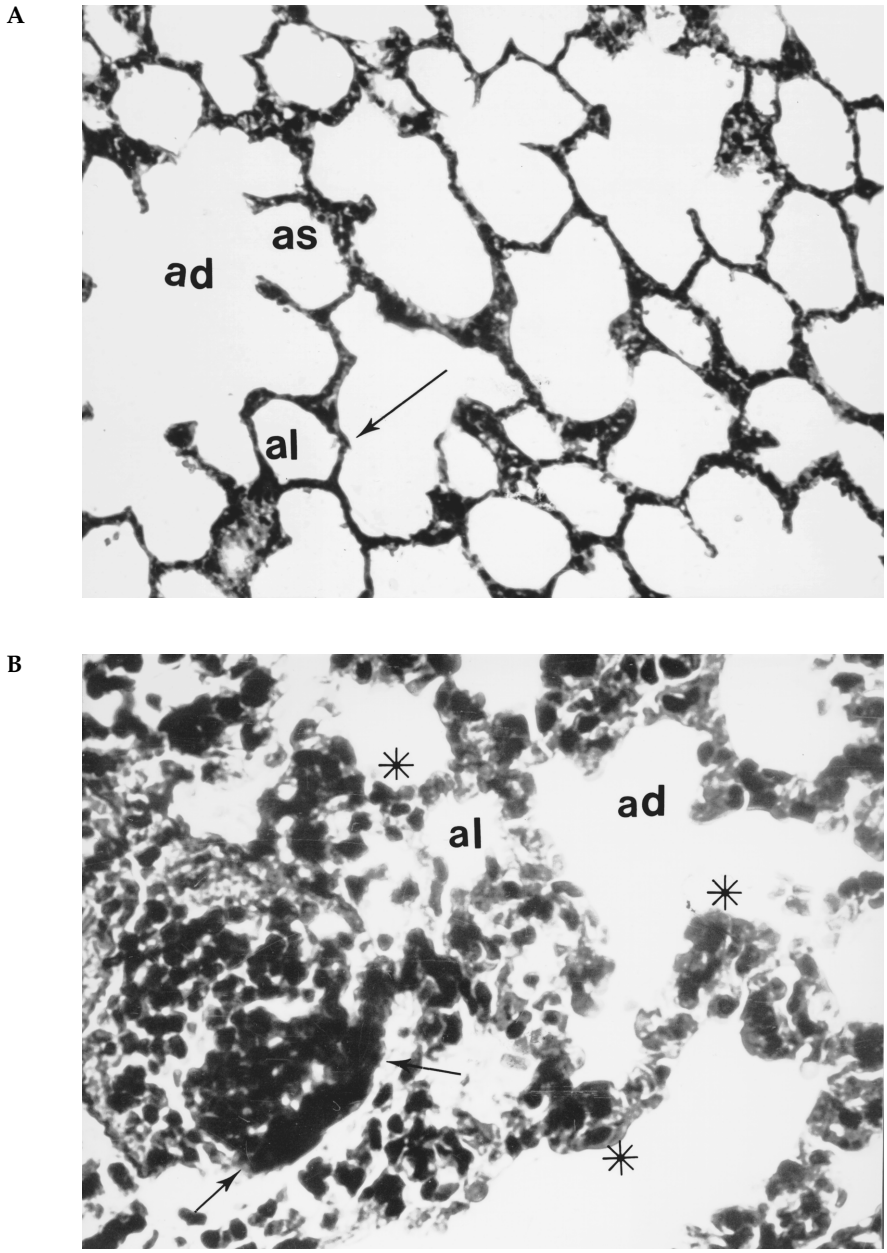

Figure 1.12.3.3.2 **Typical alveolar changes. (A)** Control rat in which the alveolar ducts (ad), sacs (as), and alveoli (al) are all normal; the arrows point to an alveolar wall of normal thickness. **(B)** Alveolar hemorrhage (arrows) in a rat after 30 days of treatment with 30 mg/kg/day of intraperitoneal cocaine; the lumen of the ducts and alveoli are narrowed by fibrous wall thickening. **(C)** After 45 days of treatment, intense cellular proliferation and increasing thickness of the alveolar walls result; arrows in the upper right show a collection of macrophages with cytoplasmic granulation. **(D)** After 75 days of treatment, the alveoli are deformed and the interstitial space is filled with necrotic cells; arrows point to occluded and collapsed capillaries. All four sections were stained with Masson's Trichrome, 100×. (From Barroso-Moguel, R. et al., *Toxicol. Lett.*, 110(1–2), 113–118, 1999. With permission.)

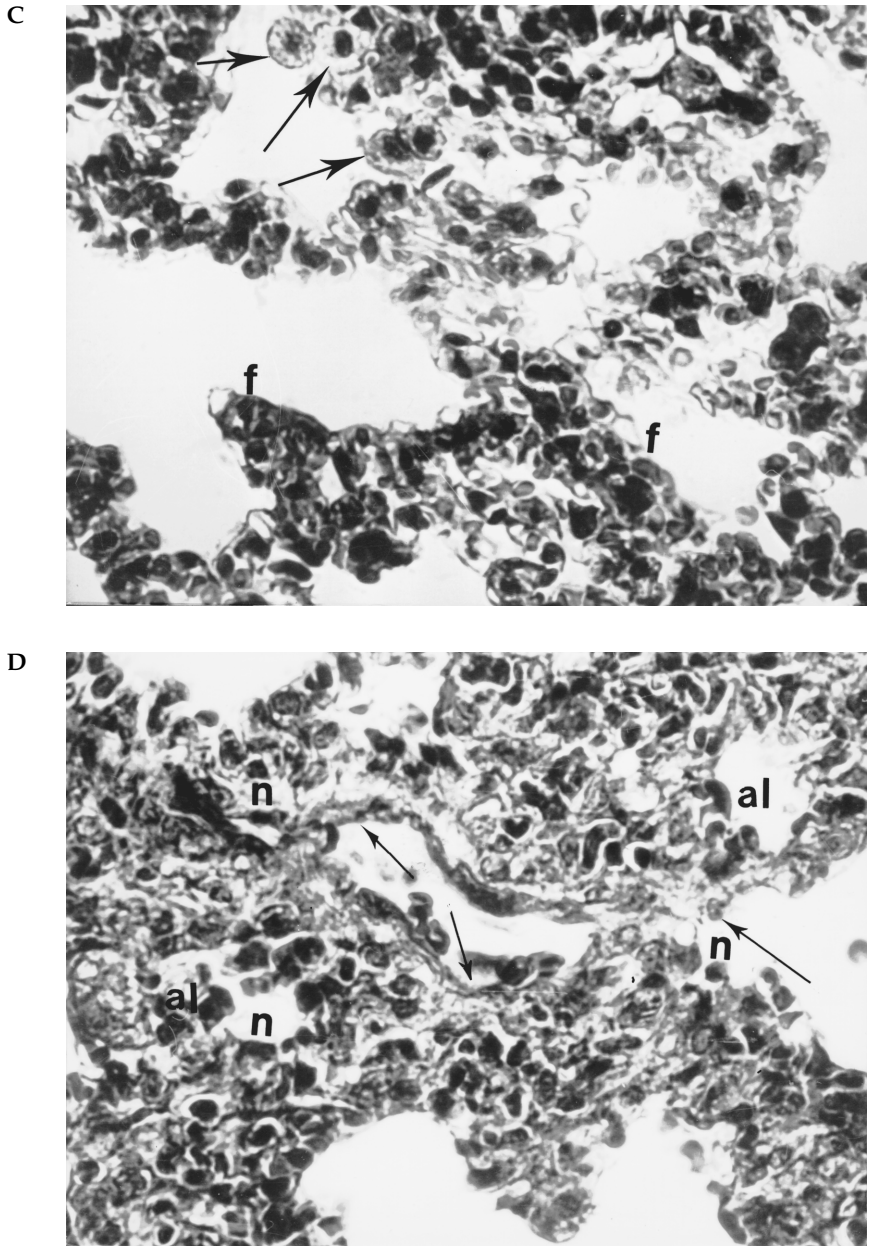

Figure 1.12.3.3.2 **Typical alveolar changes (continued).**

human "crack" smokers have shown that regular smoking of tobacco alone or with other substances increases alveolar epithelial permeability. Habitual smoking of cocaine and/or marijuana has no measurable effect on alveolar permeability unless tobacco is smoked at the same time (Tashkin et al., 1997).

Even though interstitial fibrosis is a common occurrence in cocaine users, the incidence of this change is much higher in narcotic abusers (>90%) (Kringsholm and Christoffersen,

1987). This finding may simply be the result of alveolar deposition of particulate matter (Klinger et al., 1992). Thus, the presence of iron-containing macrophages has little diagnostic value and is, in fact, more consistent with a history of narcotic abuse than with cocaine abuse.

The smoking habits of "crack" smokers can sometimes produce diagnostic changes in the appearance of their sputum. The sputum is often very dark in color due to intracellular pigment found within pulmonary alveolar macrophages, and extracellular carbonaceous pigment fragments can be found floating free. Fragments may measure up to 1 mm across. Similar changes may be seen in the sputum of city dwellers living in regions with poor air quality, but the changes seen in "crack" smokers are of a different magnitude. It has been suggested that the black sputum is a consequence of the smoking habits of "crack" users. As "crack" is smoked, a dark tarry residue forms in the "crack" pipe. Some "crack" smokers believe that the residue contains concentrated cocaine, so they scrape it off and smoke it. Normally, pulmonary macrophages would collect and remove the concentrated residue, but, if the process is repeated enough times, it can overload the normal clearance mechanisms of the lungs, and black sputum results (Greenebaum et al., 1993).

Prior to the advent of smokable cocaine, mentions of cocaine-related pulmonary disease were rare. As smoking cocaine became more popular, reports of patients with inflammatory infiltrates, sometimes associated with fever, hypoxia, hemoptysis, and even respiratory failure, began to appear (Forrester et al., 1990). Specimens from several of these patients have demonstrated diffuse alveolar damage with hyaline membrane formation and type II cell hyperplasia, as well as intra-alveolar and interstitial inflammatory infiltrates with eosinophilia. Some cocaine users for whom x-rays demonstrated inflammatory infiltrates have had peripheral eosinophilia (Mayron et al., 1972; Murray et al., 1988) while others did not (Cucco et al., 1987; Kissner et al., 1987; Patel et al., 1987; Forrester et al., 1990; Talebzadeh et al., 1990; Oh and Balter, 1992; Nadeem et al., 1994).

A recent case report describing a sarcoid-like syndrome in a 39-year-old "crack" smoker who presented with shortness of breath raises the possibility that inhaled contaminants might be responsible for some of the pulmonary changes. X-rays showed bilateral interstitial pulmonary infiltrates and hilar adenopathy, diffuse pulmonary uptake of gallium, and markedly elevated serum angiotensin-converting enzyme activity. An open lung biopsy demonstrated interstitial and perivascular collections of histiocytes containing retractile, polarizable material, presumably inhaled along with the cocaine. Paratracheal lymph nodes were enlarged and reactive, and contained similar polarizable material, but non-necrotizing granulomas, of the type expected in cases of sarcoid, were absent (Dicpinigaitis et al., 1999). It is tempting to conclude that either the birefringent material itself, or some other agent inhaled along with it, was responsible for the change.

Hypersensitivity-induced lung disease occurs. Biopsy specimens from symptomatic cocaine users have shown deposition of IgE in both lymphocytes and alveolar macrophages (Forrester et al., 1990), and eosinophilic infiltrates have been observed in the hearts of some of these individuals (see Section 1.12.2.11 for a discussion of eosinophilic infiltrates in myocardium). The pulmonary findings could be just another manifestation of the same underlying process. Both Goodpasture's syndrome (diffuse alveolar hemorrhage with extremely acute respiratory distress followed by renal failure with anuria) (Garcia-Rostan y Perez et al., 1997) and cocaine-induced Churg–Strauss eosinophilic angiitis (relapsing fever, bronchoconstriction, arthralgias, and weight loss, with pulmonary infiltrates, arthritis, microhematuria, skin rash, and mononeuritis multiplex) (Orriols et al., 1996) have been reported in cocaine users. The difficulty with ascribing cause and effect is that victims are inevitably polydrug abusers, and there is no way to know which drug is the culprit.

Finally, the high rate of HIV infection among intravenous drug users should not be forgotten. Most of the pathology encountered in cocaine users is noninfectious. But, like other patients with HIV infection and AIDS, any number of opportunistic and nonopportunistic infections can be encountered. Univariate analysis of HIV seropositive individuals with bacterial pneumonia has shown that "crack" smoking is a more powerful predictor than the CD4 count (Caiaffa et al., 1994).

1.12.3.4 Vascular adaptations

Observations from several case reports suggest that "crack" smokers may be subject to vasospasm, sometimes sufficiently intense to simulate the radiographic appearance of pulmonary embolism (Delaney and Hoffman, 1991; Smith et al., 1995). Hypertrophy of the smooth muscle in the walls of pulmonary arteries along with proliferation of the elastic fibers, changes consistent with the diagnosis of pulmonary hypertension, can occur. This alteration is seen in the lungs of heroin abusers and is the result of intravascular deposition of foreign materials that have been injected along with the heroin. Granuloma formation results and sets in motion a series of events that eventually leads to pulmonary hypertension. The three agents most commonly responsible for granuloma formation are talc, cornstarch, and microcrystalline cellulose (Radow et al., 1983). All three materials are strongly birefringent. Starch granules are particularly simple to identify because they exhibit the "Maltese cross" pattern when viewed with polarized light. Particles can also be differentiated by their staining properties. Both starch and cellulose are PAS-positive, while microcrystalline cellulose stains black with GMS stain (Tomashefski and Hirsch, 1980; Tomashefski et al., 1981).

A different mechanism appears to be involved in cocaine abusers; α_1-adrenergic receptors are present on vascular smooth muscle cells that regulate vascular tone and growth in the lung. Those receptors, located on the small- and medium-sized pulmonary arteries, are exquisitely sensitive to the presence of α_1-adrenergic agonists. Excessive stimulation of these receptors causes smooth muscle to contract, but, perhaps more importantly, it also causes smooth muscle in the vessel walls to grow. Abnormally high concentrations of α_1-adrenergic agonists are always present when hypoxia occurs or when exogenous agonists, such as appetite suppressants (e.g., fenfluramine), methamphetamine, or cocaine, are administered (Salvi, 1999).

In autopsy studies of heroin and polydrug abusers, the incidence of medial hypertrophy of small- and mid-sized pulmonary arteries has ranged from 8% (Hopkins, 1972) to as high as 40% (Rajs et al., 1984). The mechanism, however, remains controversia. In at least two controlled studies intravenous drug users with multiple talc-induced granulomas there was no more medial hypertrophy than in controls (Tomashefski et al., 1981; Kringsholm and Christoffersen, 1987). Medial hypertrophy and talc granulomas can also be seen in the lungs of cocaine users. Murray et al. (1989), examined the lungs of 20 individuals who had died of cocaine intoxication. Individuals with histories of polydrug abuse, or with toxicology screens that were positive for drugs besides cocaine, were specifically excluded from the study. Also excluded were cases in which birefringent material was found within the lungs. Four of the patients studied (20%) were found to have medial hypertrophy involving either the small- or medium-sized pulmonary arteries. Murray and co-workers suggest that chronic exposure to cocaine-induced high levels of catecholamines may have resulted in pulmonary hypertension. Other authors have made the same suggestion (Itkonen et al., 1984). The variable rates of medial hypertrophy found in different autopsy studies may be explained by the drug-use practices of the local populations. Narcotic abuse is not associated with catecholamine excess, but stimulant abuse is.

The problem with the catecholamine thesis is that patients with pheochromocytoma frequently develop pulmonary edema (Okada et al., 1999; Huddle et al., 1991; Fahmy et al., 1997) but are not prone to pulmonary hypertension, except as a consequence of heart failure (Rose et al., 1988). The patients in Murray's study with medial hypertrophy had no other signs of heart disease. Without more data, the significance of medial hypertrophy in the lungs of cocaine users is impossible to assess, especially because granulomatous changes can also be seen in the lungs of individuals who only sniff cocaine. Cellulose granulomas were identified in a patient who denied intravenous drug use and who had no occupational exposure to cellulose products (Cooper et al., 1983). Talc granulomas have been identified in two other patients (Buchanan et al., 1981; Oubeid et al., 1990).

Finally, the great vessels of the neck are subject to mechanical injury. "Pocket shooters" may lacerate the brachial, subclavian, or jugular veins. Hemothorax, hematoma, and pseudo-aneurysm are all recognized complications of central venous injection. Because the material injected is far from sterile, local and distant complications may occur. Mycotic aneurysm formation, local cellulitis, and abscess formation have all been described, although the incidence is much higher in heroin than in cocaine users (McCarroll and Roszler, 1991).

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1.12.4 Gastrointestinal disorders

Most of the gastrointestinal problems associated with cocaine use are due to catecholamine-mediated effects on blood vessels. However, cocaine metabolites, and possibly cocaine itself, may be directly toxic to the liver. Norcocaine is hepatotoxic in experimental animals, and so is cocaethylene, which is synthesized by the liver in the presence of ethanol. The overall toxicity of cocaethylene is very similar to that of cocaine itself. In spite of convincing animal studies, there is no evidence that cocaine use results in any significant human hepatotoxicity.

1.12.4.1 Ischemic bowel and stomach injuries

Ischemic colitis due to cocaine abuse, a well-recognized entity (Fishel et al., 1985), was first described in 1985 and regular reports have been published since then (Nalbandian et al., 1985; Mizrahi et al., 1988; Garfia et al., 1990; Endress and King, 1990; Freudenberger et al., 1990; Hon et al., 1990; Nathan and Hernandez, 1990; Czyrko et al., 1991; Riggs and Weibley, 1991; Yang et al., 1991; Endress et al., 1992; Hall et al., 1992; Mustard et al., 1992; Hazanas et al., 1993; Brown et al., 1994; Ottolini and Foster, 1994; Fishel et al., 1985; Kodali and Gordon, 1995; Pugh et al., 1995; Jawahar et al., 1997; Niazi et al., 1997; Hoang et al.,

1998; Simmers et al., 1998; Papi et al., 1999). In spite of all the case reports, the actual incidence of cocaine-related ischemic bowel is low. The case originally described by Fishel was that of a 37-year-old with right lower quadrant pain and diarrhea. A right hemicolectomy was performed for removal of a mass that proved to be an inflamed cecum. Microscopic examination of the removed bowel disclosed "findings consistent with pseudomembranous colitis and some areas that were suggestive of ischemic colitis." In the case reported by Endress, the ilium had zones of hemorrhage and ulceration, but no particularly distinctive features (Endress and King, 1990). Since that original report, cocaine-related pseudomembranous enteritis has also been described (Niazi et al., 1997).

In the largest series published to date, which was comprised of seven patients, endoscopy demonstrated lesions that were restricted to the left colon, including hemorrhagic edema of the mucosa, pseudopolyps, and ulcerations. Rectal involvement, which is not generally considered a feature of ischemic colitis, was seen in five patients. These histologic changes were classified as acute/subacute in two of the five patients and as subacute/chronic in the other three (Niazi et al., 1997). Given that genital cocaine application is not that uncommon, it could be that the rectal involvement noted in two of the cases had as much to with sex practices as with drug-induced ischemia.

Mounting evidence suggests that "crack" cocaine smokers may constitute a specific subgroup of patients with ulcer perforation due to an acute ischemic event, rather than as a complication of chronic ulcer disease (Lee et al., 1990). In the early case reports, perforation appeared more likely to be duodenal than gastric (Abramson et al., 1989; Fennell et al., 1995). More recent studies implicate *Helicobacter pylori* and suggest that, at least in the inner cities, the frequency of this disorder is rising rapidly. A report published in 1999 described 50 consecutive patients with juxtapyloric perforations related to "crack" smoking who were seen in one inner-city hospital over a 4-year period. All but two of the patients were men, with a mean age of 37 years. However, in addition to being "crack" smokers, all had histories of chronic alcohol abuse. A 3- to 5-mm juxtapyloric perforation, usually in the prepyloric area, was found in all the patients. Antral mucosal biopsies were performed through the juxtapyloric perforation in five patients, and urease testing was positive for infection with *H. pylori* in four (Feliciano et al., 1999).

Ulceration in cocaine users could be a direct result of ischemia or excess acid accumulation due to arteriolar vasoconstriction in the gastric mucosa that allows excess acid to accumulate (Marrone and Silen, 1984); what factors, if any, favor the growth of *H. pylori* in this subgroup are yet to be established. Furthermore, it remains unclear whether ischemia itself is a consequence of recurrent vasospasm or is the result of celiac axis and superior mesenteric artery thrombosis, both of which have been demonstrated (Herrine et al., 1998; Hoang et al., 1998).

Maternal cocaine use appears to be in some way related to the occurrence of necrotizing enterocolitis in the neonate. The etiology of this disorder is not known, and cocaine abuse is far from the only factor thought to be related to its occurrence (Downing et al., 1991; Amoury, 1993). Cocaine is just the most recent addition to the list. The likelihood of a connection is strengthened by the fact that identical pathologic changes have been induced in a rat model (Büyükünal et al., 1994). Whatever the etiology, air accumulates in the submucosal or subserosal layers of the bowel wall, sometimes coalescing into visible blebs, with fluid and blood accumulating in the lumen.

The ileum and proximal colon are the segments most commonly involved; however, the distribution of lesions can be very spotty, with diseased and normal segments interspersed. The mucosa is inflamed, with fluid and blood extravasated into the bowel wall. Gangrenous changes are not uncommon, though differentiating hemorrhagic from gan-

grenous segments at the time of surgery may be difficult. Single or multiple perforations may be present and are usually found on the antimesenteric aspect of the bowel. Localized swelling in any portion of the bowel may allow it to act as a lead point for intussusception (Ottolini and Foster, 1994). Interestingly, the incidence of this disorder seems to have decreased, with no new case reports having been published for several years.

Mesenteric blood flow in swine injected with cocaine decreases enough to produce ischemic changes in the bowel wall (Hebra et al., 1993). The role of catecholamine excess is strongly suggested by the occurrence of bowel obstruction and ischemia, with similar pathologic findings, in patients with pheochromocytoma (Bravo and Gifford, 1993). Obstruction is also seen as a complication of multiple endocrine neoplasia (Grobmyer et al., 1999). Khafagi et al. (1987) described a patient with extremely high catecholamine levels who developed pseudo-bowel obstruction that rapidly resolved with intravenous phentolamine infusions. In fact, catecholamine-mediated gastrointestinal lesions have been recognized since the 1930s, when treatment of asthmatics with nebulized epinephrine came into fashion. Occasionally, treatment was complicated by tracheal hemorrhages and ulceration of the gastrointestinal mucosa (Galgaini et al., 1939).

Szakacs et al. (1959) systematically studied the effects of chronic catecholamine administration in experimental animals and humans. Szakacs and his co-workers reported that fibrinoid degeneration and necrosis could be seen in the arteriolar walls of vessels, both in the heart and in the gastrointestinal tract. Prolonged norepinephrine infusion induced endothelial proliferation, occasionally sufficient to cause "complete obstruction of small arteries of the gastrointestinal tract, leading to infarction and perforation of the bowel" (Szakacs et al., 1959). Similar lesions are observed in experimental animals and in patients with pheochromocytoma. More than 40 years after Szakacs first presented his observations, precisely the same lesion has been identified in cocaine users (Garfia et al., 1990). Thrombotic lesions have also been described, presumably caused by the same sequence of events that lead to thrombosis in the heart and other blood vessels (Ottolini and Foster, 1994). The bowel is not the only part of the gastrointestinal tract subject to ischemic injury. There is at least one report of spontaneous hepatic rupture in a pregnant cocaine user, presumably a result of the same mechanism responsible for ischemic gut injury (Moen et al., 1993).

1.12.4.2 Hepatic disease

Hepatocellular necrosis can be produced in animal models of cocaine toxicity. Clinical studies of chronic cocaine abusers have provided contradictory results. One study found significant transaminase elevations in chronic cocaine users (Marks and Chapple, 1986), but other studies failed to demonstrate liver function abnormalities or showed only minimal enzyme changes (Kothur et al., 1991). Normal liver function has been observed in both parenteral (Rippetoe et al., 1991) and non-parenteral users, provided the users were not hepatitis B carriers (Tabasco-Minguillan et al., 1990). In the only large autopsy series where the liver was examined, the only abnormality consistently present was passive venous congestion (Karch et al., 1999a). This is in some contrast to findings for other stimulant drugs, particularly methamphetamine, where hepatic steatosis is a relatively frequent finding (Karch et al., 1999b).

The relative absence of cocaine-related liver disease in humans has to do with the fact that oxidative cocaine metabolism plays a very minor role in humans. In animals, however, cytochrome P-450 and flavin-adenine-dinucleotide-containing monooxygenase metabolize significant amounts of cocaine to norcocaine. Further enzymatic breakdown yields *N*-hydroxynorcocaine and norcocaine nitroxide (Shuster et al., 1977). Norcocaine nitroxide,

once thought to be a highly reactive free radical, is now known to be stable. It does not react with either proteins or glutathione (Rauckman et al., 1982). However, further oxidation to the norcocaine nitrosodium ion produces a compound that is highly reactive with glutathione (Ndikum-Moffor et al., 1998).

If glutathione stores fall below a certain level, lipid peroxidation goes unopposed and cocaine metabolites accumulate, bind to hepatic proteins, and eventually lead to cell death (Evans, 1983; Kloss et al., 1984a,b). Necrosis is worse if animals are pretreated with agents that induce P-450 synthesis and less if they are treated with P-450 inhibitors. In animals, one of two different patterns may be observed. Fatty infiltration and periportal inflammation occur with periportal (Freeman and Harbison, 1981; Evans 1983) or centrolobular (Shuster et al., 1977) necrosis. Both types of necroses can be prevented if the animals are pretreated with P-450 inhibitors (Evans, 1983).

The first case of human hepatotoxicity to be reported was that of a polydrug abuser who had sustained a cardiac arrest. In addition to cocaine, his toxicology screen was positive for alcohol and barbiturates, but negative for acetaminophen. Examination of the liver disclosed a zone-1 type injury, with periportal necrosis and sparing of the centrozonal hepatocytes (Perino et al., 1987). A 24-year-old with fulminant liver failure, with toxicology testing negative for all drugs except cocaine, was described in a second case report. Morphologic features included coagulative-type perivenular and midzonal necrosis, along with periportal microvesicular fatty change (Kanel et al., 1990). Another report described a group of four patients, two with well-demarcated zone-3 necrosis identical to that seen in cases of acetaminophen poisoning (Wanless et al., 1990). In spite of these suggestive case reports, at least two separate autopsy studies of cocaine-related deaths found that the livers of the cocaine users are no more likely to show evidence of liver damage than controls (Copeland, 1989; Karch et al., 1998).

In the first study ever to report simultaneous measurements of cocaine and its metabolites in living patients, only very low concentrations of norcocaine were detected in most individuals who had ingested doses of cocaine (standard volume of distribution [V_d] calculations suggest that some of the patients in the study had consumed more than 3 g of cocaine before seeking emergency medical treatment). In 46 "crack" smokers, the mean norcocaine concentration was 40 ± 3 ng/mL compared to benzoylecgonine concentrations that were more than 33 times higher (1400 ± 40 ng/mL) (Blaho and Winberry, 2000). However, in some individuals, for reasons that remain entirely obscure, norcocaine concentrations in the 400- to 500-ng/mL range were observed, indicating that, under appropriate circumstances, humans are capable of oxidative cocaine metabolism. The fact that this ability is limited to a small percentage of cocaine users suggests the presence of a genetic link.

Most cytochrome P-450 activity is located in zone 3 of the liver, so it is not surprising to find that acetaminophen and cocaine cause similar lesions. The difficulty in predicting a pattern of injury in humans is that humans use multiple drugs, and these drugs can induce, or block, the P-450 system (Bornheim, 1998). The first patient described had used alcohol and barbiturates. Both of these agents are capable of inducing the P-450 system. Until more cases of liver injury have been reported, it would be unwise to consider any pattern of hepatic injury as diagnostic for cocaine toxicity. Conceivably, a patient could develop hepatic failure secondary to acetaminophen ingestion and incidentally test positive for cocaine metabolism. The presence of zone-3 lesions would not, then, be proof of cocaine toxicity. The likelihood of hepatic injury is increased by concurrent retroviral infection (Odeleye et al., 1992). The incidence of liver disorders in drug users may well rise as HIV infection becomes more widespread.

An additional possibility to be considered is that hepatic injury could be secondary to cocaethylene production. This compound is produced in the liver, by transesterification, but only in the presence of ethanol (Kanel et al., 1990). In animal experiments, cocaethylene is nearly as toxic as cocaine itself and, when experimental animals are simultaneously treated with ethanol and cocaine, tissue necrosis, presumably secondary to lipid peroxidation, is much worse than when the animals are treated with cocaine alone (Figure 1.12.4.2.1) (Odeleye et al., 1992). When cocaethylene is given to mice, it produces dose-dependent hepatic zone 2 (midlobular) necrosis. Pretreatment with cytochrome P-450 inducers makes the necrosis worse and shifts the zone of necrosis to zone

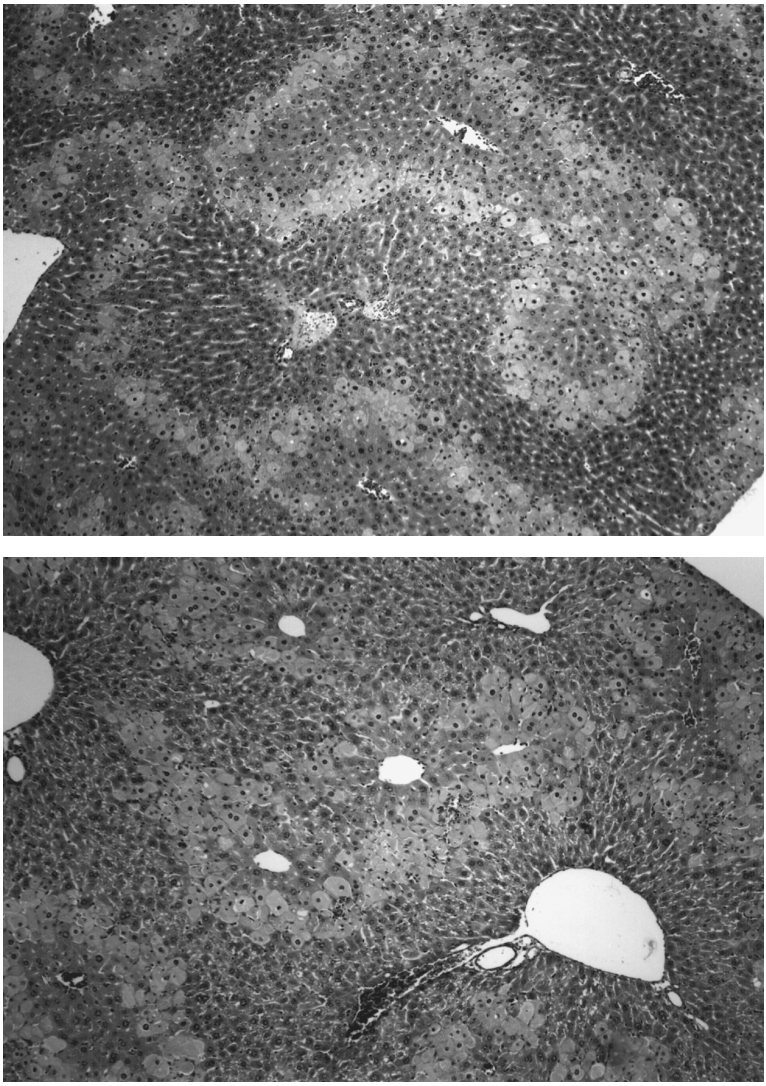

Figure 1.12.4.2.1 **Effects of cocaine and cocaethylene on the rat liver.** The upper microphotograph is from a rat treated with cocaine; the lower one is from a rat treated with cocaethylene. The patterns of injury are the same. (Courtesy of Stephen M. Roberts, Center for Environmental and Human Toxicology, University of Florida, Gainesville.)

1 in the periphery. Treatment with inhibitors, such as cimetidine, reduces toxicity. This is essentially the same pattern seen in mice given cocaine, suggesting that both cocaine and cocaethylene share common mechanisms of toxicity (Roberts et al., 1992; Roth et al., 1992; Boelsterli et al., 1993), but liver damage in humans, related to cocaethylene, has never been reported, even in autopsy studies where its occurrence was specifically sought (Karch et al., 1999b).

Hepatic amyloidosis has been described in cocaine users, but it is not entirely clear that cocaine is responsible. A report published in 1993 described clinical biopsy findings in 4 liver biopsies and 12 autopsies of individuals who had developed chronic suppurative skin ulcers as a consequence of both intravenous and subcutaneous cocaine and heroin use. Nearly one third (5 of 16 patients) also had AIDS at autopsy. The diagnosis was made antemortem in only one third of the cases. The amyloid protein was found to be type AA in 14, and type AL in one case. None of the individuals had multiple myeloma or a plasma cell dyscrasias. Amyloid distribution in the liver was both parenchymal and vascular. The histological pattern of amyloid distribution within the liver did not predict the type of amyloid protein that was identified (Osick et al., 1993). There have been no additional reports since the original index report was published, although one case report was published in 1995 describing another subcutaneous cocaine injector who developed renal amyloid (Tan et al., 1995). Cerebral amyloid angiopathy is also known to be a predisposing factor for intracerebral hemorrhage, but the relationship to cocaine use, if any, remains unclear (Kase, 1995).

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1.12.5 *Neurologic disorders*

The first reports of neurologic complications were published almost as soon as purified cocaine became widely available. The first cocaine-related stroke was described in 1886 (Catlett, 1886), only two years after cocaine had come into widespread use as a local anesthetic. Today, neurologic complaints are the most common manifestation of cocaine toxicity, at least in patients going to the emergency room (Derlet and Albertson, 1989). During the late 1980s, cocaine-related stroke re-emerged as a significant medical problem. In patients less than 35 years of age, drug abuse is the most commonly identified predisposing condition for stroke (Kaku and Lowenstein, 1990).

The latest reports suggest that the incidence of cocaine-related stroke has stabilized and may even be falling (Blanco et al., 1999), but it remains a problem, and a poorly understood one at that. The reason for the confusion is the multiplicity of possible causes. In a 1999 paper describing arteriographic findings in five young adults with cocaine-related stroke, arteriography was said to have demonstrated thrombotic occlusion in three cases, segmental narrowing in one case, and wall irregularities in another, implying that different mechanisms were involved in each instance (Blanco et al., 1999).

At the molecular level, experimental studies have provided some surprising insights into the effects of cocaine on the brain and plausible explanations for some types of cocaine toxicity. For example, evidence is emerging that nitric oxide formation plays an important role in cocaine neurotoxicity. In mice, repeated cocaine administration produces sensitization. When the same dose of cocaine is given to mice on a daily basis, seizures became worse and worse; initially well-tolerated doses become lethal after less than a week of cocaine administration. But pretreatment with agents that inhibit nitric oxide synthetase completely abolished the sensitization process, and all of the test animals survived (Itzhak and Martin, 1993). Whether similar changes occur in humans remains to be determined.

Another important element is involvement of the *N*-methyl-D-aspartate (NMDA) type of glutamate receptors which, at least in experimental animals, appears to be key to the induction and maintenance of kindling generated by daily cocaine injections in mice. Studies using cocaine analogs show binding to the NMDA receptors and marked increase in NMDA receptor densities in the striatum, amygdala, and hippocampus. They also show that receptor upregulation persists for days after the last dose of cocaine (Itzhak and Martin, 2000). All abused drugs, not just cocaine, activate immediate-early gene expression in the striatum, although each drug induces somewhat different changes. Most activate immediate-early gene expression in several additional forebrain regions, including portions of the extended amygdala, lateral septum, midline/intralaminar thalamic nuclei, and even the cerebral cortex. It is believed that common neuropharmacological mechanisms are responsible for activation of immediate-early gene expression in the forebrain, and that usually it is the dopaminergic and glutamatergic systems that are involved (Harlan and Garcia, 1998).

These changes are especially striking in the case of cocaine. Within minutes of cocaine administration, there is increased expression of several different genes. Increased expression of c-*fos*, the transcriptional regulator, is one of the first changes to occur (Graybiel et al., 1990), followed by an increase in production of mRNA coding for tyrosine hydroxylase and tryptophan hydroxylase. These two enzymes catalyze the rate-limiting steps in the production of both dopamine and serotonin, the neurotransmitters most obviously involved in the ability of cocaine to cause both euphoria and seizures.

Postmortem studies have shown that, in humans, the numbers of both D1 and D2 dopamine receptors are altered by cocaine use (Seeman and Van Tol, 1994). The brains of cocaine abusers usually contain an elevated number of cocaine recognition sites on striatal dopamine transporters, although no such increase is seen in victims of excited delirium. Chronic cocaine abuse also produces striking decreases in the density of the D1 receptor subtype throughout the striatal reward centers, probably as a result of receptor downregulation, which also probably explains why cocaine users quickly become tolerant to the euphoriant effects of cocaine (Staley et al., 1994; Staley and Mash, 1996). Similar changes in D1 receptor sensitivity and gene expression are also seen in experimental animals (Laurier et al., 1994).

Since these changes were first reported, the effects of chronic cocaine abuse on transcriptional regulation of the human dopamine transporter (DAT) mRNA have been studied in more detail. In midbrain, dopaminergic neurons reverse DAT/cyclophilin mRNA ratios in the substantia nigra and were found to be unchanged in cases of cocaine overdose, at least when compared to age-matched and drug-free controls. In contrast, DAT mRNA levels were decreased significantly in decedents with excited delirium (67%, $p = 0.05$). These findings suggest that cocaine has relatively little impact on the steady-state content of DAT mRNA in normal cocaine abusers, but a significant impact on gene expression in cocaine abusers at risk for excited delirium (Chen et al., 1999).

As noninvasive measurement techniques have become more sophisticated, cocaine-related changes in cerebral blood circulation have become easier to demonstrate, though they are still not fully understood. Magnetic resonance imaging (MRI) studies of human volunteers have shown that cocaine administration induces dose-related vasoconstriction, even when low doses of cocaine are given, and even in the absence of other risk factors (Kaufman et al., 1998). Studies with transcranial Doppler sonography, a technique that can be used to continuously measure cerebral blood flow velocity, show a significant increase in mean and systolic blood flow velocity after intravenous cocaine injection. This change lasts only for a few minutes, but it is seen even with relatively low doses of cocaine. Increases in systolic velocity in the large vessels of the brain only occur when they are constricted, demonstrating that cocaine, apparently in all users, induces a transient period of cerebral vasoconstriction (Herning et al., 1999).

This observation is confirmed by other studies demonstrating a transient, but fairly marked, decrease in total cerebral blood flow occurring after intravenous doses of cocaine, as small as 40 mg (Wallace et al., 1996). The results of other related scanning studies suggest that chronic cocaine users may have an accelerated age-related decline in temporal lobe gray matter volume and a smaller temporal lobe volume compared to normal controls (Bartzokis et al., 2000). The significance of these observations is not entirely clear, but the changes raise obvious questions about brain damage as a consequence of long-term cocaine abuse. The difficulty in interpreting sophisticated imaging studies is that they are capable of demonstrating changes that are not visible to the naked eye. Some studies suggest that as many as 3% of completely asymptomatic cocaine users show MRI evidence of cerebrovascular dysfunction, even though at autopsy gross abnormalities (excluding hemorrhages, of course) are rarely apparent (Chang et al., 1999).

The clinical features of cocaine-associated psychiatric disorders, especially psychosis, appear to be different from those seen in true schizophrenia and different also from the pattern seen in amphetamine abusers. Clinicians used to dealing with both types of mental derangement have little trouble separating the two (Serper et al., 1999). The neurotoxicity produced by some amphetamines, as evidenced by chemical measurements and morpho-

logic observations, does not occur in conjunction with cocaine abuse (Yeh and Desouza, 1991). Rats chronically treated with high doses of either cocaine or amphetamine show pronounced degeneration in fasciculus retroflexus, but cocaine, unlike amphetamine, does not cause significant damage in the striatum (Ellison and Switzer, 1993).

Cocaine-related impairment is frequently an issue in court proceedings, but few satisfactory answers are to be had. Regular cocaine users rapidly become tolerant to cocaine's stimulant effects, but whether or not this tolerance extends to performance and impairment is not known. The majority of studies done in human volunteers suggest that, taken in moderate doses, both cocaine and methamphetamine increase energy and alertness while at the same time improving mood. Both drugs can increase the ability to sustain attention over prolonged periods of time during performance of monotonous tasks, and both drugs have also been shown to improve performance on auditory and visual reaction time tests, other tests of psychomotor skills and attention, and tests of selective and divided attention. These findings suggest that moderate cocaine use should enhance driving performance, but that supposition has never been tested directly. (Farré et al., 1993; Stillman et al., 1993; Heishman and Karch, 2000). Modest performance improvement on a number of cognitive performance measures has also been observed after intravenous dosing (0.325 mg or 0.650 mg/kg) (Johnson et al., 1998).

1.12.5.1 Psychiatric syndromes

Cocaine-induced paranoid psychosis was recognized by the early workers in the field. Magnon (Magnan and Saury, 1889), Maier (1926), and Lewin (1931) all wrote on the topic and took pains to distinguish cocaine psychosis from symptoms induced by alcohol and other drugs. More recent studies have tended to confirm the earlier observations (Siegel, 1978; Gawin and Kleber, 1986). Transient or "binge" paranoia is common among heavy users. In one study, the incidence was nearly 70% (Satel and Gawin, 1990). What distinguishes the cocaine-associated syndrome from the syndrome induced by amphetamines is that the paranoia occurs only for a very brief period. The development of paranoia in this group of abusers is unpredictable and is not dose-related. Some individuals appear to be more vulnerable than others.

Cerebral glucose metabolism, as accessed by (^{18}F)-fluorodeoxyglucose PET of cocaine abusers in early withdrawal, increases. This increase in glucose metabolism involves all areas of the brain, but is particularly noticeable in the basal ganglia and orbitofrontal cortex. The increase in the latter two areas correlates with clinical measures of cocaine craving and is consistent with the notion that the changes are due to changes in brain dopamine activity (Volkow et al., 1991a,b,c).

Cocaine-induced changes in cerebral perfusion and glucose utilization appear to be gender related. Brain scans of cocaine-dependent women failed to disclose the abnormalities seen in the men (Levin et al., 1994). Longer lasting episodes of psychosis, due to chronic cocaine abuse can occur. When they do, chances are good that the victim will be misdiagnosed as a schizophrenic. Because drug users, schizophrenic or not, often deny drug use, routine drug screening of such patients is prudent (Shaner et al., 1993). Another important diagnosis to consider in cocaine users with psychiatric symptoms is stroke. Cocaine-induced ischemic infarcts have occasionally been mistaken for acute-onset psychosis (Reeves et al., 1995).

1.12.5.2 Cerebral infarction

The relationship between cocaine use and cerebral infarction has been questioned by some (Qureshi et al., 1997), but it has become increasingly apparent that a connection clearly

exists. Whether smoking free base is more dangerous than insufflation and what type of cerebral catastrophe is likely to result is not known. But the results of studies utilizing MRI suggest that patients with a history of "crack" smoking are at risk for white-matter damage mediated by unknown mechanisms (Bartzokis et al., 1999).

In the non-drug-using population, strokes are most often secondary to cerebral infarction. The principal causes of cerebral infarction are arterial thrombus formation, embolism, spasm, and circulatory compromise with secondary cerebral hypoperfusion. In non-drug-related cases, hemorrhage is the etiology less than 15% of the time (subarachnoid, 10%; intracerebral, 5%). An occasional case may involve a child or young adult, but stroke has always been thought of as a disease affecting the elderly. In the past, over 80% of cases occurred in individuals over 65 years old (Adams et al., 1984).

As cocaine abuse has become more common, both the age distribution and the underlying etiology of stroke appear to have changed. Individual cases are now so common they are no longer considered reportable, but in cocaine users with stroke the cause is as likely to be hemorrhage as infarction, and most of the affected individuals are in their mid-thirties. In roughly half the reported cases, onset of neurologic deficit occurred within three hours of cocaine use. Not uncommonly, however, victims wake up with a neurologic deficit after having indulged in an all-night binge (Daras et al., 1991).

A 100-year hiatus occurred between the first reports of stroke in the 1880s and Brust's report in 1977 (Brust and Richter, 1977), but case reports now appear with great frequency. Even the more exotic syndromes have been described — mesencephalic infarcts (Rowley et al., 1990), lateral medullary syndrome, anterior spinal syndrome (Mody et al., 1988), embolization from a left atrial thrombus (Petty et al., 1990), central retinal infarction (Devenyi et al., 1988; Zeiter et al., 1992; Libman et al., 1993; Sleiman et al., 1994), and massive cerebellar infarcts (Aggarwal and Byrne, 1991) — in addition to multiple reports of simple infarction (Chasnoff et al., 1986; Golbe and Merkin, 1986; Levine et al., 1987a,b; Levine and Welch, 1988; Rowbotham, 1988; Engstrand et al., 1989; Jacobs et al., 1989; Klonoff et al., 1989; Moore and Peterson, 1989; Seaman, 1990; Daras et al., 1991; Kelly et al., 1992; Konzen et al., 1995; O'Brien, 1998; Petitti et al., 1998).

Except for five instances of biopsy-proven vasculitis (Krendel et al., 1990; Fredericks et al., 1991; Scully et al., 1997; Diez-Tejedor et al., 1998) and one case of apparent embolism (Petty et al., 1990), the etiology of most cocaine-associated strokes is obscure. Papers continue to cite cocaine-induced vasculitis as a cause of stroke, but in virtually all of these reports microscopic proof is lacking and/or multiple drugs have been ingested (Mockel et al., 1999; Perez et al., 1999). Autopsy reports of cocaine users with stroke are rare (Klonoff et al., 1989; Konzen et al., 1995), but in the few cases that have been examined histologically, vasculitis has been conspicuously absent. A 1996 study reviewed selected brain samples from 14 autopsy cases of cocaine-related cerebrovascular disease; intracerebral or subarachnoid hemorrhage was present in 12 cases. Except for some nonspecific changes in the intracranial arterioles, no abnormalities were identified (Aggarwal et al., 1996).

Angiography and CT scanning studies have been equally unrewarding (Tuchman et al., 1987). In one case report, histologic changes were found to be entirely lacking, in spite of angiograms showing multifocal areas of segmental stenosis and dilatation (Martin et al., 1995). However, a second case report, published in 1995, described a striking infolding of a markedly irregular elastic lamina (Figure 1.12.5.2.1). The finding is consistent with the notion that cocaine-induced vasoconstriction had damaged the media of large cerebral vessels, perhaps enough to lead to thrombus formation (Konzen et al., 1995). More recently, MRI studies of cerebral blood vessels in human volunteers have clearly shown that cocaine

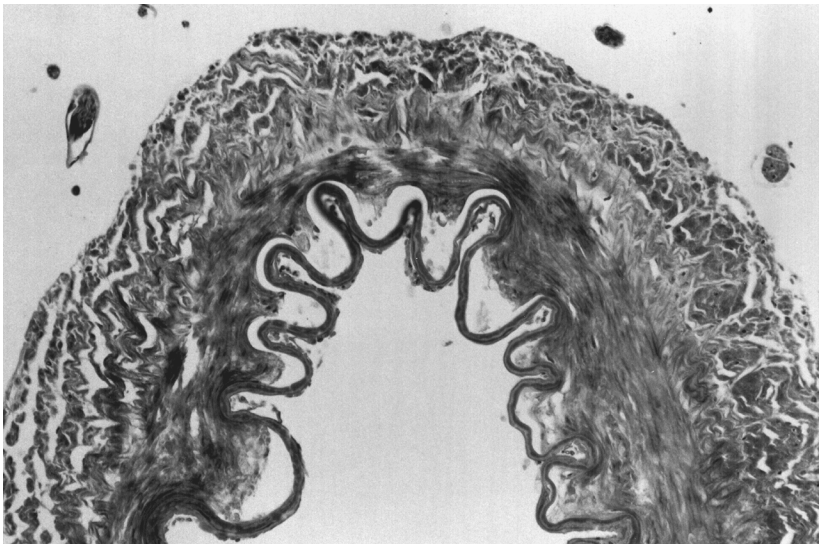

Figure 1.12.5.2.1 **Markedly infolded, irregular internal elastic lamina in the anterior cerebral artery of cocaine with ischemia stroke.** The irregularity of the elastic lamina may be a marker for cocaine-induced vasospasm. (From Konzen, J. P. et al., *Stroke*, 26, 1114–1118, 1995. With permission.)

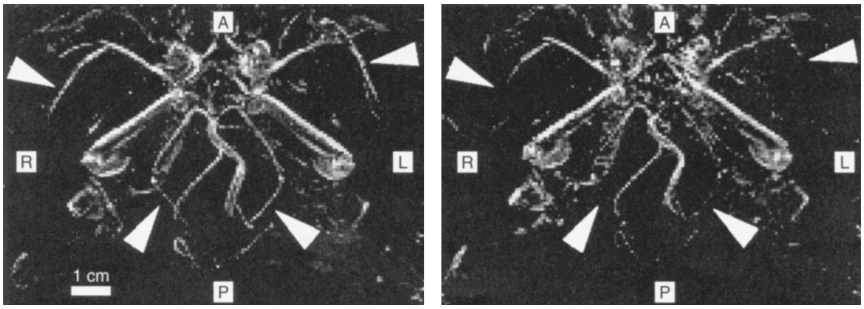

Figure 1.12.5.2.2 **Cocaine-induced vasoconstriction.** Axial maximum intensity projection images at baseline (left) and 20 minutes following intravenous cocaine (0.4 mg/kg) administration (right). Cocaine induced a signal loss at distal segments of the middle cerebral arteries (upper arrowheads) and in the posterior cerebral arteries (lower arrowheads), indicative of vasoconstriction. A indicates anterior; P, posterior; L, left; and R, right. Scale bar = 1 cm. (From Kaufman, M. J. et al., *JAMA,* 279(5), 379, 1998. With permission.)

administration causes dose-related vasoconstriction, even when low doses of cocaine are given and even in the absence of other risk factors (Kaufman et al., 1998; Herning et al., 1999). An example of cocaine-induced vasoconstriction is shown in Figure 1.12.5.2.2. It is not clear whether vasospasm in cocaine users is a result of some direct action exerted by cocaine on cerebral blood vessels or is secondary to catecholamine elevation (Levine et al., 1987a; Brust, 1993; Schreiber et al., 1994).

Increased platelet responsiveness leading to thrombosis may be the etiology for cerebral infarction in some cocaine users, but the case is far from clear, and platelet responsiveness is only one aspect of the problem. *In vitro* studies have yielded conflicting results (Heesch et al., 1996), with some studies suggesting increased responsiveness and others

just the opposite. Whole blood from some cocaine users has been found to contain higher levels of activated platelets than non-users (Rinder et al., 1994) and even higher levels of tissue plasminogen activator inhibitor (Moliterno et al., 1994). Others have found variable changes in platelet aggregation after administration of cocaine to healthy volunteers (Rezkalla et al., 1993). In one of the few *in vivo* studies to evaluate hematologic parameters and blood viscosity in chronic users treated with cocaine, transient erythrocytosis was observed, as were increases in blood viscosity and in von Willebrand factor, all changes that could favor intravascular thrombosis (Siegel et al., 1999).

Demonstrable reductions in cerebral flow persist for weeks after their last drug use (Volkow et al., 1988). Frontal lobe hypoperfusion is commonly observed in patients entering rehabilitation (Mena et al., 1990), as are multiple small superficial cortical areas of hypoperfusion. It appears that no correlation exists between the severity of these abnormalities and the amount of drug used. Other studies have shown that blood flow to the dorsolateral prefrontal cortex is still depressed 7 to 10 days after cocaine use has been discontinued and may remain that way indefinitely (Strickland et al., 1993; Bell et al., 1994). Interestingly, these flow abnormalities are much more pronounced in male cocaine users than in female users.

The sex difference remains unexplained, but because cocaine is atherogenic (Kolodgie et al., 1991; Karch et al., 1995) and because premenopausal women have fewer atherosclerotic changes than men, decreased flow in the males may just be a reflection of early atherosclerotic disease (Levine and Tebbett, 1994). Thus, cocaine users may be subject to decreased cerebral flow, even in the face of a normal cardiac output. Putting aside the issue of CNS atherosclerosis, there is no question that cocaine users are subject to accelerated atherogenesis (Dressler et al., 1990; Kolodgie et al., 1991; Karch et al., 1995). If cardiac output is reduced, blood pressure fluctuations could also lead to infarction, especially in the face of pre-existing CNS atherosclerotic lesions. Cocaine-associated cardiomyopathy (Wiener et al., 1986; Duell, 1987; Karch and Billingham, 1988; Chokshi et al., 1989; Mendelson and Chandler, 1992; Seballos et al., 1994; Willens et al., 1994) and arrhythmias (Young and Glauber, 1947; Boag and Havard, 1985; Duke, 1986; Lathers et al., 1988; Williams, 1990) are both recognized occurrences, and either of them could result in sudden blood pressure fluctuations. A sudden drop in blood pressure combined with asymptomatic stenotic lesions could lead to infarction. One report described a woman with cardiomyopathy (presumably, cocaine-related) who sustained a cerebral embolism (Petty et al., 1990). The situation is somewhat analogous to cocaine-associated myocardial infarction. The presence of pre-existing lesions may exacerbate transient flow decreases which otherwise would have been asymptomatic.

1.12.5.3 Cerebral vasculitis

The frequency of cerebral vasculitis in cocaine users is very low. The process has been documented in only a few patients. In the first case to be reported, a biopsy showed that the small vessels within an area of infarction had a transmural infiltrate of acute and chronic inflammatory cells. Occasional multi-nucleated giant cells were also present. In the second case, there was also lymphocytic infiltration of the small vessel walls with multiple cystic, necrotic, and gliotic areas in the cerebral white matter, especially in the frontal lobes. Multi-nucleated giant cells were seen in the gliotic areas. The process was most intense in the frontal lobes (Figures 1.12.5.3.1 and 1.12.5.3.2) (Krendel et al., 1990). Fredericks et al. (1991) described a second case with marked endothelial swelling and small vessel lymphocytic infiltrates. In a third report, describing a 32-year-old hypertensive man who had became hemiplegic, surgical specimens disclosed no evidence of fibrinoid

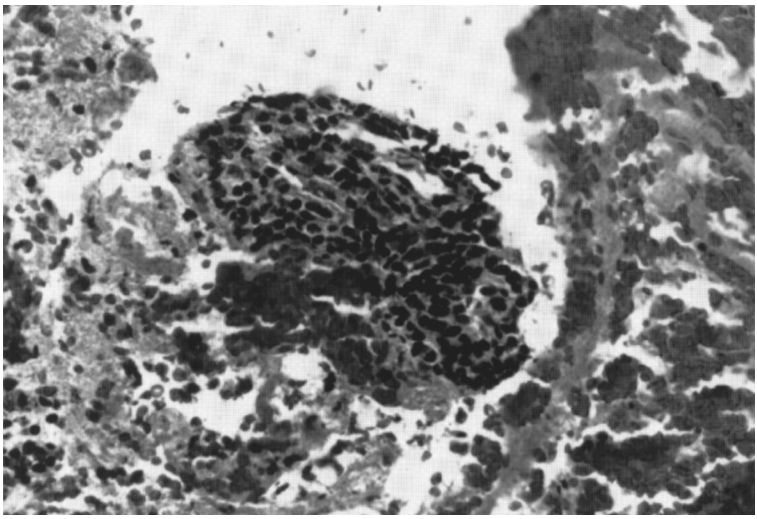

Figure 1.12.5.3.1 **Cerebral vasculitis in a cocaine user.** Biopsy specimen from patient surviving episode of vasculitis. Transmural infiltration of a small cortical vessel. Both acute and chronic inflammatory cells are present. (Original magnification 800×.) (Courtesy of Dr. David A. Krendel, Section of Neurology, The Emory Clinic, Atlanta, GA.)

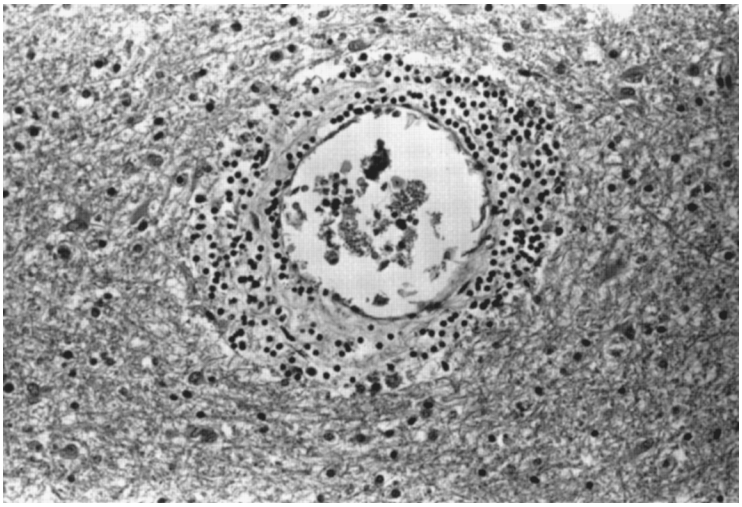

Figure 1.12.5.3.2 **Cerebral vasculitis in a cocaine user.** Autopsy specimen from another patient with cerebral vasculitis. Illustration shows a lymphocytic infiltrate around a small cerebral vessel. (Original magnification 800×.) (Courtesy of Dr. David A. Krendel, Section of Neurology, The Emory Clinic, Atlanta, GA.)

necrosis or giant cells, but there was vasculitis involving venules and arterioles, which were infiltrated with neutrophils, lymphocytes, and foamy macrophages. The endothelial cells were enlarged and, in addition, there was evidence of white-matter damage (Scully et al., 1997).

In the fourth case report, a 21-year-old male cocaine user with encephalopathy, apraxia, and left hemiparesis and hemisensory loss, cerebral angiography showed a lack of vascularization in the left precentral and central arterial groups. A corticomeningeal cerebral biopsy demonstrated perivascular cell collection and transmural lymphomonocytic infiltration of the small cortical vessels. Although the symptoms remitted with steroid therapy, the patient returned again, four years later, with severe encephalopathy. A cerebral MRI showed subcortical and periventricular lesions suggesting ischemic damage in small-sized vessel areas as well as cortical atrophy (Diez-Tejedor et al., 1998).

Even when vasculitis has been systematically sought, it has been difficult to find. A study published in 1996 described selected brain samples from 14 autopsy cases of cocaine-related cerebrovascular disease. Intracerebral or subarachnoid hemorrhage was present in 12 cases, but in each case the intracranial arterioles were either normal or showed only nonspecific changes (Aggarwal et al., 1996).

If cocaine does cause cerebral vasculitis, it probably does so by virtue of some direct toxic effect, unrelated to catecholamine toxicity. Patients with pheochromocytoma and animals treated with exogenous catecholamines generally do not show signs of CNS inflammation. Small, perivascular hemorrhages can be induced in animals by giving massive amounts of epinephrine, but in this model, cerebral vessel wall necrosis and infiltrates do not occur (Stief and Tokay, 1935).

Necrotizing angiitis is a form of periarteritis nodosa associated with the abuse of amphetamine and other stimulant drugs (Citron et al., 1970; Mockel et al., 1999). It has never been seen in cocaine users, except insofar as they used cocaine along with intravenous amphetamines and heroin. This disorder was first described in the early 1970s, but its incidence seems to have steadily declined over the last 20 years. The fact that this disorder has essentially disappeared, while intravenous amphetamine abuse has not, suggests that the originally reported cases may have been due to a contaminant introduced into the amphetamine during the course of manufacture and/or distribution.

1.12.5.4 Subarachnoid and intraventricular hemorrhage

Cocaine users seem to be particularly at risk for dying of subarachnoid hemorrhage. Nearly half the strokes associated with cocaine abuse are due to either intracerebral or subclavial hemorrhage (Caplan et al., 1982; Lichtenfeld et al., 1984; Schwartz and Cohen, 1984; Wojak and Flamm, 1987; Lehman, 1987; Lowenstein et al., 1987; Mittleman and Wetli, 1987; Mody et al., 1988; Jacobs et al., 1989; Klonoff et al., 1989; Mercado et al., 1989; Nolte and Gleman, 1989; Tardiff et al., 1989; Green et al., 1990; Rowley et al., 1990; Daras et al., 1991; Oyesiku et al., 1993) or subarachnoid hemorrhage (Chynn, 1975; Lundberg et al., 1977; Lichtenfeld et al., 1984; Schwartz and Cohen, 1984; Rogers et al., 1986; Cregler and Mark, 1987; Altes-Capella et al., 1987; Lowenstein et al., 1987; Mittleman and Wetli, 1987; Wojak and Flamm, 1987; Levine et al., 1988; Jacobs et al., 1989; Klonoff et al., 1989; Tardiff et al., 1989; Willis and Harbit, 1989; Daras et al., 1991; Oyesiku et al., 1993; Davis and Swalwell, 1996; Nolte et al., 1996; Nanda et al., 2000). Subarachnoid hemorrhage is more common than intracerebral hemorrhage by a ratio of 4:3. As is the case with cocaine-related infarction, individuals are in their early thirties.

Most (80%) subarachnoid hemorrhages are the result of saccular aneurysms. The majority involve the anterior communicating artery, with the posterior communicating system being the next most frequent site. The remainder have been found scattered throughout the cerebral circulation. Intracerebral hemorrhage is most often the result of an arteriovenous malformation, although in half of the cases no underlying lesions are

demonstrable. Bleeding into the basal ganglia and thalamus is the most common pattern (Green et al., 1990; Nolte et al., 1996).

Saccular aneurysms involving the arteries at the base of the brain occur in 1–2% of the adult population, and are often found incidentally at autopsy. Usually they are located at arterial bifurcations. They form as a result of multiple factors, including atheroma, degenerative changes, and secondary flow abnormalities (Sekhar and Heros, 1980). The role of hypertension in the formation and rupture of saccular aneurysms is still unclear (Graham, 1989), but the role of hypertension in cocaine-associated subarachnoid bleeding is becoming increasingly recognized (Kibayashi et al., 1995).

Intracerebral hemorrhage is usually due to hypertension, although in some series the number of cases due to vascular malformation roughly equals the number due to hypertension (Gras et al., 1991). Intracerebral hemorrhages occur as a consequence of structural changes in the small perforating vessels of the cerebral hemispheres and brain stem (Figure 1.12.5.4.1). They produce deeply situated hemorrhages in the cerebral hemispheres (basal nuclei and thalamus) and brain stem (Kase, 1995, 1999). Much less often, bleeding may occur in the subcortical white matter and cerebellum. Hemorrhage in the white matter is usually the result of amyloid angiopathy and probably has little to do with hypertension. The most common site for hypertensive hemorrhage is the basal ganglia, outnumbering the second most common site, the cerebral white matter, by a ratio of 7:1 (Adams et al., 1984).

Several studies have addressed the problem of intracerebral hemorrhage in cocaine users. In one study (Kibayashi et al., 1995), autopsy findings in 26 individuals with cocaine-induced intracerebral hemorrhage were compared with autopsy findings in 26 cases of cocaine-induced cerebral aneurysm rupture. Hypertensive cardiovascular disease was much more common in the former (mean heart weights of 497 vs. 380 g), suggesting very strongly that hypertensive cardiovascular disease, which itself can be a consequence of cocaine use, predisposes to cocaine-induced intracerebral hemorrhage. A 1997 study (Fessler et al., 1997) reviewed the findings in 33 cocaine abusers with neurologic deficits who presented at a large inner-city hospital. Of those patients, 16 were diagnosed with subarachnoid hemorrhage, and 12 of them subsequently underwent four-vessel cerebral arteriography, which revealed 14 aneurysms. Six patients presented with intracerebral hemorrhage and seven patients with evidence of ischemic stroke. More than half of the patients noted onset of their symptoms while they were using cocaine, and in almost all cases symptom onset was within six hours of use. Delayed onset of symptoms and delayed presentation at the emergency room seem to be more characteristic for patients with ischemic infarction. Perhaps the most interesting findings were that, among the patients with aneurysm, the cocaine users were much younger than a control group of non-drug users (32.8 vs. 52.2 years) and the size of the aneurysms in the cocaine-using group was much smaller (4.9 vs. 11.0 mm).

If long-term cocaine use can lead to hypertensive cardiovascular disease and intracerebral hemorrhage, even occasional use could lead to transient blood pressure elevations sufficient to cause the rupture of pre-existing malformations or bleeding into a tumor (Yapor and Gutierrez, 1992; Herning et al., 1999). Experimental evidence shows that cocaine potentiates the increases in blood pressure and cerebral blood flow produced by the administration of norepinephrine (Muir and Ellis, 1993). Because cocaine users have elevated circulating levels of norepinephrine, potentiation of the normal response to catecholamines may account for much of the reported pathology. Hemorrhage in individuals without underlying lesions, as in a recently reported case of spinal epidural hematoma (Huff, 1994), remains unexplained.

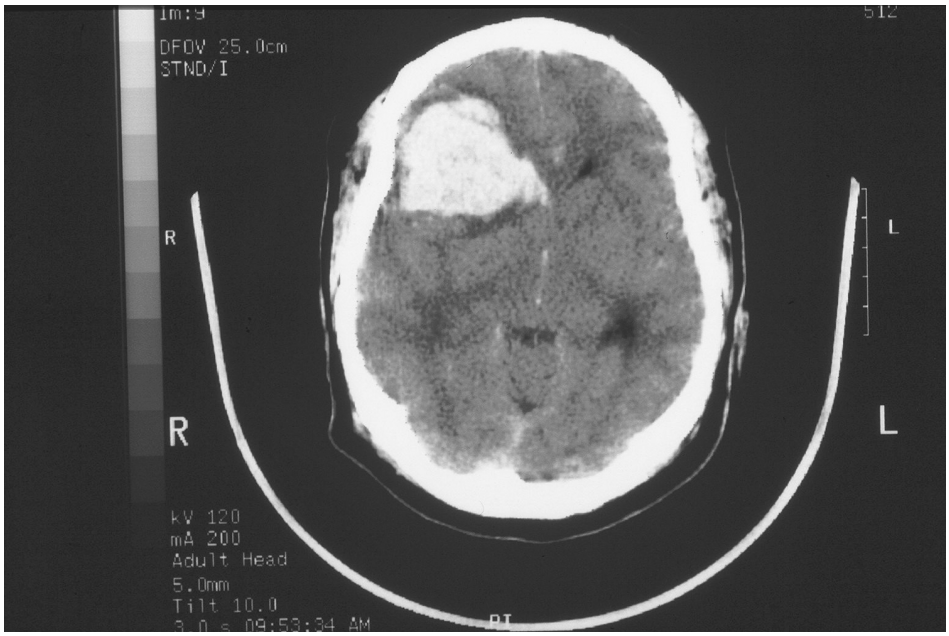

Figure 1.12.5.4.1a **Intracerebral hemorrhage in a young crack cocaine smoker.** Stimulant abuse is becoming an increasingly common cause of stroke in young people. Scan shows massive hemorrhage in the temporal–frontal region. (Courtesy of Dr. Kari Blaho, University of Tennessee, Memphis.)

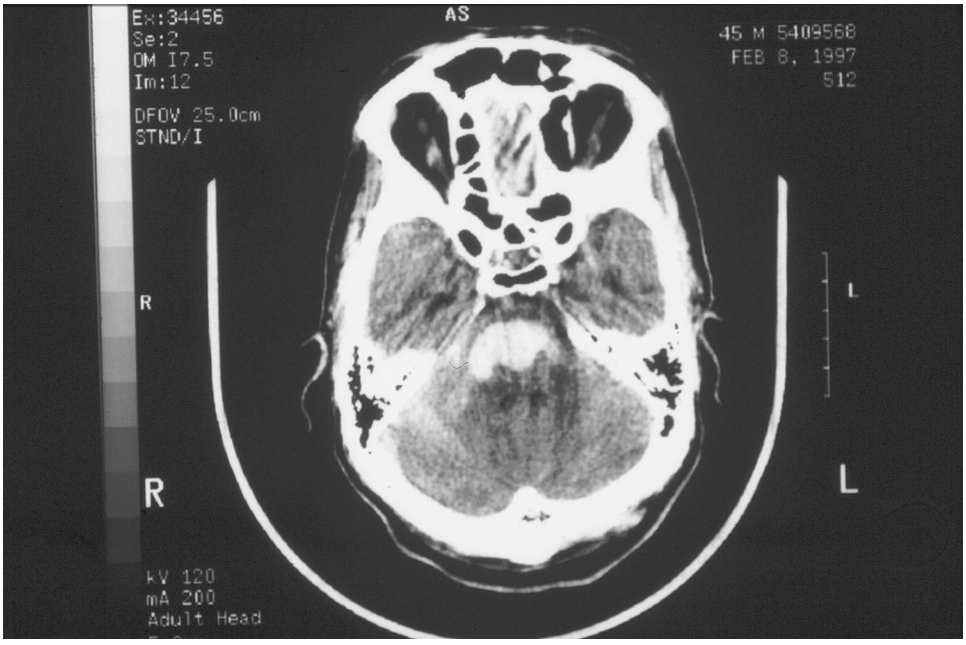

Figure 1.12.5.4.1b **Intracerebral hemorrhage involving the brain stem of a young "crack" cocaine smoker.** Brain hemorrhages in young drug abusers frequently involve pre-existing, previously undiagnosed A–V malformations and aneurysms. (Courtesy of Dr. Kari Blaho, University of Tennessee, Memphis.)

1.12.5.5 *Seizures*

Grand mal seizures in cocaine users are, in fact, a not very common occurrence. That may well explain why so little is known about them (Winberry et al., 1998). When they do occur, they may be a consequence of stroke or intracerebral hemorrhage or even of massive overdose. They may also be a manifestation of a pre-existing seizure disorder that was exacerbated by cocaine use. Various series have placed the incidence of this complication at somewhere between 2 and 10% (Lowenstein et al., 1987; Derlet and Albertson, 1989). In one series of nearly 1000 patients treated for acute medical complications of cocaine use, seizures were noted in nearly 10%. Only four of these patients had status epilepticus, and all of them were victims of massive overdose (Dhuna et al., 1991). Interestingly, in that same report seizures were three times as common in women as in men (18.4 vs. 6.2%). This finding is consistent with the results of other studies suggesting that pregnancy and other hormonal alterations can exacerbate cocaine toxicity (Plessinger and Woods, 1990; Sharma et al., 1992).

"Kindling" is a term used to describe the development of generalized convulsions in response to repeated subconvulsive brain stimuli in animals. Cocaine-induced kindling has been demonstrated in animals. Whether this process also occurs in humans as a consequence of cocaine or any other kind of drug use has been debated for some time. It has been speculated, but without proof, that kindling, or some similar process, is the mechanism responsible for seizures in chronic cocaine abusers. The possibility that cocaine kindling could occur in humans is suggested by the well-described case of a 37-year-old woman who experienced generalized tonic–clonic seizures immediately after smoking "crack." She then went on to develop generalized seizures even when she was not using cocaine (Dhuna et al., 1991). The latest data suggest that cocaine kindling is associated with increased NMDA receptor binding activity in the striatum, amygdala, and hippocampus (Itzhak and Martin, 2000).

Results from animal experimentation indicate that different mechanisms are responsible for seizures and lethality. Cocaine-induced seizures are a consequence of the effect of cocaine on the serotonin transporter in concert with effects on muscarinic neurons and sigma receptors, while interactions with the dopamine transporter determine lethality (Ritz and George, 1993). It is also quite possible that other neurotransmitters such as γ-aminobutyric acid (GABA) may be involved in the process. Cocaine noncompetitively inhibits GABA-generated currents in neuronal membranes, suggesting that the GABA receptor/channel complex is also a target for cocaine, and may contribute to cocaine-induced seizures (Ye et al., 1997). Additional support for GABA involvement comes from experimental animal studies showing that drugs that enhance GABA-related neuronal inhibition, via mechanisms that are totally distinct from the mechanisms accounting for the effectiveness of barbiturates and benzodiazepines, offer the best protection against cocaine-induced seizures. Conversely, Na^+ and Ca^{2+} channel blockers offer the least protection (Chynn, 1975).

1.12.5.6 *Movement disorders*

Movement disorders, including choreoathetosis, akathisia, and Parkinsonism with tremor, have all been described in cocaine users (Daras et al., 1994; Catalano et al., 1997). This phenomenon has become so common enough that it even has a street name — "crack dancing." Symptoms are generally self-limiting and do not bring the victims to medical attention. However, one recent controlled study, using MRI scanning, demonstrated an increased incidence of basal ganglia abnormalities that were not seen in controls (Bartzokis et al., 1999).

Dystonic reactions are extrapyramidal motor abnormalities that occur whenever there is an insufficient supply of nigrostriatal dopamine. The main symptom is spasm within isolated muscle groups. Neuroleptic drugs are a known cause of dystonia and are the most frequently encountered trigger, but they can be caused by cocaine (Hegarty et al., 1991; Cardoso and Jankovic, 1993; Catalano et al., 1997; Fines et al., 1997; van Harten et al., 1998). Similar reasons may explain why cocaine users are also prone to multi-focal tics, which cocaine precipitates (Pascual-Leone et al., 1990), in addition to exacerbating the clinical manifestations of Gilles de la Tourette syndrome, and why cocaine users are at increased risk for developing neuroleptic-induced acute dystonia (van Harten et al., 1998).

1.12.5.7 Blood–brain barrier alterations

In addition to an association with stroke, evidence is accumulating that cocaine may enhance HIV-1 entrance into the brain by altering the blood–brain barrier. HIV-1 penetrates the human brain microvascular endothelial cell barrier by a paracellular route. Entrance into the brain is facilitated by the presence of increased concentrations of tumor necrosis factor-α (TNF-α). Human monocytes also produce more TNF-α when cocaine is added to the culture medium (Fiala et al., 1998; Zhang et al., 1998) (see Section 1.12.9 for further discussion).

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1.12.6 Renal disease

It is not known whether cocaine is inherently nephrotoxic, but the results of animal studies have raised that possibility (Figure 1.12.6.1) (Barroso-Moguel et al., 1995). However cocaine operates, via direct or indirect mechanisms, there is no question that cocaine users are subject to renal disease. Infarction (Sharff, 1984; Kramer and Turner, 1993; Goodman and Rennie, 1995), thrombosis (Wohlman, 1987), and even hemolytic–uremic syndrome (HUS) (Tumlin et al., 1990) have been reported as complications of cocaine use.

The most common kidney disorder in cocaine users is acute tubular necrosis secondary to rhabdomyolysis. Rhabdomyolysis had been recognized as a complication of both

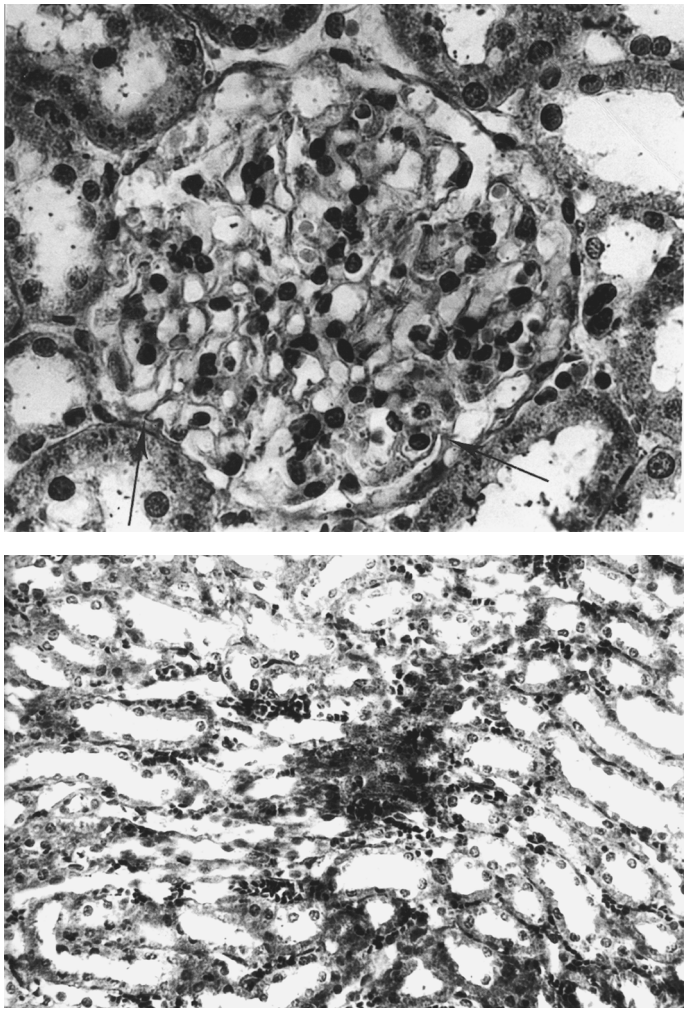

Figure 1.12.6.1 **Glomerular and tubular lesions.** In experimental models, long-term treatment with cocaine causes both glomerular and tubular lesions. These photographs are from rats sacrificed after 60 days of treatment. In the top figure, the glomerular tufts are distended and have few mesangial cells remaining. Capillary lumens are reduced, and numerous adhesions to Bowman's capsule can be seen. In the bottom figure, foci of hemorrhage and necrosis are evident in the distal tubules. (From Barroso-Moguel, R. et al., *Toxicology*, 98(1–3), 41–46, 1995. With permission.)

narcotic abuse (Richter et al., 1971) and stimulant abuse (Kendrick et al., 1977) long before the current wave of cocaine popularity. The first case directly related to cocaine was described in 1987 (Merigian and Roberts, 1987). Case reports have been published regularly ever since (Daras et al., 1995; Korzets et al., 1995; Lampley et al., 1996; Vanek et al., 1996; Counselman et al., 1997; Effiong et al., 1997; Ruttenber et al., 1997, 1999; Farah and Ghayad, 1999; Kumar et al., 1999). In a large percentage of these cases, rhabdomyolysis occurs as a component of the excited delirium syndrome, where very high core temperatures and extreme physical activity combine to cause muscle breakdown (see Section 1.12.2.12).

Except for cases of excited delirium, the underlying process by which stimulant drugs produce rhabdomyolysis is poorly understood. In some cocaine-related cases, the relationship to prolonged seizure activity is clear; however, seizures have been absent in most of the cocaine-associated cases. In other settings, pressure-related injury seems to be the most likely explanation (Singhal and Faulkner, 1988; Singhal et al., 1989, 1990; Korzets et al., 1995; Vanek et al., 1996). Cocaine-induced vasospasm leading to myocyte necrosis has also been proposed as a mechanism (Roth et al., 1988), but this mechanism has never been reproduced in the laboratory or even described in other case reports. Accelerated renal artery arteriosclerosis, with histologic changes reminiscent of those occasionally observed in cocaine users' coronary arteries, has also been reported (Bacharach et al., 1992; Fogo et al., 1992; van der Woude and Waldherr, 1999).

A common thread in many, but not all, cases is hyperthermia (Rosenberg et al., 1986; Campbell, 1988; Menashe and Gottlieb, 1988; Pogue and Nurse, 1989; Lomax and Daniel, 1990). The results of some studies suggest that cocaine can be directly toxic to skeletal muscle. In an *in vitro* study, exposure to moderate levels of cocaine resulted in increased leakage of creatinine kinase from slow-twitch muscle, such as soleus, but not from fast-twitch muscles, such as extensor digitorum (Pagala et al., 1993). In the most recent reports, the data suggest that, excluding cases where obvious pressure necrosis is present, most rhabdomyolysis simply represents just another, albeit delayed, component of the excited delirium syndrome.

Epidemiologists have tested this hypothesis by using meta-analysis to compare data from 150 previously reported cases of cocaine-associated rhabdomyolysis with autopsy registry data on 58 victims of fatal excited delirium and 125 victims of fatal acute cocaine toxicity. Patients with rhabdomyolysis and fatal excited delirium were found to be similar with regard to age, sex, race, route of cocaine administration, degree of temperature elevation, absence of seizures, and presence of excited delirium. The same overlap was seen when the rhabdomyolysis patients were compared with victims of fatal acute cocaine toxicity. Because cocaine-associated rhabdomyolysis and excited delirium have similar clinical features, risk factors, and demographics and because they can be explained by the same pathophysiologic processes (changes in dopamine metabolism), it is reasonable to conclude that both hyperthermia and excited delirium really just represent different stages of the same syndrome (Ruttenber et al., 1999). The histologic changes accompanying the process are uncharacterized. In one report describing two cases, the skeletal muscle was seen to be necrotic, but no signs of vasculitis were apparent, nor were any polarizable foreign bodies or other specific lesions seen, although contraction band necrosis was very prominent in some fibers (Nolte, 1991).

Cocaine-associated tubular necrosis is a multifactoral disorder. Hypovolemia, renal arterial vasoconstriction, and myoglobinuria all combine to produce the syndrome. Except for one case report (Turbat-Herrera, 1994), morphologic alterations in cocaine users have not been described (Merigian and Roberts, 1987; Schwartz and McAfee, 1987;

Herzlich et al., 1988; Krohn et al., 1988; Lombard et al., 1988; Menashe and Gottlieb, 1988; Reinhart and Stricker, 1988; Singhal and Faulkner, 1988; Anand et al., 1989; Jandreski et al., 1989; Parks et al., 1989; Rubin and Neugarten, 1989; Brody et al., 1990; Justiniani et al., 1990; Kokko, 1990; Singhal et al., 1990; Welch and Todd, 1990; Welch et al., 1991). In the one instance when a renal biopsy was done, no abnormal antibody deposition or myoglobin was identified in the tubules, and the picture was otherwise typical for acute tubular necrosis, with vacuolation, fragmentation, and desquamation of the proximal lining tubular epithelial cells and pigmented casts in some distal nephrons (Turbat-Herrera, 1994).

Renal failure without rhabdomyolysis also occurs and has been reported by Tumlin et al. (1990) and Leblanc et al. (1994). In the first case, a 28-year-old woman with nausea, vomiting, and severe abdominal pain developed anuria, hemolytic anemia, and thrombocytopenia (i.e., HUS). Renal biopsy showed patchy cortical necrosis associated with the characteristic changes of thrombotic microangiopathy. Electron microscopy demonstrated extensive detachment of the endothelium from the basement membrane, with the accumulation of electron lucent material and red cell debris in the subendothelial area.

Acute renal failure in cocaine users can also be the result of microangiopathy. A recent case report describes a 38-year-old woman who developed hemolytic anemia, thrombocytopenia, and acute renal failure after smoking "crack" cocaine. A renal biopsy demonstrated thrombotic microangiopathy and glomerular ischemia. Whether the underlying mechanism involved direct injury to the epithelium or some as yet uncharacterized antiplatelet or procoagulant activity is not known (Volcy et al., 2000).

Another possibility, and one that seems increasingly likely, is catecholamine toxicity; both thromboxane generation and acute hypertensive reactions are well-known sequela of cocaine use, and any or all could lead to HUS or microangiopathy. After the initial endothelial injury, intravascular coagulation and the other elements of HUS could result. This possible mode of action is supported by the observation that not all cases with hemolysis and thrombocytopenia have demonstrable histologic lesions. A 1994 case report described a 16-year-old girl who developed renal failure three days after snorting cocaine. A renal biopsy was unremarkable except for the rare dilatation of tubular lumens. Immunofluorescence staining was nonspecific (Leblanc et al., 1994). The findings are most consistent with transient vasospasm.

The focal type of glomerulosclerosis associated with heroin-related nephrotic syndrome has not been reported in cocaine or stimulant abusers, but similar lesions have been produced in rats (Barroso-Moguel et al., 1995), and the results of several *in vitro* studies suggest that cocaine use may be a risk factor for this disorder (Mattana et al., 1994; Pan and Singhal, 1994; Onuchic et al., 1998). Mesangial cell expansion is generally considered to be a precursor for glomerulosclerosis and, at least *in vitro*, cocaine modulates mesangial cell proliferation via interaction with the secretory products (interleukin-6 and transforming growth factor-β) produced by macrophages after cocaine exposure. Substantial numbers of heroin users also inject themselves with cocaine (Diaz et al., 1994; Karch et al., 1998), so that when glomerulosclerosis is seen in a cocaine abuser it is impossible to tell whether the glomerular changes are due to cocaine or heroin, or both.

The presence of glomerulosclerosis in cocaine abusers should also raise the suspicion of HIV infection, as the most common renal lesion in AIDS patients is a similar sort of focal segmental glomerulosclerosis (Sanders and Marshall, 1989). Sometimes the picture becomes quite confusing because cocaine users, who may be HIV positive, can present with refractory hypertension and renal failure, but only modest proteinuria and no renal shrinkage or cardiomegaly (Dunea et al., 1995). Renal biopsies are no longer routinely

performed in patients with end-stage renal disease and evidence of accelerated hypertension, so the etiology in such cases may never be determined.

Cocaine-related progressive glomerulonephritis due to antiglomerular basement membrane (anti-GBM) antibodies also occurs. A 1999 case report describes a 35-year-old man who was an occasional intranasal cocaine user who developed acute renal failure. No evidence of rhabdomyolysis was present, but circulating anti-GBM antibodies were found and a renal biopsy showed linear IgG and C3 deposits, a sure diagnostic sign for antiglomerular basement membrane disease (Peces et al., 1999). The occurrence of anti-GBM antibodies, in conjunction with pulmonary hemorrhage (Goodpasture's syndrome) was recently documented in a 32-year-old "crack" smoker (Garcia-Rostan y Perez et al., 1997), but because this is the only report linking Goodpasture's syndrome to cocaine use, its significance should be interpreted with some caution.

Case reports describing congenital abnormalities of the genitourinary tract (Chavez et al., 1989) have never been substantiated by controlled surgical or autopsy studies; however, a prospective study using ultrasound to evaluate 100 consecutive infants exposed to cocaine *in utero* failed to find any consistent teratogenic effect (Rosenstein et al., 1990). A similar study repeated in 1995 yielded almost identical results. Renal ultrasound scans performed on 79 infants born to cocaine-using mothers demonstrated abnormalities in 11 of the babies, including one case each of horseshoe kidney, unilateral abnormal small kidney, duplex kidney, and hypospadias. Renal tract dilation was seen in several of the children. The authors of the study concluded that the risk of urogenital malformation might be slightly increased, but a much larger study would be needed to reach any conclusion (Battin et al., 1995). Such a study has never been undertaken and, indeed, it has been six years since the last paper was even published on this subject.

Finally, even though renal disease may be associated with cocaine abuse, organ donation is still a reasonable consideration. One-year survival rates for individuals receiving kidneys from cocaine abusers appear to be no different than rates for drug-free donors (Leikin et al., 1994). Donor hearts from cocaine abusers are similarly unaffected, with survival rates comparable to those for drug-free donors (Freimark et al., 1994).

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1.12.7 Hematologic abnormalities

Thrombocytopenic purpura was recognized in heroin users more than a decade before the spread of HIV infection (Adams et al., 1978). The etiology of that index case is not known, but today thrombotic thrombocytopenic purpura in heroin users is almost always linked to HIV infection (Karpatkin and Nardi, 1988; Karpatkin, 1990; Orser, 1991). For the moment, at least, that does not appear to be the case among cocaine users. One study described seven HIV-seronegative intravenous cocaine abusers with extensive cutaneous petechiae, ecchymoses, and heme-positive stools. The patients all had normal bone marrow or, at most, increased numbers of megakaryocytes. Platelet counts in each of the individuals all improved promptly after steroid administration. No other etiology for their condition could be identified. Only a handful of other cases have been reported (Koury, 1990; Keung et al. 1996), and the relationship between cocaine use, and thrombocytopenic purpura, if it truly exists, remains unclear.

As with many of the other cocaine-associated syndromes, possible etiologies include toxic contaminants or metabolites, as well as immune reactions to the cocaine itself. There are many other ways cocaine could affect platelet function. The most obvious is cocaine-related catecholamine excess. Circulating catecholamines are elevated in cocaine users, and elevated catecholamine levels can alter α and β receptors located on circulating lymphocytes and on platelets (Maki et al., 1990).

Cocaine can cause increased thromboxane generation *in vitro*; however, the consequences of this fact have not been clinically confirmed (Togna et al., 1985, 1996). Studies of platelet and clotting mechanisms in cocaine users have yielded conflicting results (Cook and Randall, 1996), while *in vitro* studies of platelet behavior cannot always be relied upon to give a valid picture of what happens in patients. Thus, in the pig model, the administration of cocaine increases the reactivity of platelets exposed to cardiac subendothelium, a result that suggests that, in pigs at least, cocaine has a prothrombotic effect by virtue of its ability to facilitate the interaction of platelets with damaged arteries (Zurbano et al., 1997).

Volunteers given very modest doses of cocaine (2 mg/kg) have higher concentrations of plasminogen activator inhibitor (PAI-1) than controls (Moliterno et al., 1994), and increased PAI-1 activity favors thrombosis. Chronic cocaine users are also said to have higher circulating levels of activated platelets (e.g., platelets displaying the α-granule protein P-selectin on their membrane surface) (Rinder et al., 1994). Even though other studies have found just the opposite (Kugelmass and Ware, 1992; Jennings et al. 1993; Rezkalla et al. 1993), the most recent *in vivo* studies strongly favor the idea that cocaine use may trigger platelet adhesion, aggregation, and intravascular thrombosis.

In a study reported in 1999, changes in hemoglobin concentration, hematocrit, and red blood cell counts were measured in a group of chronic cocaine users, both before and after cocaine administration. Hemostatic parameters, including von Willebrand factor, fibrinolytic activity, fibrinogen, plasminogen activator inhibitor antigen, and tissue-type plasminogen activator antigen, were also measured. Hemoglobin levels, hematocrit, and red blood cell counts all increased significantly within 30 minutes or less after the cocaine had been given. At the same time, there was no change in white blood cell or platelet

counts, but concentrations of von Willebrand factor increased by 40% over baseline levels. Thus, it is apparent that cocaine induces a transient erythrocytosis that may increase blood viscosity and concentrations of von Willebrand factor (Siegel et al., 1999).

An epidemiologic survey of patients with myocardial infarction (Determinants of Myocardial Infarction Onset Study, DMIOS) showed that, among the subset of patients who were cocaine users, the risk for onset of myocardial infarction onset was elevated 23.7 times over baseline (95% CI, 8.5 to 66.3) in the 60 minutes after cocaine was used, but within the first hour the risk rapidly returned to that of the general population (Mittleman et al., 1999). Because the observed hematologic changes seem to precisely match the timing of the transient increases in von Willibrand's factor, platelet agreeability, and the risk for acute myocardial infarct, it is tempting to suppose that all of these events are related.

Another hematologic abnormality associated with cocaine use, at least indirectly, is methemoglobinemia. Street-level cocaine is occasionally diluted with benzocaine or other related local anesthetics, and oxidation of ferrous (Fe_2) hemoglobin to the ferric (Fe_3) state is a well-recognized complication of benzocaine administration. One case report described a 27-year-old man with a massive overdose who developed classic methemoglobinemia. Blood levels were not measured; however, urine cocaine levels were 106 mg/L, while benzocaine levels were 3.8 mg/L (McKinney et al., 1992). Cocaine itself has never been implicated as a cause of this disorder, and additional reports of this complication are lacking.

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1.12.8 Hormonal alterations

Even though cocaine is classically thought of as a re-uptake inhibitor exerting its effects on tissue and organs that are responsive to catecholamines and serotonin, it also acts on the endocrine system. In many ways, these effects resemble the effects exerted by monoamine oxidase inhibitors. In particular, acute cocaine administration stimulates the release of gonadotropins, adenocorticotropic hormone (ACTH), and cortisol or corticosterone, while at the same time it suppresses prolactin concentrations (Mello and Mendelson, 1997).

Prolactin is episodically secreted by the hypothalamus. During sleep, the amplitude of the secretory pulses increases. Unlike other pituitary hormones, hypothalamic secretion of prolactin is under tonic inhibition by dopamine and possibly by GABA. Release of prolactin is favored by increasing concentrations of thyroid-releasing hormone, vasoactive intestinal polypeptide, and serotonin (Molitch, 1992; Van de Kar et al., 1996). Initially, it had been thought that acute administration of cocaine produced a drop in prolactin levels, followed later by rebound hyperprolactinemia (Mello et al., 1990; Teoh et al., 1990). However, more recent studies from other laboratories have yielded conflicting results, suggesting that cocaine has no predictable effects on prolactin levels (Baumann et al., 1995).

Even if changes in prolactin concentration do occur, they may not be of very great clinical significance. Under normal circumstances, prolactin's main function is to stimulate lactation in the postpartum period. It does not appear to play a role in normal gonadal function, but its secretion can be altered in different physiologic states. Many drugs, especially dopamine antagonists, cause changes in prolactin secretion. Nonetheless, measuring changes in prolactin levels could be of some clinical value. Markedly depressed levels are a good confirmation of recent drug use. High levels, which have been noted in detoxification patients, are consistent with withdrawal. It has been suggested that very high levels may be a marker for those detoxification patients who subsequently fail treatment and resume drug use (Teoh et al., 1990). The usefulness of prolactin levels in monitoring the detoxification process is limited by the fact that the effect of cocaine on anterior pituitary hormones is, in some way, mediated by gonadal function (Mello et al., 1995). Until these actions are better understood, prolactin levels are of little evidentiary value and of even less use clinically, at least in cocaine users.

Effects on other human hormonal systems have been difficult to demonstrate, mainly because humans also use alcohol and other drugs that also alter hormone production. However, experimental studies have consistently shown neuroendocrine function is altered in rats and rhesus monkeys, with disruptions of the estrous cycle in rats and the menstrual cycle in rhesus monkeys. These changes appear to mimic those that have been observed in human female cocaine abusers (Mello and Mendelson, 1997).

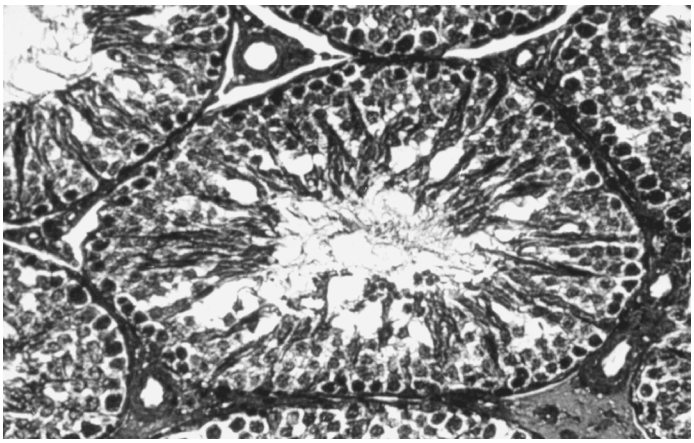

Figure 1.12.8.1 **Testicular atrophy in chronic drug abusers is generally attributed to life-style and dietary deficiency.** However, rats chronically exposed to moderate doses of cocaine undergo Lydig cell degeneration. Whether this is also true for humans is not known. (From Barroso-Moguel, R. et al., *J. Appl. Toxicol.,* 14(1), 37–41, 1994. With permission.)

Testosterone levels in chronic cocaine abusers have not been characterized, and laboratory studies on gonadal uptake have produced conflicting results. Mice testes avidly bind labeled cocaine (Yazigi and Polakoski, 1992), but rat testes do not show high levels of cocaine uptake (Som et al., 1994). Even so, chronic cocaine administration, at least in rats, produces testicular lesions (Figure 1.12.8.1), which results in decreased testosterone production and depressed spermatogenesis (Barroso-Moguel et al., 1994; Sarnyai et al., 1998). Depressed sperm production may be the result of cocaine-induced apoptosis, a process that has been demonstrated in rat testes but not in humans (Li et al., 1999).

Currently, the area of most intense research involves the relationship between the hormone leptin and CART-containing neurons of the ventromedial and ventrolateral arcuate nucleus (Kristensen et al., 1998). Functional studies in experimental animals have shown that CART and other related peptides are important regulators of food intake and that CART production is partly controlled by leptin receptors located in the hypothalamus (Meister, 2000). Such a relationship would, of course, help to explain the appetite suppression and weight loss that are such common features of chronic cocaine abuse.

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1.12.9 Immune system abnormalities

Chronic cocaine use alters the immune response, but how and to what extent remain a matter of debate. Almost all of the published data have been derived from animal and *in vitro* experiments. Drawing conclusions from animal studies is difficult because not all animals respond to cocaine in the same way. In mice, for example, chronic cocaine administration results in the suppression of all immunological parameters except for lymphocyte transformation. Because lymphocyte transformation is the test most widely used to screen for drug-induced immunosuppression, it would appear that the mouse may not be a good model for studying cocaine immunotoxicity (Ou et al., 1989). Rats chronically treated with cocaine have altered T-cell subsets with decreased numbers of CD8+ (suppressor) cells, and a normal population of CD4+ (helper) cells (Bagasra and Forman, 1989).

Two types of cellular immune response are now recognized: Th1 and Th2. Evidence has accumulated from animal models to suggest that Th1-type lymphokines are central to the causation of organ-specific autoimmune diseases, such as experimental allergic encephalomyelitis or insulin-dependent diabetes mellitus. Studies in humans seem to confirm the occurrence of a Th1 lymphokine profile in target organs of patients with organ-specific autoimmunity. Th2-cell predominance is found in the skin of patients with chronic graft-vs.-host disease, progressive systemic sclerosis, systemic lupus erythematosus, and allergic diseases. Both types of response are required for normal immune function, and a balance between the two is required; otherwise, protective responses are converted to pathologic ones (Singh et al., 1999). The results of human studies seem to indicate that using acute cocaine enhances Th1-type immune responses and inhibits Th2-type response (Gan et al., 1998).

Only a handful of human *in vivo* studies have been conducted. In one of the most recent, cocaine infusions (40 mg) and placebo saline were given to 15 chronic cocaine users and to an equal number of controls. Effects on interferon-γ (IFN-γ) and interleukin-10 (IL-10) cytokine secretion were examined. In addition, pre- and post-cocaine-infusion peripheral blood mononuclear cells (PBMCs) were harvested, cultured, and stimulated with

phytohemagglutinin A. Baseline IFN-γ levels were lower and IL-10 levels were higher in addicted subjects compared to those in control subjects, but treatment with cocaine increased IFN-γ secretion and decreased IL-10 secretion. Cocaine treatment failed to cause any increase in secretion of cytokines by the harvested white cells. On the other hand, the white blood cell and total lymphocyte counts, along with the CD4+ and CD8+ counts, were all increased. *In vitro* cocaine treatment of PBMCs from addicted subjects suppressed both IL-10 and IFN-γ secretion (Gan et al., 1998).

Of major concern is the close link between cocaine use and HIV infection. In spite of the limitations inherent in the animal models, there is increasing evidence that cocaine use facilitates HIV infection. *In vitro* studies of human cell lines tend to support the animal experiments, the results of which suggest cocaine in some way diminishes the body's resistance to HIV infection. Unstimulated peripheral blood mononuclear cells exposed to cocaine support increased levels of HIV-1 replication when compared to unexposed monocytes, although this effect is not seen in cells that are already infected (Bagasra and Forman, 1989). Phagocytic activity and T suppressor cell activity are decreased (Ou et al., 1989), and inhibition of delayed-type hypersensitivity has been demonstrated (Watson et al., 1983). Cultured human PBMCs lose much of their ability to produce superoxide anion (which is how they attack intracellular pathogens). This effect seems to be dose related (Chao et al., 1991; Baldwin et al., 1998).

While these *in vitro* studies are suggestive, other explanations for HIV infection in cocaine abusers are possible; increased permeability of the blood–brain barrier to HIV infection has been demonstrated. HIV-1 appears to penetrate the human brain microvascular endothelial cell barrier by a paracellular route. The pathway into the brain is a consequence of damage produced by TNF-α and by apoptosis of brain endothelial cells induced by direct cocaine toxicity (Fiala et al., 1998; Zhang et al., 1998). Nonetheless, the clinical relevance of all these observations has not been proven, and any correlation between cocaine use and HIV infection is likely to have as much to do with the sexual practices of the infected individuals as with an underlying immune abnormality (Kral et al., 1998; Grattendick et al., 2000b; Wang et al., 2000).

In spite of the occasional case report (Lavoie et al., 1993), no convincing evidence exists that chronic cocaine users are more vulnerable to bacterial, fungal, or other viral infections than members of the population at large. Indeed, a number of recent *in vitro* studies have shown quite convincingly that cocaine has antiviral properties (Lefkowitz et al., 1997; Grattendick et al., 2000a).

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1.12.10 Pregnancy interactions

Neither the prevalence nor the long-term effects of prenatal cocaine exposure are known with any degree of certainty. Early surveys, based on the results of urine-testing programs, understated the problem. Studies utilizing meconium and hair testing to assess prevalence are much more sensitive and suggest that 12 to 20% or more of the children born at inner-city hospitals have been exposed to cocaine (Forman et al., 1992; Martinez et al., 1996), although the findings of more recent studies tend to suggest that the real prevalence of exposure is at the lower end of the range. A 1997 study of infants born in Georgia using dried blood spot analysis to assess exposure found that 4.7/1000 children had been born to cocaine-using mothers (Henderson, et al., 1997).

Most of the abnormalities that have been identified in the offspring of pregnant cocaine users, including low birth weight, prematurity, and intrauterine growth retardation, are more directly related to the life-style of the drug user than to any pharmacologic effect of cocaine. Women who use cocaine during pregnancy are likely to be older (Richardson and Day, 1994), less likely to seek prenatal care (Cherukuri et al., 1988), more likely to be malnourished (Knight et al., 1994), and more likely to suffer from HIV infection, syphilis, and hepatitis (Ellis et al., 1993). They are also more likely to be cigarette smokers, and cigarette smoking is the apparent explanation for the lower birth weight of children born to cocaine-using mothers (Miller et al., 1995; Shiono et al., 1995).

Cocaine also stimulates human myometrial contraction, both *in vitro* and *in vivo*. Strips of uterus obtained at the time of Caesarean section contract much more forcefully when they are exposed to modest concentrations of cocaine (Monga et al., 1993). This increased force of contraction is mediated both by α-adrenergic stimulation and other factors that have yet to be identified (Hurd et al., 1998). Cocaine use during pregnancy is also associated with downregulation of myometrial β-adrenergic receptors, a change that could inhibit uterine relaxation and speed labor (Smith et al., 1995; Wang et al., 1996).

Whether or not this increased force of contraction actually translates into accelerated labor is a matter of some debate. In one study, the mean duration of labor in 16 cocaine users was 7.9 hours vs. 14.7 hours in 14 cocaine-free women (Dempsey and Vittinghoff, 1994). In a second study involving 1000 women, cocaine-using women were found to be older, of greater parity, and admitted to the hospital with greater degree of cervical dilatation (4.63 vs. 3.96 cm, $p = 0.05$). The time elapsed from admission to birth was substantially shorter in the cocaine users, (336 vs. 565 minutes, $p = 0.001$), but after controlling for type of delivery, parity, birth weight, and prenatal care, the difference proved to be insignificant (Wehbeh et al., 1995).

It has also been suggested that cocaine users are at increased risk for placenta previa (Cherukuri et al., 1988; Macones et al., 1997), but the increased risk, if real, is trivial compared to the greater than 2.3-fold increased risk of placenta previa seen in cigarette smokers (Kistin et al., 1996; Slotkin, 1998). Maternal cocaine use has been linked with placental abruption, but the actual incidence of this disorder is not known with any certainty, partly because abruption is a recognized complication of hypertension and preeclampsia, which means that after controlling for parity and prenatal care, it may be impossible to assess the contribution of cocaine to the problem.

Still, cocaine does interact with the placenta. Cocaine binds to serotonin and norepinephrine transporters located in the brush-border membrane of human term placenta (Ganapathy and Leibach, 1994). Depending on the physiologic status of the vascular receptors, elevated levels of serotonin, epinephrine, or norepinephrine could cause constriction of uterine blood vessels, resulting in decreased uteroplacental blood flow. In addition, human placenta exposed to cocaine produces more thromboxane and less prostacyclin than controls which could ultimately decrease uteroplacental blood flow (Monga et al., 1994), again leading to growth retardation and lower birth weights. While the changes in thromboxane and prostacyclin are relatively easy to demonstrate in experimental animals, they have been difficult to substantiate in humans. Nonetheless, it is clear that infants exposed *in utero* are more likely to have a lower birth weight (Bateman et al., 1993) and smaller head circumference than controls (Nulman et al., 1994). Controlled studies have also shown that maternal cocaine blood levels during the third trimester correlate inversely with birth weight and head circumference (Knight et al., 1994).

Numerous anecdotal case reports describing cocaine-associated malformations (Chasnoff et al., 1985, 1988; Hoyme et al., 1990; Ho et al., 1994; Hume et al., 1994) have been published but never confirmed in subsequent controlled studies (Kalter and Warkany, 1983; Hutchings, 1993; Snodgrass, 1994), nor has an alleged increased risk for SIDS been substantiated in well-designed, controlled studies (Bauchner et al., 1988; Kain et al., 1991; Fares et al., 1997; Ostrea et al., 1997). Similar considerations apply to reports linking cocaine use with antepartum fetal intracranial hemorrhage (Sherer et al., 1998). Studies of sheep exposed to cocaine *in utero* demonstrate an increased incidence of hypoxic lesions with gliosis, perivascular edema, hemorrhages, and neuronal death (Akoka et al., 1999), but the relevance to humans has not been established.

Hypertension and other clinical symptoms typical of preeclampsia have been observed in conjunction with cocaine use (Towers et al., 1993), and elevated levels of endothelin-1 have been detected in pregnant cocaine users (Samuels et al., 1993). However, the fact remains that hypertension in most pregnant women is the consequence of pre-existing hypertension or a consequence of gestation itself and not the result of cocaine use (Redline and Wilson-Costello, 1999). The observation is of considerable forensic interest, as hypertension itself can lead to pregnancy complications and even fetal demise; the detection of

low concentrations of cocaine in a fetus does not prove that cocaine was the cause of death or even the cause of hypertension.

Some link does appear to exist between *in utero* cocaine exposure and gastrointestinal abnormalities. Human fetal exposure to cocaine induces bilirubin-metabolizing pathways, making neonatal jaundice less likely (Wennberg et al., 1994). Evidence is accumulating that implicates fetal cocaine exposure in the development of necrotizing enterocolitis (Downing et al., 1991; Czyrko et al., 1991). Necrotizing enterocolitis is a poorly defined syndrome with a significant mortality rate and a host of predisposing risk factors (asphyxia, hypoxia, apnea, jaundice, etc.) (Downing et al., 1991; Porat and Brodsky, 1991; Amoury, 1993; Levy, 1993; also see Section 1.12.4 for clinical and pathologic findings), but strangely no new case reports dealing with cocaine-related enterocolitis have been published since 1995.

Human histopathologic studies of both the cocaine-exposed fetus and placenta are rare. Detailed examination of placentas from 13 pregnancies with cocaine-related complications failed to demonstrate any specific changes (Gilbert et al., 1990). Vascular changes have, however, been documented in the human fetus by noninvasive means. Doppler studies have shown renal artery vasoconstriction and a simultaneous decrease in urine output (Mitra et al., 1994). Neonatal myocardial infarction and reversible myocardial calcification have both been described (Bulbul et al., 1994; Yap et al., 1994), and the incidence of arrhythmia in the neonatal period seems to be increased (Frassica et al., 1994). All of these abnormalities could be explained by exposure of the fetal heart to high circulating levels of catecholamines *in utero*, but it is difficult to draw any firm conclusion based solely on isolated clinical reports, especially in the virtual absence of histopathologic studies.

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1.13 When is cocaine the cause of death?

Cocaine-related deaths pose a forensic problem of considerable and increasing importance. If cocaine is listed as the cause of death, then in many jurisdictions the death is classified accidental. Many insurance policies exclude death by the self-administration of drugs, but double indemnity claims can occur if death is deemed accidental, a decision most insurance companies will not willingly accept. The role of cocaine can be equally important in criminal cases. The social stigma associated with the diagnosis of drug-related death cannot be ignored, if for no other reason than the lawsuits sometimes brought by the family members who claim that the deceased never used drugs.

Given the importance of the subject, it is disappointing to see how often deaths caused by cocaine are misclassified (see Figure 1.13.1). Many misconceptions about cocaine-related deaths persist, largely because death certification practices are not standardized. Sometimes use of the *ICDM 9* classification system may even obscure important aspects of cocaine-related deaths, leading to both misdiagnosis and inaccurate mortality statistics (Young and Pollock, 1993). The worst, and perhaps most blatant, example of death misclassification is the mistaken belief that cocaine users suffering from excited delirium die because of the way they have been restrained, rather than from the changes cocaine has produced in their hearts and brains.

The mere presence of cocaine, or any other drug for that matter, does not prove that it was the cause of death or even the cause of toxicity. Drug use is pervasive in the U.S., and postmortem testing frequently reveals the presence of cocaine metabolite, or cocaine

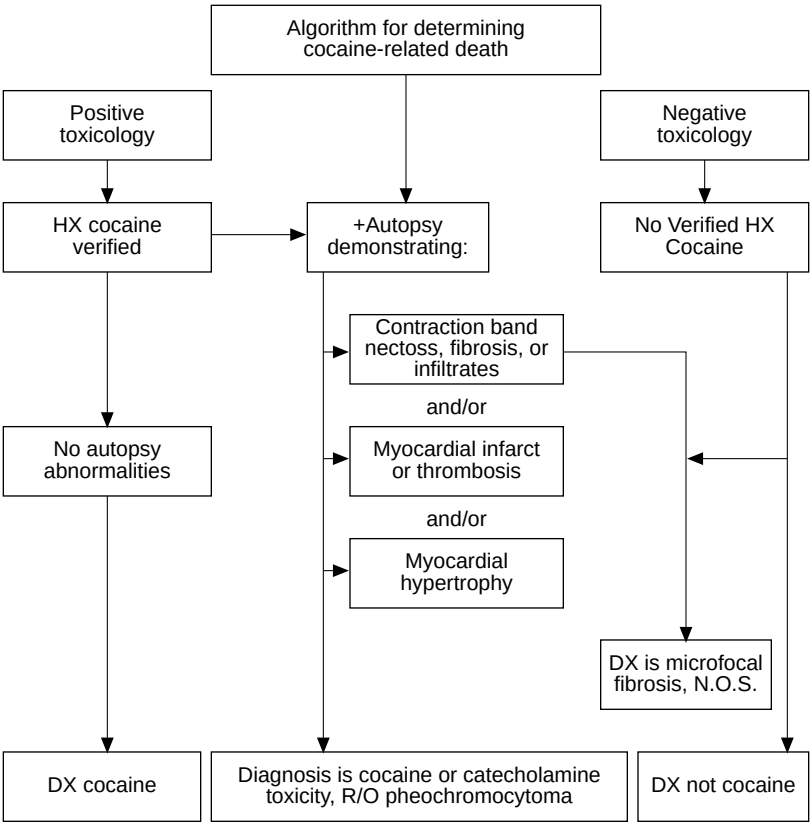

Figure 1.13.1 **When is cocaine the cause of death?** Suggested algorithm.

itself, in very low nanogram quantities (in the 5- to 15-ng range). The presence of such low levels is only proof of environmental exposure or, at most, use of cocaine within the last week or so of life. There is convincing evidence of prolonged cocaine excretion in chronic users (Weiss and Gawin, 1988; Cone and Weddington, 1989; Burke et al., 1990), so it follows that there must be reservoirs, such as skin or fat, where cocaine is stored (Levisky et al., 2000). It may well be that very low cocaine or cocaine metabolite concentrations measured in postmortem samples are the result of drug released from these reservoirs, and that the drug was not even present in the blood at the time of death.

Cocaine levels of less than 50 ng/mL do not produce measurable physiologic effects, let alone toxicity. In the absence of any confirmatory histopathologic changes, cocaine levels of less than 50 ng/mL should not be deemed the cause of death. On the other hand, if the appropriate histologic changes are present, cocaine may be the cause of death, even when blood cocaine levels are zero. To ensure the correct diagnosis, physical and laboratory findings must be integrated with information from detailed case histories and meticulous scene investigations. Measurement of blood cocaine and benzoylecgonine levels only permits a very rough estimation of when and perhaps how much drug was taken. The half-life of cocaine varies greatly from individual to individual, and the volumes of distribution (V_d) of the cocaine metabolites have never even been measured. Because of all the unknowns, it probably is *not* legitimate to assume that, because cocaine concentrations are

high and metabolite concentrations are low, that ingestion occurred in close proximity to the time of death.

Blood concentrations alone also cannot be used to determine whether cocaine was the cause of death, because tolerance occurs (Smart and Anglin, 1987). The rapid emergence of tolerance explains why cocaine-related deaths are not dose related (Karch and Stephens, 1991; Karch et al., 1998). Blood levels of over 5000 ng/mL may merely be incidental findings. No upper concentration limit can be guaranteed fatal and, in chronic users with abnormal hearts, no lower concentration limit can be guaranteed safe. Anatomic alterations resulting from chronic cocaine use may persist indefinitely, even after drug use is discontinued. These changes may be the cause of death, even when no cocaine or metabolite is detectable.

While cocaine-related deaths are not dose related, they can reasonably be divided into those deaths resulting from acute toxicity and those due to chronic toxicity. The very first dose of cocaine may lead to myocardial infarction from coronary spasm, particularly if significant underlying coronary artery disease is present, but the amount of cocaine present must be at least sufficiently great to cause transient blood pressure elevations. The concentration can only be guessed at, but obviously a postmortem blood concentration of 15 ng is unlikely to be associated with any measurable effects; a concentration of several hundred nanograms per milliliter almost certainly would be.

Cocaine-induced pressure rises may lead to the rupture of a pre-existing Berry aneurysm or A–V malformation. Cardiac standstill can be another manifestation of acute toxicity, but usually only at the very high blood concentrations (>20 mg/L) seen in drug smugglers with massive amounts of cocaine sequestered in their bowels. All local anesthetics have toxic effects on the myocardium and can cause marked depression of cardiac output (Rhee et al., 1990; Strichartz, 1987), leading to infarction or asystolic arrest secondary to ion channel blockade (Nademanee et al., 1994; Xu et al., 1994).

The mechanisms of chronic cocaine toxicity are becoming clearer. Chronic cocaine abuse causes a number of changes in the structure of the heart, and all of these changes favor the occurrence of arrhythmias. Chronically high concentrations of cocaine result in myocardial hypertrophy, a change that is much more prevalent than had previously been appreciated (Brickner et al., 1991; Escabedo et al., 1992; Karch et al., 1995). Myocardial hypertrophy is a powerful and independent predictor for sudden cardiac death (Kannel et al., 1969; Dunn and Pringle, 1993). Even in the absence of cocaine, myocardial hypertrophy is associated with increased collagen production and fibrosis (Yamazaki et al., 1999), but it also appears that cocaine itself is capable of stimulating collagen production (Besse et al., 1997). Myocytes destroyed by contraction band necrosis heal by fibrosis (Karch and Billingham, 1988). Fibrosis favors the occurrence of re-entrant arrhythmias, and the presence of this anatomic alteration can disrupt conduction long after cocaine use has been discontinued.

The degree of myocardial hypertrophy seen in cocaine users, while highly significant, is nonetheless modest (less than 10% above predicted weight). Because the increase is small, it is likely to go unrecognized. The only way to make the diagnosis is by comparing the heart weight of the deceased to a standard nomogram (Kitzman et al., 1988) (see Section 1.12.2.6 and the Appendix). Some confusion may arise in the case of competitive athletes with an enlarged heart; however, the pattern of hypertrophy seen in athletes (eccentric) is different from that seen in hypertensives (concentric), and the two are easily distinguishable. There is another important difference between hypertrophy resulting from stimulant abuse and hypertrophy due to aerobic conditioning: the degree of angiogenesis in athletes is much greater (Chen et al., 1994; Gavin et al., 1998).

Though it is not generally recognized, myocardial perfusion may be decreased, even when the large epicardiac arteries do not manifest high-grade obstruction. Reduced perfusion may occur as a consequence of microvascular disease. This disorder is just as likely to go unnoticed as are mild degrees of myocardial hypertrophy. In many jurisdictions, the heart is not examined microscopically or, if it is, only one or two sections may be evaluated, and mild thickening of the media of the smaller, intramyocardial arteries, with a proportional reduction in luminal size, is likely to go unrecognized. This abnormality has already been demonstrated in cocaine users and can lead to myocardial ischemia just as surely as obstruction of the large arteries, albeit by a somewhat different mechanism.

Small vessel disease almost certainly accounts for some of the in-custody deaths that are seen after police confrontations with psychotically agitated cocaine abusers. Myocardium that is relatively underperfused (decreased microvascular circulation combined with increased myocyte size), even in the resting state, would become dangerously ischemic during any intense physical activity. Ischemia predisposes to sudden cardiac death, and there is no need to speculate about the contributory role of "hog-tying" or "positional asphyxia."

In summary, in the presence of a strong history of cocaine abuse with typical myocardial pathology, cocaine is the cause of death, even in the face of negative toxicology. Presuming that appropriate measures have been taken to rule out pheochromocytoma, there simply is no other diagnosis. On the other hand, if typical pathologic findings are present, but toxicology and history are both negative, the diagnosis must be microfocal fibrosis or microvascular disease (perhaps syndrome X) (Picano, 1999), etiology "not otherwise specified." In the event that additional information becomes available at a later date (for example, exhumation with hair testing), the diagnosis can be revised, but the presence of isolated myocardial alterations is not sufficient for diagnosis. For that reason, many states (California is an exception) simply list the cause of death as "drug-related." Such a designation covers all deaths not considered to be suicide, but rather unexpected complications of chronic drug usage. It is unnecessary, therefore, to attempt to make the artificial separation between toxicity and poisoning.

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chapter two

Natural stimulants

Cocaine is certainly not the only plant that contains psychoactive alkaloids; at least four other species contain alkaloids capable of producing amphetamine-like effects, and a number of other New World plants contain potent hallucinogens. Four species contain alkaloids that behave more like stimulants than like hallucinogens: absinthe, caffeine, khat, and ephedra. The latter two compounds are both classified as phenethylamines.

Absinthe abuse ceased being a problem at the turn of the century; however, the key herbal ingredients contained in absinthe are sold as "health food supplements," and absinthe liqueurs are now produced in the Czech Republic and in some Eastern European countries. Absinthe is now sold at fashionable bars in London (Shaw, 1999). Khat, which had been confined to the sub-Sahara for more than 1000 years, is now used in many parts of Africa and is even grown clandestinely in the U.S. (Wallace, 1998). Xanthine derivatives, especially caffeine, are the world's most widely consumed natural stimulants.

The other important naturally occurring stimulant is ephedrine. When smoked, or injected intravenously, ephedrine is a potent stimulant. Ephedrine was widely abused in Asia during World War II, and was considered a major threat to public health in Japan during the 1950s. Today, ephedrine is important mainly because it can be used as a precursor in the illicit production of methamphetamine. It is also used as a food supplement, promoted for its effectiveness in weight-loss programs and for improving athletic performance.

Except for caffeine, very little is known about the human pharmacotoxicology of these agents, and not that much more is known about their effects in animals. Almost nothing is known about the pathologic changes associated with the abuse of any of these agents.

2.1 Absinthe

2.1.1 Incidence

Absinthe is not mentioned in any of the Drug Abuse Warning Network (DAWN) reports published in the 1990s (DAWN methodology requires at least 10 deaths per year caused by a particular substance for that substance to qualify for inclusion in the report). The lack of DAWN mentions does not necessarily mean that no episodes of toxicity have occurred. None of the ingredients in absinthe would be detected by standard toxicology screening tests, either in the emergency room or at autopsy, so the true incidence of toxicity remains unknown. However, the same toxic monoterpene ketones found in absinthe are also present in the essential oils of eucalyptus, fennel, hyssop, pennyroyal, rosemary, sage, savin, tansy, thuja, and other popular herbal remedies; published case reports have described seizures and even status epilepticus following the use of some of these oils (Burkhard et al., 1999).

2.1.2 Epidemiology

Absinthe is not specifically mentioned in the National Household Survey. Packages of *Artemisia absinthium,* containing wormwood and other herbs (hyssop, anise, fennel, sweet melissa, and others), are sold in "head shops." Homebred absinthe is easily produced by adding the premixed packets to alcohol (Burkhard et al., 1999). Absinthe is now sold as an aperitif in the Czech Republic and other Eastern European countries. Buyers of these products have never been surveyed, so their age, sex, and occupational profiles remain unknown.

2.1.3 History

Absinthe is a French word for wormwood (*Artemisia absinthium* and *Artemisia pontica*), a perennial herb related to sage (*Salvia officinalis*). The Egyptians used wormwood for medical purposes. Pliny, in the first century A.D., recommended it as a vermifuge, and wormwood is mentioned in several of Shakespeare's plays (Arnold, 1989). In *Romeo and Juliet*, Act I, Scene 3, the nurse discourses:

> For I had then laid wormwood to my dug,
> Sitting in the sun under the dove-house wall;
> My lord and you were then at Mantua: —
> Nay, I do bear a brain: — but, as I said,
> When it did taste the wormwood on the nipple
> Of my dug, and felt it bitter, pretty fool…

Late in the 1700s, techniques for the mass production of grain alcohol were introduced, and shortly afterward herb-based liqueurs appeared on the market. A French general practitioner, working in Switzerland, is credited with first devising the formula (Lachine, 1967). In early 1797, he sold the formula to Henri-Louis Pernod, who ushered in the era of absinthe abuse when he opened his factory in Pontarlier. Pernod's liquor became immensely popular in France and throughout Europe (Arnold, 1989). By the time of the Parisian Exposition Universelle in 1867, most boulevard cafes in Paris had their equivalent of a "happy hour," except that it was called the *heure verte* ("green hour") because of absinthe's green color.

The main ingredients in absinthe are the essential oils of five herbs: wormwood, angelica, anise, marjoram, and calamus. The toxicity of absinthe has always been attributed to wormwood, but some of these other plants contain pharmacologically active compounds. Angelica (*Angelica archangelica* L., Umbeliferae) contains ferulic acid, which acts both as a cyclooxygenase and as a thromboxane A2 synthetase inhibitor (Kuenzig et al., 1984; Lanhers et al., 1992).

Calamus (*Acorus calamus* L. var. *americanus* Wulff or *A. calamus* L. var. *vulgaris* L., Araceae) is a hallucinogen and a potential carcinogen (Vohora et al., 1990). The β-asarone in calamus causes cancer in experimental animals but is found only in the calamus grown in Europe and Asia; α-asarone, also found in calamus, is similar in structure to reserpine. The structures of both α- and β-asarone bear a strong resemblance to the structure of "Ecstasy" (3,4-methylenedioxymethamphetamine, or MDMA) (Vargas et al., 1998). Asarones tend to decompose over time, losing their psychoactive properties within a few months of harvesting. The possibility exists that, once dissolved in alcohol, the psychoactivity of asarones may be longer lasting. Calamus is still used as a "recreational" hallucinogen in the U.S., although its popularity is somewhat limited by the nausea that accompanies its use (Karch, 1999).

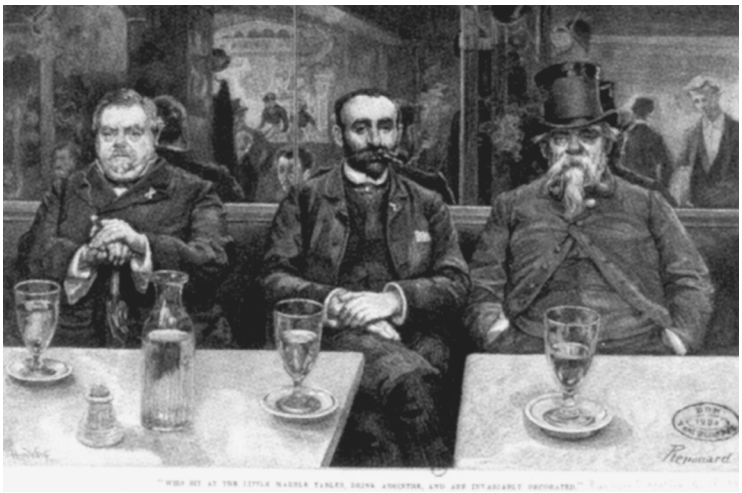

Figure 2.1.3.1 **Absinthe drinkers.** These gentlemen were obviously intoxicated, but whether from the terpenes or the alcohol in their drinks is not entirely clear. Some evidence suggests that the active ingredients in this drink may have been very similar to those in marijuana. (From *Harper's Magazine*, April 1889.)

Absinthe drinking became popular just a few years before Angelo Mariani started selling his coca-fortified wines, and the popularity of both coca and absinthe rose almost in parallel. French impressionist painters left an enduring record of just how popular the drink was (see Figure 2.1.3.1). During the 1860s and 1870s, Degas and Manet immortalized images of absinthe drinking. Toulouse-Lautrec painted van Gogh with a glass of absinthe (Morrant, 1993). Some even speculate that Van Gogh's mental illness was related to his abuse of absinthe, either as a consequence of its direct toxicity or because it exacerbated an undiagnosed (and at the time not even recognized) case of acute intermittent porphyria (see discussion below) (Bonkovsky et al., 1992).

Toulouse-Lautrec's painting of van Gogh was completed just 3 years after Freud published his infamous paper *Über Coca* (Freud, 1884). Baudelaire used both cocaine and absinthe, but wrote about only the latter. Valentine Magnan studied the medical complications of both cocaine and absinthe (Magnan, 1874) and sounded warnings about the potential toxicity of each. Just as American and European manufacturers of cocaine-containing patent medicines minimized the medical problems associated with cocaine use, so did the manufacturers of absinthe cordials.

Public relations campaigns mounted by the absinthe makers (and the cocaine manufacturers) attempted to minimize the risks, and sales boomed. From 1875 to 1913, annual consumption of absinthe per French citizen increased by 1500% (Arnold, 1989). However, the success of the advertising campaigns was short lived, and, just 2 years before the Harrison Narcotic Act banned cocaine from patent medications in the U.S., the French government passed legislation limiting the alcohol and absinthe content of commercial products. In 1915, the sale and manufacture of absinthe were banned entirely. Since the breakup of the former Soviet Union, absinthe production has resumed in several Eastern European countries, particularly the Czech Republic. In the U.K., a buyers' cooperative has been established to import absinthe. At the moment, the best known import is "Hills Absinthe." It contains 70% ethanol, in addition to the standard mix of thujone-containing herbs (Shaw, 1999). Many other brands are sold in English pubs and at bars throughout Europe.

2.1.4 *Physical constants*

Absinthe is prepared either as a distillate of aromatic herbs or as a solution made by steeping the herbs in alcohol, so the physical characteristics of any particular sample will depend on the production techniques used by the manufacturer. It will also vary from batch to batch, particularly if the absinthe is home brewed or if the liqueur is made with components purchased from a "head shop." A fairly high concentration of alcohol is required to keep the various essential oils in solution. According to the older classifications, absinthe ordinaire contained 47.6% alcohol, absinthe demi-fine contained 68% alcohol, and premium grade, also known as absinthe Suisse, contained 80.66% ethanol (Vogt and Montagne, 1982). Some of the components, such as thujone, are found in other plants (sage, in particular) (Ishida et al., 1989; Loza-Tavera, 1999).

2.1.5 *Sources*

Absinthe liqueurs are not legally sold in the U.S., but they can be purchased in some European countries. In the U.S., all of the herbs used to produce absinthe can be legally purchased, and absinthe can be brewed at home. If distillation is used, home production would come under the same federal regulations that apply to home brewing.

2.1.6 *Routes of administration*

Absinthe is only taken orally. Resultant blood concentrations of the individual herbal components are not known. The ethanol content can be exceedingly high, but whether or not the herbal components have any effects that would alter the rate of absorption or excretion has not been determined.

2.1.7 *Metabolism and pharmacokinetics*

Three different kinds of terpenoids are found in absinthe: thujones (α and β) (see Figure 2.1.7.1), camphor, and pinenes. The structure of thujone, the principal terpene extracted from wormwood, was published in 1900. Modern clinical studies of terpenoids are all but nonexistent, although the synthetic route by which they are formed in nature is known. All of the monoterpenes are 30-carbon compounds and may contain one, two, or no ring structures. They are produced by monoterpene synthetases using geranyl pyrophosphate as a substrate (Loza-Tavera, 1999).

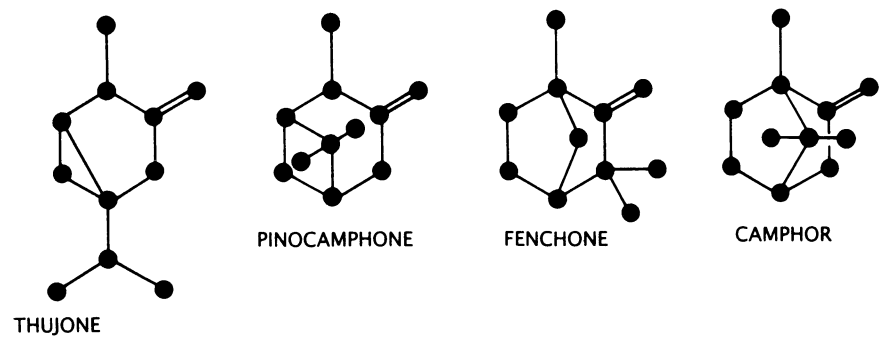

Figure 2.1.7.1 **Terpenes.** Absinthe contains many different compounds; thujone is the principal agent.

In metabolic studies of experimental animals, the carbonyl group of thujone is reduced to yield a series of secondary alcohols. *In vitro* studies, done with chick embryo liver cells, have shown that these molecules have the ability to cause increased porphyrin production (Ishida et al., 1989). These findings suggest that individuals with impaired heme synthesis, such as those with acute intermittent porphyria, may be at risk if they are exposed to absinthe or wormwood oil in any form. Eucalyptol has already been implicated in precipitating attacks of porphoryia (Bonkovsky et al., 1992). The pharmacokinetics of these compounds has not been studied.

More recent studies suggest that wormwood, along with lemon balm (*Melissa officinalis*), contains compounds that bind to human brain acetylcholine receptors (Perry, 2000). The cholinergic system modulates neurotransmitter systems in the brain and controls activities that depend on selective attention. Drugs that can antagonize muscarinic receptors also have the ability to induce hallucinations, and reduce the level of consciousness (Perry et al., 1999). That ability may explain, at least partially, the "high" experienced by absinthe drinkers.

Human metabolic studies are lacking, but in animals, enzymatic reduction (possibly by a cytosolic ketone reductase) of thujone to thujol and neothujol, has been demonstrated in rabbit, but not mouse, liver. The mouse liver microsomal P-450 system rapidly converts thujone to 7-hydroxythujone and to smaller amounts of the 4-hydroxythujone diastomer and other hydroxythujones. Dehydrothujone is also formed. It is presumed that the various hydroxythujones then undergo conjugation and excretion. In animal toxicity studies, brain concentrations of 7-hydroxythujone metabolite are severalfold greater than concentrations of thujone, suggesting that the metabolite may also be toxic (Hold et al., 2000).

2.1.8 Tissue concentrations

Tissue concentrations of thujone have not been determined in clinical trials, nor have blood and tissue concentrations for camphor-associated deaths ever been measured in humans.

2.1.9 Toxicity by organ system

Reports from the 1920s and 1930s suggest that α- and β-thujone produce clinical effects that are indistinguishable from those of camphor. Camphor is a potent central nervous system (CNS) stimulant and, before the introduction of electroconvulsant therapy, camphor was used to treat depression. Small doses of camphor cause stimulation and euphoria, but ingestion of larger amounts (>30 mg/kg) can result in convulsions, coma, and death. In pediatric poisonings, camphor ingestion of greater than 50 mg/kg are almost always associated with obvious neurologic toxicity, including prolonged, generalized, tonic-clonic seizure (Gouin and Patel, 1996; Burkhard et al., 1999). Just what sort of lesions are to be seen, if any, is not known. Presumably, the findings would not be any different than in any other patient with status epilepticus. Because of the potential toxicity of camphor, camphor-containing over-the-counter products must contain less than 11% camphor. Allowable concentrations in other countries are slightly higher (Food and Drug Administration, 1983).

Without knowing the thujone, camphor, pinene, or asarone content of the absinthe being consumed or what other herbs and secret ingredients have been added, it is difficult to say how much of the various terpenoids absinthe drinkers are actually getting, let alone whether that amount is sufficient to cause toxicity. It seems likely that the amount actually required would be far less than the 30 mg/kg suggested as the fatal dose in the older literature (Amory, 1868).

The molecular structures of thujone and tetrahydrocannabinol are, in some respects, very similar. Because of those similarities, it has been suggested that the psychological effects ("high") experienced by absinthe users are really just another variety of marijuana intoxication (del Castillo et al., 1975). More recent studies, using radioligand receptor binding assays, have shown that not to be the case. Thujone is the only component of wormwood oil that has any affinity at all for the CB1 cannabinoid receptor, and then only in massive doses far exceeding those that could conceivably be encountered in any absinthe drinker (Meschler and Howlett, 1999). A more plausible explanation for the intoxicant effects of absinthe may have to do with the recent finding that thujones are γ-aminobutyric acid type A ($GABA_A$) receptor agonists. Drugs that block this channel, such as picrotoxin, are powerful convulsants. In small doses, GABA channel blockers are analeptics, producing intoxicating and disinhibiting effects (Hold et al., 2000; Olsen, 2000).

Stomach upset was a common complaint of absinthe drinkers in Paris during the late 1800s. Vincent van Gogh wrote several letters to his brother Theo complaining of stomach upset after bouts of absinthe drinking (Morrant, 1993), and a syndrome strongly resembling Reye's syndrome has been described in children treated with camphor-containing products (Jimenez et al., 1983). However, the two disorders are distinct histologically. Marked hepatic steatosis is seen in both Reye's syndrome and in cases of absinthe toxicity, but exposure to camphor does not produce evidence of cellular necrosis, bile stasis, Mallory bodies, or mitochondrial abnormalities. Camphor is still a common ingredient in many over-the-counter medications (Camphophenique®, Mentholatum®, Vicks Vaporub®, Sloan's Liniment®, etc.) and is responsible for occasional episodes of toxicity (Gibson et al., 1989). Treatment consists of airway maintenance and seizure control (Liebelt and Shannon, 1993; Emery and Corban, 1999), although so few cases have been reported that the appropriate treatment is not really known.

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2.2 Caffeine

2.2.1 Incidence

Caffeine is the most widely used stimulant in the world. Annual consumption is more than 100,000 tons. Estimates suggest that over 80% of the U.S. population drinks coffee or tea, and formidable amounts of caffeine are also consumed in soft drinks, cold medications, and pain-relief formulas. In spite of the widespread use of this drug, neither the Medical Examiner's component nor the Emergency Room component of the most recent DAWN survey (1999) makes any mention of caffeine, suggesting that episodes of serious toxicity are very uncommon (Kissin et al., 2000a,b).

2.2.2 Epidemiology

Table 2.2.2.1 shows the caffeine content of some commonly consumed beverages and medications. The average American adult consumes 2.4 mg/kg/day of caffeine. Intake for children between the ages of 5 and 18 is thought to be half that amount. European consumption is said to be even higher: 3.5 mg/kg/day (Communities, 1983). An average cup of coffee contains 40 to 100 mg of caffeine, and the average American drinks two cups a day; the average European, three. The content of cola drinks is lower, ranging from 30 to 65 mg per 8-ounce serving, but the caffeine intake of some cola drinkers is substantially higher than that of coffee or tea drinkers.

Table 2.2.2.1 Caffeine Content of Some Common Beverages and Medications[a]

Beverage	Caffeine (mg)
Carbonated beverages (12 oz can)	
Coca Cola®	64.7
Dr. Pepper®	60.9
Mountain Dew®	54.7
Diet Dr. Pepper®	54.2
Pepsi-Cola®	43.1
RC Cola®	33.7
Tea bags (average per cup)	
Black teas	21–33
Green teas	9–19
Coffee (average per cup)	
Instant	62
Electric percolator	100
Stove percolator	105
Drip	140
Starbuck's tall latte	375
Starbuck's grande (470 mL)	>500
Coca	10–17
Medications	
Norgesic Tablets®	30.0
Darvon Compound 65®	32.4
Fiorinal Capsules®	40.0
Excedrin Extra Strength®	65.0
Caffergot Tablet®	100.0
No Doz Tablets®	100.0
No Doz Maximum Strength®	200.0

[a] Data for caffeine-containing beverages taken from Bunker, M. and McWilliams, M., *JADA*, 74, 28–32, 1979. Current labeling requirements do not require manufacturers to list caffeine content. Values may have changed since the Bunker and McWilliam paper was published. Data for medications taken from current PDR.

2.2.3 Chemical constants

Caffeine is 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione or 1,3,7-trimethylxanthine. Other older names were methyltheobromine and thein. The formula for caffeine is $C_8H_{10}N_4O_2$, and it has a molecular weight of 194.19. It is composed of 49.5% carbon, 5.2% hydrogen, 28.9% nitrogen, and 16.5% oxygen. Purified caffeine crystallizes into hexagonal prisms with a melting point of 238°C. It is a basic alkaloid with a pKa of 0.8 (Budavari et al., 1996).

2.2.4 History

The origins of coffee drinking are a mystery. According to legend, the prior of a Muslim convent observed that goats eating beans from certain trees tended to stay up all night. He assumed that the beans were responsible and concluded that using the beans might help him and his followers stay awake during their long prayer vigils in the mosque. The

prior brewed a beverage called "kahweh" and was said to have been quite pleased with the results. The first convincing evidence of its widespread popularity is from the sixteenth century. In 1511, when a new Egyptian governor arrived in Mecca, he noticed people sitting around the mosques drinking coffee. He asked what they were doing, and he was told that they were drinking coffee to give them the energy they needed to pray all night.

The governor had his doubts about the propriety of the practice, and he convened a meeting of clerics and elders to discuss the subject. The governor feared that coffee might be some sort of intoxicating agent, and its use would be prohibited by the *Koran*. The assembly concluded that coffee was indeed an intoxicant, and therefore should be banned. Sales of coffee were prohibited and stocks were burned. Had the new governor bothered to check with his superiors, he would have found that the Sultan of Cairo was an avid coffee drinker; the Sultan promptly overruled the governor's decision, and coffee drinking in Mecca has been legal ever since.

Venetian traders introduced coffee to Europe. In London, the first coffee shop opened in 1652 and was located in St. Michael's Alley, Cornhill. Its owner, Pasqua Rosee, advertised extensively, making mostly medicinal claims for the drink. According to Rosee, coffee was "a very good help to the digestion … and makes you fit for business"(Thompson, 1928). In spite of Rosee's claims, coffee drinking was at first suspect among the Europeans. Coffee drinkers were said to have a haggard appearance and to be "subject to fits of agitation and depression." Coffee drinking had been introduced into France nine years earlier and by 1690, 250 coffee houses were registered in France; by 1782, that number had risen to 1800. Some of the coffee houses were quite opulent, with marble tables and crystal chandeliers. Like the English, the French also had some doubts about the habit. Medical literature from that period contains reports both praising and condemning the effects of coffee. It was alleged that coffee caused inflammation of the liver and spleen, and that it even caused kidney stones.

Suspicions that coffee drinking is unhealthy have never entirely disappeared. Even Virchow classified caffeine, along with alcohol, as an addictive substance. Lewin (1931), who generally thought that coffee drinking was a good thing, accepted reports of "delirium, vertigo, trembling, and even convulsions" as an occupational disease in coffee roasters. In modern times, epidemiological investigations have focused on possible links between caffeine intake and myocardial infarction, sudden death, and fibrocystic disease. Alleged links to cancer have never been proven (Stavric, 1992). The histopathologic changes associated with caffeine abuse have been studied only in animals (Strubelt et al., 1976), but convincing histologic lesions have never been demonstrated in humans. Interestingly, the same suspicions have never been entertained about other caffeine-containing beverages such as cocoa, and certainly never about tea, even though both contain substantial amounts of caffeine. Indeed, it has become increasingly apparent that tea consumption may actually protect against cancer (Hirose et al., 1999; Okabe et al., 1999).

2.2.5 Sources

Caffeine is a methylated purine derivative and, like cocaine, is classified as an alkaloid. The term *alkaloid* was originally introduced to describe compounds extracted from plants, the salts of which were crystallizable. The caffeine used to make medicines, food supplements, and even some food products comes not from the coffee beans but from other plants entirely. Caffeine is found in kola nuts, cocoa beans, tea (*Camellia sinesis*), and guarana. Depending on the type of bean, chemical extraction of roasted coffee beans yields from 8 to 20 mg of caffeine per gram of coffee (Zuskin et al., 1983).

Teas (beverages made from the leaves of *Camellia sinesis*) also contain caffeine, but herbal teas made by soaking other plant leaves, such as mint, in hot water do not contain caffeine, nor does it appear that they contain the antioxidants thought to prevent cancer. Green teas, such as Gunpowder tea, are made from tea leaves that are heated immediately after they are picked, then rolled and crushed, thereby preserving the natural constituents of the leaves, including their color. Black teas, such as Pekoe, are picked, allowed to dry, and then packaged. Fermentation partly digests some of the components of the leaf, giving black tea its reddish-brown color (Karch, 1999). The caffeine content of a cup of tea depends partly on which leaves are used and on how the leaves are brewed; however, the caffeine content of *Camellia sinesis* is not high enough to make extraction for other purposes worthwhile.

Much greater quantities of caffeine can be extracted from a South American plant known as guarana (*Paullinia cupana* Mat. var. *Sorbilis,* Sapindaceae). Guarana seeds contain more caffeine (4 to 5%) than any other plant and are the main source of commercial caffeine. In addition, the leaves contain large amounts of theobromine (Carlson and Thompson, 1998), a close relative of caffeine. Guarana also contains a number of tannins, some very similar to those found in tea (the same ones that are thought to provide beneficial antioxidant effects) (Morton, 1992). At least nine different antioxidants/tannins have been identified in the oil extracted from guarana; two of them, estragole and anethol (Benoni et al., 1996), are thought to be psychoactive. In Brazil, guarana is used to make an extremely popular carbonated soft drink. In laboratory studies, low concentrations (1.2 μg/mL) of guarana inhibit lipid peroxidation. No histopathologic changes secondary to guarana ingestion have been detected, even in animals treated with very large amounts (250 to 2000 mg/kg) of this drug (Mattei et al., 1998).

Two main varieties of the coffee plant are used for brewing coffee: robusta and arabica. As its name implies, the robusta plant is the hardier of the two, but at a price. Beverages produced from it do not have nearly the flavor of arabica beans, which is why most robusta beans are used to make instant coffee or are used in the least expensive coffee blends. While robusta beans may be lacking in flavor, their caffeine content is about twice that of arabica.

2.2.6 Routes of administration

Most caffeine is consumed orally, either in beverages or in medications, particularly those used to treat headache and migraine (Pradalier et al., 1985). Caffeine is also given intravenously to help prevent headache after spinal anesthesia (Yucel et al., 1999), and to treat apnea in pre-term infants (Tobias et al., 1998). The pharmacokinetics of caffeine remains the same, regardless of the route of administration (Fredholm et al., 1999).

2.2.7 Metabolism

Caffeine and theophylline are metabolized by the P-450 system, specifically cytochrome CYP1A2 (Figure 2.2.7.1). Activity of this enzyme is low at birth but gradually increases, reaching its peak in early adulthood, only to decrease again in old age (Tanaka, 1998). Low CYP1A2 activity partially explains why theophylline toxicity is more likely to occur in neonates than adults. In premature neonates, CYP1A2 activity responsible for the *N*-demethylation of theophylline is so low as to be effectively absent. As a consequence, approximately half of a given dose of theophylline will be excreted unchanged in the urine, while the remainder undergoes conversion to other xanthines. After giving theophylline to a neonate, at steady state, caffeine concentrations average 30% of the theophylline concentration.

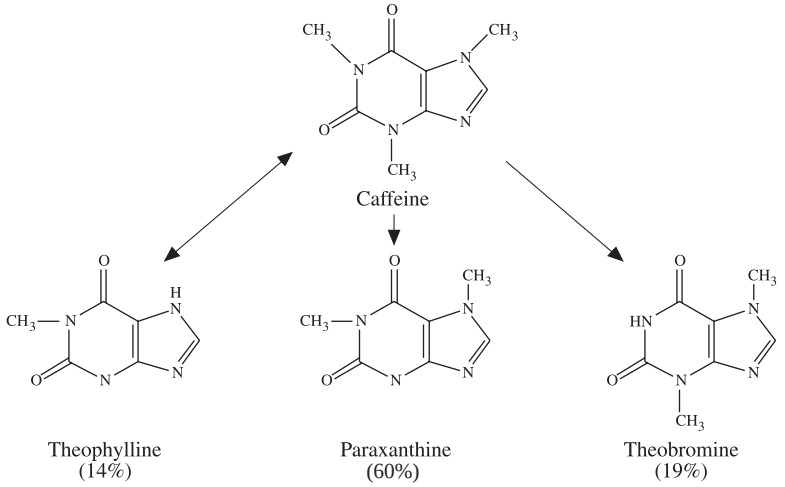

Figure 2.2.7.1 **Caffeine metabolism.** Assuming an average caffeine intake of roughly 500 mg per day, 60% will be excreted as paraxanthine, 20% as theobromine, and 14% as theophylline. The results may be quite different in smokers and patients with cirrhosis.

Both caffeine and theophylline are converted almost entirely to other xanthines, then excreted in the urine. At least 14 different caffeine metabolites have been identified in human urine (Rodopoulos and Norman, 1994). On average, 14% of ingested caffeine is excreted as theophylline and 60% as the demethylation product paraxanthine (1,7-dimethylxanthine). Paraxanthine is not found in nature but is found as a metabolite in many different species (Ullrich et al., 1992), and has sympathomimetic effects comparable to those of caffeine itself (Benowitz et al., 1995). In humans, paraxanthine is either acetylated or further demethylated to a compound devoid of sympathetic activity (Sawynok and Yaksh, 1993).

Many commonly prescribed meditations are potent CYP1A2 inhibitors. These include serotonin re-uptake inhibitors (Prozac™), antiarrhythmic drugs such as mexiletine, antipsychotics (clozapine), psoralens, and phenylpropanolamine. It is not known whether the other ephedrine isomers are CYP1A2 inhibitors. This interaction could have important clinical implications, resulting in higher than anticipated caffeine concentrations. It has been suggested that unsuspected interactions might inadvertently cause athletes to exceed the 12-mg/L urinary caffeine concentration limit set by the International Olympic Committee (IOC) and other sports regulatory bodies (Carrillo and Benitez, 2000).

2.2.8 Mechanisms of action

Caffeine ingestion increases the concentration of circulating free fatty acids and plasma epinephrine. Until recently, it had been presumed that the former was a consequence of the latter. However, studies carried out in quadriplegic patients (who, therefore, have impaired sympathoadrenal responses) show quite clearly that caffeine, in physiologic doses, causes transient increases in blood pressure and circulating free fatty acids by acting directly on muscle and adipose tissue (Van Soeren et al., 1996). But, because caffeine also causes adrenal release of epinephrine, it can be presumed that individuals with an intact sympathetic nervous systems would experience even greater effects.

For many years, caffeine's cardiovascular effects were thought to be a consequence of its ability to act as a phosphodiesterase inhibitor, leading to increased formation of cyclic AMP and cyclic GMP (Wells and Kramer, 1981). More recent studies have shown that caffeine is a relatively nonspecific phosphodiesterase inhibitor, and that caffeine concentrations much higher than those that result after a few cups of coffee are required to produce measurable vasoconstriction in humans (Casiglia et al., 1992).

Most of caffeine's cardiovascular effects appear to be the result of adenosine blockade. Adenosine is a vasodilator, and any compound that blocks adenosine will increase vascular tone and raise blood pressure. Four different types of adenosine receptors have been identified, with differences in both location and action: type A1 and type A2a. When A1 receptors are stimulated, the formation of adenylcyclase is inhibited and cellular potassium channels are activated (Fredholm, 1995). Almost the exact opposite occurs when A2a receptors are stimulated; the formation of adenylcyclase is promoted and voltage-activated calcium channels are opened (Fredholm, 1995). Because both types of receptors can be found in the same tissue, the results of blockage (or stimulation) can be difficult, if not impossible, to predict (Nurminen et al., 1999).

The actions of adenosine are not confined to inducing vasodilation. Adenosine also prevents the central release of some neurotransmitters, including dopamine and norepinephrine (Fredholm, 1995). Some suggest that the alertness and energy experienced by coffee drinkers are the result of the ability of caffeine to block endogenous adenosine which would, in turn, allow the additional release of some neurotransmitters (Fredholm et al., 1999). Surprisingly, a connection between coffee consumption and Parkinson's disease seems to exist: higher caffeine consumption is associated with a lower risk of developing Parkinson's disease (Ross et al., 2000a,b). Type A2 adenosine receptor agonists exert a dopamine-like effect and prevent symptoms of Parkinson's in experimental animals treated with chemicals designed to produce Parkinson-like symptoms (Grevele et al., 2000). The dopamine-like effect seems to be related to the fact that adenosine tonically inhibits dopaminergic transmission. As an adenosine antagonist, caffeine would abolish adenosine-mediated inhibition of dopamine release (Przuntek, 2000).

Some of the effects of coffee have nothing to do with caffeine. For example, coffee generally stimulates the gastrointestinal tract and causes the gallbladder to contract, even when the caffeine has been removed (Boekema et al., 1999). Coffee's gastrointestinal effects may also be due to waxes contained in coffee beans. The waxes (carboxy-5-hydroxytryptamides) contained in coffee would be removed by the coffee filter (Boekema et al., 1999). In controlled studies, endurance is increased, even after drinking decaffeinated coffee (though not nearly as much as drinking coffee with caffeine) (Boekema et al., 1999). The lipid compounds cafestol and kahweol, contained in unfiltered coffee, exert hyperlipemic effects in their own right (Urgert and Katan, 1997).

Theophylline, and to a lesser degree caffeine, causes increased urine production, and the pattern of excretion of both fluids and electrolytes is similar to the pattern seen with thiazide diuretics (Serafin and Baber, 1996). The underlying mechanism is not known, but it has been shown that the process does not involve increased production of atrial naturetic factor (Nussberger et al., 1990). In a double-blind controlled study, 642 mg of caffeine given to 12 healthy volunteers led to an increase in 24-hour urine excretion of 753 ± 532 mL, a corresponding negative fluid balance, and a concomitant decrease in body weight of 0.7 ± 0.4 kg. Total body water decreased by 1.1 ± 1.2 kg (or 2.7%), and urinary excretion of sodium and potassium increased by 66 and 28%, respectively (Neuhauser et al., 1997).

2.2.9 *Pharmacokinetics*

Caffeine is essentially 100% bioavailable, and its peak concentrations occur 30 to 45 minutes after oral ingestion (Massey, 1998). Caffeine levels in saliva are easily measured, and accurately reflect arterial blood levels. This generalization applies even in newborn and children. When 30 mg/kg was administered once a day to neonates for seven days, measurable caffeine concentrations in serum ranged from 0.28–93.3 mg/L in blood and from 0.35–91.5 mg/L in saliva, with a mean blood/saliva ratio of 0.924 (Lee et al., 1996).

Caffeine is taken up mainly by lean body tissue. A dose of caffeine calculated in milligrams per kilogram of body weight will produce much higher blood levels in older than in younger adults (Massey, 1998). Similar considerations apply to the newborn, for whom lean body mass is reduced in proportion to the amount of fat present (Anderson et al., 1999). The half-life of caffeine is extremely variable, depending partly on the age of the individual (Table 2.2.9.1), lean body mass, and CYP1A2 activity. Smoking enhances CYP1A2 activity, while some drugs decrease the rate at which caffeine is metabolized.

The half-life for caffeine in healthy adults is 3 to 7 hours (Levy and Zylber-Katz, 1982), but even wider ranges have been reported (Baselt and Cravey, 1995). In adults, but not necessarily in children, caffeine has a low volume of distribution, 0.4 L/kg. Because of the higher fat content of neonates and the hydrophilic nature of caffeine, the volume of distribution may be more than three times as high in neonates (Anderson et al., 1999). Human trials have shown the caffeine kinetics to be nonlinear; clearance decreases and the elimination half-life is prolonged when larger doses (500 vs. 250 mg) of caffeine are given (Troger and Meyer, 1995; Kaplan et al., 1997).

Similar considerations apply to the caffeine metabolite theophylline (1,3-methylxanthine); initial demethylation is followed by acetylation (Troger and Meyer, 1995). The volume of distribution is also low (0.46 to 0.90 L/kg) (Sanchez-Alcaraz et al., 1991; Rump et al., 1997; Soto and Alsar, 1997); theophylline clearance corrected for body weight is substantially higher in young adults than it is in the elderly (0.52 mL/min/kg for those over age 56 vs. 0.72 to 0.77 mL/min/kg in individuals ages 20 to 50 years). The pharmacokinetics of caffeine is essentially the same, no matter whether the caffeine is given orally or intravenously (Fredholm et al., 1999).

Over the last several years, caffeine has become increasingly popular as a probe with which to assess CYP1A2 activity. Caffeine clearance, 3-*N*-demethylation, measurement of the amount of ^{13}C–caffeine expired in the breath, and calculation of the ratio of different xanthine metabolites can all be used to indirectly assess CYP1A2 activity. The ability to do so is of more than academic interest. A number of drugs besides caffeine, some potentially quite toxic (phenacetin, clozapine, imipramine, tacrine), are metabolized by this same enzyme system, and CYP1A2 activity is deficient in part of the human population (Spigset et al., 1999).

Table 2.2.9.1 Half-Life of Caffeine vs. Age

Age	Half-life of caffeine (hr)
Premature, at birth	65–102
Term, at birth	82
3–4.5 months old	14.4
5–6 months old	2.6
Adult	3–7.5

2.2.10 Tissue concentrations

A healthy adult drinking two cups of very strong coffee would be expected to have urine caffeine levels no greater than 3 to 6 μg/mL. Plasma measurements made one hour after drinking two cups of coffee showed a peak caffeine value of 5.3 μgm/mL (Marks and Kelly, 1973). Peak levels can be expected to occur anywhere from 30 to 45 minutes after ingestion. The clearance rates for both theophylline and paraxanthine decrease in chronic users. Tissue measurements in rats have shown that, after dosing with caffeine, concentrations of caffeine and theophylline are equal in most tissues except the brain, where caffeine levels are 25% higher than theophylline levels (Stahle, 1991; Stahle et al., 1991). If this is also the case in humans, it might explain the different clinical profiles of theophylline and caffeine.

Newborns, like adults, can convert caffeine to theophylline and theophylline to caffeine, but the direction and degree of conversion are not always predictable. Measurements of cord blood caffeine levels in children born to cocaine-abusing mothers have shown that these women are likely to be abusing caffeine and nicotine, as well; caffeine may be present in substantial concentrations (up to 10 mg/L) (Dempsey et al., 1998). In three newborns treated with therapeutic doses of intravenous aminophylline, the highest levels were observed in the blood and then the brain. Decreasing levels were found in the heart, liver, lung, and kidney. Brain theophylline levels ranged from 6 to 30 μg/g, while caffeine levels ranged from 2.1 to 3.7 μg/g. Caffeine can be detected in most biofluids, including saliva, semen, and breast milk (Bonati et al., 1982), but levels have not been systematically studied. Ingestion of even modest amounts of caffeine by naïve mothers can produce significant effects on maternal and fetal circulation (Miller et al., 1994). Infants born to heavy coffee drinkers have high caffeine levels at birth (Khanna and Somani, 1984), but there is no evidence that the elevated concentration causes toxicity in these children.

Two special situations are of clinical and forensic interest. In infants, because of the immaturity of the CYP1A2 system (Tanaka, 1998), the plasma half-life of caffeine is 17 times longer than in healthy adults (Labow, 1983). Accordingly, infants being treated with aminophylline run a real risk of toxicity from caffeine, which continues to accumulate in their blood as aminophylline is converted to caffeine. Similar results can occur in patients with hepatic insufficiency or decreased cardiac output (Lacroix et al., 1985; Bechtel et al., 2000). Treatment with aminophylline under these circumstances runs the risk of caffeine toxicity. Measurement of both theophylline and caffeine levels in individuals at risk would be prudent.

Altered caffeine metabolism is also observed in children with cystic fibrosis, but the alterations remain poorly characterized. Some evidence suggests that xanthine oxidase activity is increased in these children (Hamelin et al., 1994). These children may be especially vulnerable to theophylline/caffeine toxicity because they frequently require antibiotic therapy. Some of the more popular antibiotics, such as ciprofloxacin, may inhibit caffeine metabolism (3-*N*-demethylation), resulting in dangerously high caffeine blood levels (Parker et al., 1994).

2.2.11 Toxicity by organ system

Individual reactions to caffeine, at least at low doses, vary widely. Some of the intra-individual variation has do to with age-related differences in metabolism, while other differences may be accounted for by smoking, by the use of other drugs concurrently, and

by genetic heterogeneity. The list of possible confounding factors is hardly complete, and other differences remain unexplained. The problem is made more complex by the interconversion of theophylline and caffeine in humans. The ratio of plasma theophylline to caffeine after caffeine administration is 8:6, and it is not clear whether toxic reactions, when they are observed, are really the result of caffeine or theophylline excess. After theophylline administration, the ratio of theophylline to caffeine is nearly the same (Stavric, 1988).

2.2.11.1 Neurologic

A 250-mg dose of caffeine (approximately 2.5 cups of coffee) is enough to reduce cerebral blood flow for 90 minutes. The decrease in cerebral flow is unexplained. It is not due to changes in the general circulation or in CO_2 levels, but it might be the result of the ability of caffeine to block adenosine receptors. Adenosine is a powerful cerebral vasodilator and it may be that adenosine receptor blockade results in decreased cerebral flow. Interactions with the adenosine receptor have also been suggested as a possible mechanism in caffeine-related seizures, though this suggestion also remains unproven (Morgan and Durcan, 1990), as does the role of adenosine receptors in caffeine-related hypertension (Nurminen et al., 1999).

The elderly are more sensitive to the psychological effects of caffeine, including increased alertness and improved performance on certain psychological tests (Massey, 1998). Older adults also seem to be more likely to experience insomnia after consuming caffeine than are younger individuals (Brezinova, 1976). The suggestion has also been made that a caffeine-dependence syndrome exists, and that this syndrome meets all the generic criteria for substance dependence, including the fact that affected individuals continue to use caffeine in spite of persistent problems related to its use (Holtzman, 1990). In one controlled study, dependence was diagnosed in 16 of 99 individuals who were evaluated. The median daily caffeine consumption in this group was only 357 mg per day (Strain et al., 1994).

Since this observation was first published, caffeine addiction has been added as an official diagnosis in *ICDM 9*. This decision is disputed by many and is not supported by any convincing body of experimental evidence. For example, other abused drugs lead to predictable increases in cerebral function and dopamine release in the shell of the nucleus accumbens. Caffeine does not. Except in massive doses, caffeine does not cause an increase in nucleus accumbens glucose utilization, as do drugs such as heroin, cocaine, and methamphetamine (Fredholm et al., 1999; Nehlig 1999). These results strongly suggest that caffeine does not act on the dopaminergic structures related to addiction.

2.2.11.2 Cardiovascular

Caffeine, regardless of the source, acutely raises blood pressure in naïve individuals, but only for a short time and not to a very great degree (Cameron et al., 1990). In the case of individuals who consume caffeine on a regular basis, results are difficult to predict because tolerance to the effects of caffeine is quickly acquired and quickly lost, probably within 24 hours from the time the drug is last taken (James, 1997). Evidence exists that increasing age is associated with increasing response to the pressor effects of caffeine (Massey, 1998). Some epidemiological studies suggest that regular coffee consumption may be harmful to those with established hypertension (Nurminen et al., 1999), and that a very large intake by individuals with coronary artery disease substantially increases the risk for sudden cardiac death (de Vreede-Swagemakers et al., 1999).

It is tempting to assume that the pressor response induced by caffeine is catecholamine related. Caffeine is a methylxanthine, and all methylxanthines are phosphodiesterase inhibitors. Their excessive use causes typical symptoms of sympathetic stimulation. The results of early studies did suggest that caffeine was capable of stimulating the release of catecholamines from the adrenal medulla (Robertson et al., 1978), but the results of more recent research suggest that caffeine-related catecholamine perturbations are minimal. Human volunteers given a mean dose of 250 mg of caffeine exhibited statistically insignificant increases in catecholamines (Cameron et al., 1990). Such a limited rise in catecholamines is in marked contrast to the increases seen with cocaine and amphetamines, and may explain why, even though enormous quantities of caffeine are consumed, few histologic abnormalities have been reported in the hearts of coffee drinkers. In experimental animals, contraction band necrosis and myofibrillar fragmentation are seen four hours after an LD_{50} dose is given intravenously (Kemi et al., 1996), but, except for such extreme situations, myocardial lesions related to caffeine simply have not been identified.

All the other methylxanthines have additional effects on cardiac myocytes; they cause the release of calcium ions from the sarcoplasmic reticulum, and they lower the effective concentration of calcium required for myofilament contraction. Some methylxanthines exert more potent effects than others. The differences in potency appear to be a function of differences in membrane permeability to the different methylxanthines (Donoso et al., 1994). In animal studies, caffeine enhances the cardiotoxicity of doxorubicin, apparently because the two compounds interact to disrupt the regulation of calcium within muscle sarcoplasmic reticulum (Hosenpud et al., 1995).

A relationship between caffeine intake and ventricular ectopy has always been presumed, but electrophysiologic studies of patients with recurrent ventricular tachycardia have failed to confirm any such action. In fact, some patients with ventricular ectopy have fewer extra heart beats after they are given coffee (Chelsky, 1990). Signal-averaged electrocardiograms (ECGs) of normal subjects before and after administration of 5 mg/kg of caffeine show small but statistically significant prolongation of the signal-averaged QRS complex. The finding is consistent with, but far from proof of, the notion that excessive caffeine intake might be a risk factor for serious arrhythmias (Donnerstein et al., 1998). Similarly, dogs given caffeine intravenously can be made to fibrillate, but only with massive doses of caffeine. After low doses comparable to those seen in coffee drinkers, either no arrhythmias or only inconsequential arrhythmias occurred, suggesting that the arrhythmogenecity of caffeine is dose related (Mehta et al., 1997).

Cardiac alterations similar to those reported in animals have not been mentioned in the few published human autopsies. In a case of overdose, with a postmortem caffeine level of 113.5 mg/L and clinical evidence of acute heart failure, right atrial dilation, acute pulmonary edema, and passive congestion of the liver, no specific cardiac lesions could be identified (Bryant, 1981). Neither could an anatomic basis for death be found in a second case reported to have even higher caffeine levels (181 mg/L), pulmonary edema, and passive congestion of the liver (Alstott et al., 1973; McGee, 1980). The failure to demonstrate myocardial lesions is consistent with the fact that caffeine toxicity is not associated with marked elevations in circulating catecholamines. It may be that the modest sympathomimetic activities of caffeine are sufficient to produce toxicity only in the presence of some other adrenergic agonist (Strubelt et al., 1976). Relative sparing of the myocardium is also illustrated in a case report describing an 1860-g child, 31 weeks old, who was accidentally given a caffeine overdose as a treatment for apnea. The initial serum concentration was 2175 mg/L 36.5 hours after dosing. Toxic manifestations included heart failure, pulmonary

edema, gastric dilatation, metabolic acidosis, and hyperglycemia. Nonetheless, the child made an uneventful recovery (Anderson et al., 1999).

Several case reports of alleged caffeine-related infarction and arrhythmia have been published, but it is difficult to know how they should be interpreted. One case involved a 20-year-old bulimic woman who ingested 20 g of caffeine in a suicide attempt. After being evaluated and discharged from the emergency department, she was re-admitted with ECG changes, and ultimately found to have sustained a subendocardial infarction. Angiography was not performed (Forman et al., 1997).

2.2.11.3 Renal

Analgesic nephropathy is a slowly progressive renal disease, characterized by renal papillary necrosis. Recently, diagnostic criteria for this disease have been defined based on renal computed tomography scanning performed without contrast. The observation of a decreased renal mass of both kidneys, combined with either bumpy contours or papillary calcifications, has been found to have high diagnostic specificity and sensitivity. However, the question remains as to what kind of analgesics can cause analgesic nephropathy. In the majority of early reports about this condition, phenacetin was singled out as the nephrotoxic culprit. However, during the last decade the nephrotoxic potential of non-phenacetin-containing preparations has become apparent. Individuals who abuse analgesics often abuse them in combination; analgesics combined with caffeine and/or codeine are especially popular. In contrast, abuse of products containing only aspirin (acetylsalicylic acid) or paracetamol (acetaminophen) is seldom described, and associated renal disease is only occasionally reported (Elseviers and De Broe, 1999).

2.2.11.4 Hematologic

Caffeine reacts with type A2a adenosine receptors. Under normal circumstances, blood concentrations of adenosine are sufficient to tonically activate platelet A2a receptors. Because caffeine is capable of blocking these receptors, the possibility exists that caffeine consumption might alter platelet function. *In vitro* studies of platelets obtained from healthy human coffee drinkers have shown that chronic caffeine intake can lead to upregulation of adenosine A2a receptors, with reduced platelet aggregability, even with relatively modest caffeine intake (600 mg/week) (Varani et al., 2000). The clinical significance of this observation is yet to be determined.

2.2.11.5 Erogenegic effects

Perhaps the most important, but least discussed, effect of caffeine is its ability to improve athletic performance. In one controlled study, elite marathon runners given 9 mg/kg of caffeine before testing were able to increase their time on a treadmill by an average of 70% (Graham and Spriet, 1991). This improvement was achieved without evidence of toxicity, and without exceeding the requirement of the IOC that testing reveal no more than 12 μg/mL of caffeine or the National Collegiate Athletic Association's even more generous limit of 15 μg/mL.

Very similar results were obtained by Kovacs et al. (1998), who showed that moderate supplementation with caffeine prolonged endurance without ever exceeding IOC limits on the permissible amount of caffeine in urine. These researchers found that, whatever the mechanism, it did not involve increased availability of free fatty acids, which were the same in controls and those treated with caffeine. This observation has been confirmed by some researchers (Van Baak and Saris, 2000), but refuted by others, perhaps because of differences in methodology or experimental design.

A separate study, also reported in 1998, measured the effects of acute ingestion of caffeine, ephedrine, or the two drugs in combination, on time to exhaustion during high-intensity exercise (Bell et al., 1998). Neither drug by itself produced any significant effect, but in combination they significantly increased time to exhaustion when compared to placebo. In contrast to the earlier studies by Kovacs and by Van Baak, free fatty acid concentrations were significantly increased by caffeine, though not by ephedrine. Simultaneous treatment with the two drugs significantly increased catecholamine concentrations as well, but the improved performance was attributed to increased CNS stimulation (Bell and Jacobs, 1999).

It had been argued that performance improvement, at least at doses of 5 mg/kg or less, is the result of increased lipolysis and glycogen sparing. Athletes who can metabolize lipids will have glycogen available for a longer period of time, and that should increase endurance (Smith and Perry 1992; Cole et al., 1996). Similar results were also reported by Graham et al. (1998), who demonstrated prolonged endurance, but only when caffeine was administered as coffee, not as the pure pharmacologic agent. All of these studies were carried out with modest doses of caffeine, but performance improvement seems to be even more impressive with larger doses, so further clandestine experimentation with doses high enough to produce toxicity seems likely. It is also quite likely that, at very high doses, mechanisms other than fat mobilization may come into play.

2.2.11.6 Fetal effects

Caffeine and theobromine cross the placental and the blood–brain barrier, and thus have the potential to cause toxicity (Eteng et al., 1997), but the results of clinical studies indicate that caffeine is not a major cause of malformations. In the most recent study, serum paraxanthine was used as a marker for caffeine ingestion. Concentrations were measured in 591 women who had had spontaneous abortions before completion of the second trimester, and were compared with paraxanthine concentrations in 2087 control coffee drinkers. Paraxanthine concentrations were lower in the controls (583 vs. 752 ng/mL), but the odds ratios for spontaneous abortion were no different, except in a group of extreme outliers with very high concentrations (>1845 ng/mL) of paraxanthine. Based on this, the largest clinical trial to date, it seems unlikely that moderate caffeine consumption has any effect on pregnancy outcome (Klebanoff et al., 1999).

2.2.11.7 Autopsy studies

A 1980 case report described two patients who expired after using repeated coffee enemas. Both had underlying malignancies and both appeared to have succumbed to fluid and electrolyte abnormalities, not to any toxic effect of caffeine. In fact, both of these women had negligible caffeine levels at the time of death (Eisele and Reay, 1980). Blood concentrations in cases of fatal intoxication have ranged from 79 to 1560 mg/L (McGee, 1980; Mrvos et al., 1989). In 1985, Garriott reported on five fatalities — three cases of combined caffeine and ephedrine and two cases of caffeine only. Blood concentrations ranged from 130 to 344 mg/L. The report did not comment on histologic findings, if any. Another case report describes a 22-year-old woman who committed suicide by taking an unknown number of caffeine tablets. Death appeared to have been the result of cardiac arrhythmia. Blood obtained during attempted resuscitation had an extraordinarily high caffeine concentration of 1560 mg/L. As is true in experimental animals, postmortem findings in this case consisted mainly of pulmonary edema and visceral congestion (Garriott et al., 1985). Another report describes a woman, age 19, who also died of a ventricular arrhythmia. At

autopsy, her caffeine blood level was 181 mg/L, and no histopathologic alterations could be identified (Mrvos et al., 1989).

Caffeine concentrations reported in other studies have been in comparable ranges. Reisselmann et al. (1999) described an 81-year-old female suicide, for whom caffeine concentrations in the heart and stomach were almost identical (180 and 190 mg/L, respectively). Coffee is not, of course, the only cause of caffeine poisoning. Reisselmann also described the death of a 19-year-old woman who died after taking an unknown number of guarana capsules. Her stomach caffeine was 2000 ng/mL, with a femoral blood concentration of 222 mg/L and a heart-blood concentration (side unspecified) of 260 mg/L. Caffeine concentration in the liver was 350 mg/g. As with all of the abused drugs, tolerance occurs (although the mechanism is not clear), and high caffeine levels have been recorded in patients who survived fairly massive caffeine overdoses. Blood levels of 200 mg/L were recorded in a woman who took 24 g of caffeine in an unsuccessful suicide attempt. Her theophylline level was 17.2 mg/L (Benowitz et al., 1982). Another report described the case of a 27-year-old man who regularly ingested coffee grounds in order to get "high." On one occasion, he doubled his usual dose and swallowed half a kilogram of ground coffee. He arrived at the hospital comatose, febrile, hypertensive, tachycardic, and seizing. He survived but required intense treatment with beta blockers and anticonvulsants. His caffeine blood concentration was 29 mg/L (Wurl, 1994).

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2.3 Ephedrine

2.3.1 Incidence

The Medical Examiner component of the 1999 DAWN report lists 59 cases for which death was thought to be ephedrine related. That number amounts to 0.52% of all deaths reported to DAWN that year (Kissin et al., 2000). Whether ephedrine was actually responsible for all 59 deaths is difficult to say. Ephedrine is the preferred precursor for methamphetamine manufacture, and because clandestine chemists do not always carry the reaction to completion, unconsumed ephedrine may be present along with methamphetamine in the finished product. It is not uncommon to detect ephedrine as an incidental finding in the urine of individuals dying of methamphetamine toxicity, and unless chiral separation is carried out, there is no way to tell whether ephedrine or one of its isomers, such as pseudoephedrine, is actually present.

2.3.2 Epidemiology

The frequency with which ephedra is abused in the U.S. is not known. The National Household Survey for 2000 makes no mention of ephedrine or *Ephedra* species (Greene et al., 2000). Most of the ephedrine consumed in the U.S. is in the form of "food supplements" sold to bodybuilders or to individuals seeking to lose weight, or as a component of some medications, mostly over-the-counter ones. Occasional reports of ephedrine "abusers" have appeared in the literature. Most of these individuals have been in their 20s, but there are too few reports to make any generalizations.

2.3.3 *History*

Ephedra plants have been identified at European Neanderthal burial sites dating from 60,000 B.C. (Lietava, 1992). Traditional Chinese healers used ephedra extracts thousands of years before Pliny, and the ancient Romans accurately described both the ephedra plant and its medical uses. Chinese texts from the fifteenth century recommended ephedra as an antipyretic and antitussive. At about the same time that the Chinese began using ephedra, Russian herbalists were using ephedra extracts to treat joint pain, and recent laboratory studies confirm that ephedra might be useful for that purpose (Ling et al., 1995). In the 1600s, Indians and Spaniards in the American Southwest used ephedra as a treatment for venereal disease (Grinspoon and Hedblom, 1975). That idea may have had some merit, as a novel antibiotic called *transtorine* has been isolated from ephedra (Al-Khalil et al., 1998, 1999). Settlers in the American West brewed ephedra teas, which were referred to by a variety of names, including teamsters' tea, Mormon tea, and chaparral tea (Max, 1991).

The modern rediscovery of ephedrine can be attributed to the work of Nagayoshi Nagi, a Japanese-born, German-trained chemist, who first isolated and crystallized ephedrine in 1885 (Holmstedt, 1991). Nagi's original observations were confirmed by Merck chemists, who thought that ephedrine might have commercial value, but sales were never very great and ephedrine production was all but abandoned until 1930, when Chen and Schmidt published a paper recommending ephedrine as a primary treatment for asthma (Chen and Schmidt, 1930). Following the publication of Chen and Schmidt's report, ephedrine quickly replaced epinephrine as the first-line treatment for asthma.

Ephedrine became such a popular drug that there were concerns that demand would exceed supply. The possibility of an ephedrine shortage fostered research on methods to synthesize the substance. Amphetamines were created largely as a byproduct of those efforts. The anticipated ephedrine shortage never emerged, but ironically ephedrine sales soared during the 1990s because ephedrine is the preferred precursor for use in the illicit manufacture of methamphetamine. Government controls on the sales of drug precursors have now limited the use of ephedrine for this purpose. In many areas, ephedrine has been replaced by its enantomers, phenylpropanolamine (now withdrawn from the market), as the precursor of choice in clandestine laboratories (Anon., 1999b), although availability of phenylpropranolamine, now that it has been withdrawn from the market, is just as limited as that of ephedrine.

In addition to being an effective bronchodilator, ephedrine in large doses is a potent CNS stimulant (Martin et al., 1971). Ephedrine injections called *philopon* (which means "love of work") were given to Japanese Kamikaze pilots during World War II. A major epidemic of ephedrine abuse occurred in postwar Japan. Abusers injected themselves with ephedrine, then called *hiropon*, in much the same way that methamphetamine is injected today (Deverall, 1954). Filipinos have, for many years, smoked a mixture of ephedrine and caffeine called

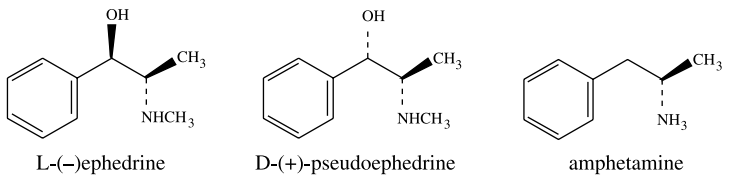

Figure 2.3.4.1 **Ephedrine and pseudoephedrine.** The principal importance of ephedrine is its role as a precursor in the illicit production of methamphetamine; however, ephedrine is a potent stimulant in its own right and has significant abuse potential.

shabu. In the late 1980s, *shabu* smoking gave way to the practice of smoking methamphetamine ("ice"). In what is perhaps a tribute to the past, some "ice" is sold under the *hiropon* name. Today, ephedrine has been largely replaced by more effective decongestants and treatments for asthma, but it is still widely used for the prophylaxis and treatment of hypotension caused by spinal anesthesia (Flordal and Svensson, 1992; Goyagi et al., 1998; Yap et al., 1998). Ephedrine consumption surged yet again in the late 1990s, when food supplement manufacturers began marketing ephedra-containing products for weight control.

2.3.4 Chemistry

Ephedrine is [1-(methylamino)ethyl]benzene-methanol]. Its formula is $C_{10}H_{15}NO$, with a molecular weight of 165.23. It is composed of 72.7% carbon, 9.2% hydrogen, 8.5% nitrogen, and 9.7% oxygen. Isomeric forms include (±)-ephedrine and (±)-pseudoephedrine (Figure 2.3.4.1). The two naturally occurring isomers are (–)-ephedrine and (+)-pseudoephedrine. Racemic (±)-ephedrine forms whitish crystals with a melting point of 79°C. Both ephedrine and pseudoephedrine are weak bases, with a pKa of 9.6 and 9.4, respectively (Budavari et al.,1996).

2.3.5 Sources

Ephedrine (*Ephérdre du Valais* in French and *Walliser Meerträubchen* in German) can be extracted from a group of closely related species of plants that grow in Asia, Western Europe, Southeastern Europe, and even the New World. The alkaloid content of these plants varies quite considerably. The best known species, *Ephedra sinica* (average 1.3% alkaloid content) and *E. equisentina* (average 2.2% alkaloid content) are collectively known as *ma huang* and are grown mainly in China, Northern India, and Pakistan (Cui et al., 1991). *E. geriardiana*, *E. intermedia*, and *E. major* grow in Southwest Asia, while other members of the family Ephedraceae can be found in Europe and the U.S. (*E. distachya*, *E. vulgaris*).

The most common Chinese cultivars (called *China 3*) contain 1.39% ephedrine, 0.361% pseudoephedrine, and 0.069% methylephedrine (Sagara et al., 1983). This mix is fairly typical for commercially grown ephedra plants (Zhang et al., 1989; Cui et al., 1991; Gurley et al., 1998a,b). Because the breakdown of total alkaloids found in the plants can vary from plant to plant and batch to batch, the general practice of food supplement makers is to simply specify total alkaloid content (i.e., ephedrine + pseudoephedrine + methylephedrine + norephedrine). Some dietary supplement manufacturers have illegally added synthetic ephedrine to their products, but because the total alkaloid content varies so much from species to species, unless the actually species is known, no conclusions can be drawn about whether the mixture of alkaloids present is a consequence of plant biology or medicinal compounding. *E. intermedia*, for example, contains more pseudoephedrine than ephedrine (Liu et al., 1993). Thus, demonstration of the presence of more pseudoephedrine than ephedrine in a product does not necessarily constitute proof that it has been adulterated, unless, of course, the species of ephedra used is known.

Many authors refer to all these species collectively as *ma huang*, but properly speaking that name should really be confined to the species grown in China (Namba et al., 1976). While clandestine khat cultivation seems to be increasingly common in the western U.S. (Wallace, 1998; Anon., 1999a), there is no evidence that the same holds true for ephedra. Similarly, even though ephedrine can now be produced synthetically (benzaldehyde is fermented with Brewer's yeast, followed by reductive condensation with methylamine, yielding pure (–)-ephedrine) there is no evidence that clandestine drug makers are utilizing

this approach (Dewick, 1997). When sold separately, the ephedrine enantomer (+)-norpseudoephedrine is a Schedule IV controlled substance. In 1998, the DEA published a proposed rule stating its intent to exempt legitimate ephedra products, in finished form, from regulation. The rule has yet to be finalized.

2.3.6 *Routes of administration*

Ephedra may be taken orally, injected, or smoked. The latter route is reserved for abusers, primarily in the Philippines, where the practice was popular for many years. No data on the pharmacokinetics of smoked ephedra or smoked pure ephedrine have been published. Peak ephedrine levels after an oral dose of 400 mg of *ma huang* (equivalent to 20 mg of pure ephedrine) resulted in blood concentrations of 81 ng/mL (White et al., 1997). Very nearly the same peak ephedrine levels were seen after giving an equivalent amount of pure ephedrine (25 mg) or the equivalent amount of ephedrine given in combination with other botanicals (Gurley et al., 1998a,b). In a separate study, 50 mg of ephedrine given orally to six healthy 21-year-old women produced mean peak plasma concentrations of 168 ng/mL (Vanakoski et al., 1993). The results are comparable to those obtained in studies done nearly 30 years earlier (Wilkinson and Beckett, 1968). In a recent study performed to assess the effectiveness of caffeine/ephedrine combinations as performance-enhancing agents in combat troops, volunteers (n = 20) were treated with 375 mg of caffeine, 75 mg of ephedrine, 375 mg of caffeine combined with 75 mg of ephedrine, or placebo. Modest elevations in pulse and blood pressure were seen in all the treatment groups, with peak effects occurring at one to two hours post administration. Maximal ephedrine concentrations of approximately 300 ng/mL occurred at three hours. Maximal caffeine concentrations were also reached at three hours and ranged from 7 to 8 mg/L. Drug concentrations when the two agents were taken together were no higher than when they were taken separately (Douglas Bell, pers. comm.). Anesthesiologists occasionally give ephedrine intravenously to counter the hypotensive effects of spinal anesthesia, especially during Cesarean section (Yap et al., 1998), but resultant blood concentrations after intravenous dosing in surgical settings have not been measured.

Methylephedrine is a minor component of most ephedra plants, but in Japan it is produced synthetically and used in cough and cold remedies. One of these products (called *BRON*) is very widely used and abused (Tokunaga et al., 1989; Ishigooka et al., 1991; Nakahara and Kikura, 1997; Kunsman et al., 1998). Neither BRON nor methylephedrine is sold in the U.S. Blood concentrations of methylephedrine in patients taking BRON for legitimate therapeutic purposes are usually less than 0.3 mg/L (Kunsman et al., 1998). Higher concentrations appear to produce toxic effects, usually psychiatric. In general, the methylephedrine content of most ephedra plants and therefore of herbal supplements made from them (Gurley, 2000) is so low that the amount of methylephedrine ingested in herbal supplements is not sufficient to produce any measurable responses. Indeed, results of standard volume-of-distribution calculations suggest that more than 300 "servings" of the typical dietary supplement would be required just to achieve the blood concentration of methylephedrine thought to be necessary to produce bronchodilation (see appendices for sample volume-of-distribution calculations).

2.3.7 *Metabolism and pharmacology*

Ephedra plants contain a family of closely related alkaloids, including (–)-ephedrine, (+)-pseudoephedrine, (–)-norephedrine, (+)-norpseudoephedrine (also called cathine, a

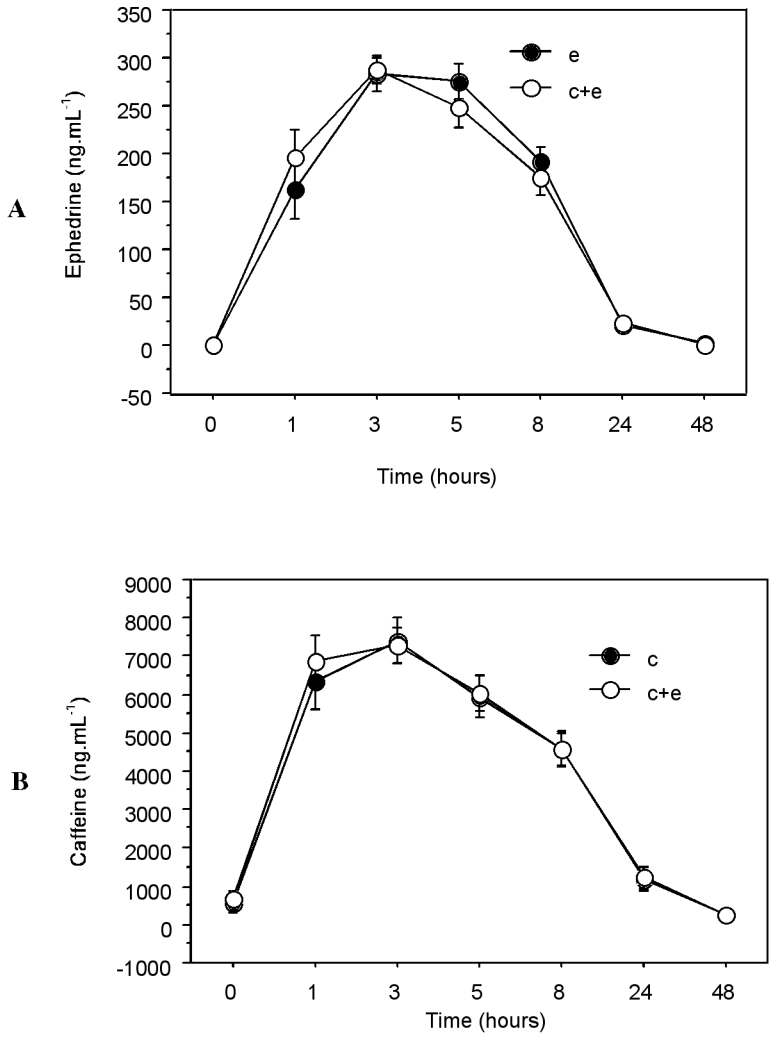

Figure 2.3.6 **Plasma ephedrine levels after ephedrine and caffeine/ephedrine ingestion.** The level of ephedrine in the plasma after ephedrine alone and after ephedrine combined with caffeine had no effect on clearance rates. Peak levels occurred between two and four hours after drug ingestion. Caffeine concentrations peaked at between one and two hours, regardless of whether the caffeine was given alone or in combination with ephedrine. (Courtesy of Douglas Bell, Defence and Civil Institute of Environmental Medicine, the Department of National Defence of Canada, Toronto, Ontario.)

major alkaloid of *Catha edulis* or khat), (–)-*N*-methylephedrine, (+)-*N*-methylpseudoephedrine, racemic and (–)-ephedrine, (+)-pseudoephedrine, and (±)-norephedrine (phenylpropanolamine). Small amounts are oxidized in the liver to norephedrine and norpseudoephedrine, both CNS stimulants, but most is excreted unchanged in the urine (Wilkinson and Beckett, 1968; Sever et al., 1975; Kanfer et al., 1993). All of the components are, to varying degrees, vasoactive and can affect the cardiovascular, respiratory, and central nervous systems.

Ephedrine stimulates both α_2 and β_1 receptors directly, and, because it also causes the increased release of norepinephrine from nerve endings, it also acts as a β_2 agonist, producing increases in pulse, blood pressure, and cardiac output. The degree of increase is somewhat unpredictable because of concomitant, but variable, increases in peripheral resistances which occur at the same time (Webb and Shipton, 1998). The findings of the most recent studies suggest ephedrine is also a β_3 agonist. Stimulation of β_3 receptors, which are thought to be located only in fat cells, may account for the ability of ephedrine to cause weight loss (Astrup and Lundsgaard, 1998; Ramsey et al., 1998; Molnar et al., 2000; (Boozer et al., 2001). Tissue culture studies with β_1, β_2, and β_3 receptors, expressed in Chinese hamster tissue culture, suggest that it is only ephedrine and not its isomers (i.e., pseudoephedrine, phenylpropanolamine, or cathine) that is responsible for fat mobilization (Vansal and Feller, 1999).

The affinity of the various ephedrine isomers for human β receptors has been measured and compared (as indicated by the amount of cyclic adenosine monophosphate [cAMP] produced compared to that of isoproterenol) in tissue culture. Activity of the different ephedrine isomers is highly steroselective (i.e., the different isomers had very different receptor binding characteristics). For β_1 receptors, maximal response (relative to isoproterenol = 100%) was greatest for ephedrine (68% for 1R,2S ephedrine and 66% for the 1S,2R ephedrine isomer). Both of the pseudoephedrine isomers had much lower affinities (53%). When binding to β_2-receptors was measured, the rank order of potency for 1R,2S ephedrine was 78%, followed by 1R,2R pseudoephedrine (50%), followed by 1S,2S pseudoephedrine (47%). The 1S,2R ephedrine isomer had only 22% of the activity exerted by isoproterenol but it was the only isomer that showed any significant agonist activity on human β_3 receptors (31%) (Vansal and Feller, 1999).

Because ephedrine is also an α agonist, it is capable of stimulating bladder smooth muscle, and at one time was used to promote urinary continence (Castleden et al., 1982; Kadar and Nelson, 1984). In animal models, when ephedrine is compared to norepinephrine, it has proven to be a relatively weak α-adrenergic agonist, having less than one third the activity of norepinephrine (Alberts et al., 1999). Ephedrine's usefulness as a bronchodilator is limited by the number of β receptors on the bronchi. The number of β receptors located on human lymphocytes (which correlates with the number found in the lungs) decreases rapidly after the administration of ephedrine; the density of binding sites drops to 50% of normal after eight days of treatment and returns to normal five to seven days after the drug has been withdrawn (Neve and Molinoff, 1986). The downregulation of receptors that occurs with ephedrine is in marked contrast to cocaine, where chronic exposure appears not to affect receptor density at all (Costard-Jäckle et al., 1989).

Each of the different ephedrine isomers has different pharmacokinetic and toxicokinetic profiles. Phenylpropanolamine is readily and completely absorbed, but pseudoephedrine is subject to gut-wall metabolism and has a bioavailability of only 38% (Kanfer et al., 1993). Pure ephedrine is well absorbed from the stomach, but absorption is slower when ephedrine is given along with other botanicals rather than in its pure form (Gurley et al., 1998a,b). Regardless of how pure ephedrine or ephedra in botanical mixtures is ingested, peak plasma concentrations occur after 2.5 to 3.0 hours. The volume of distribution of ephedrine appears to be the same whether pure drug is given or equivalent amounts are given in ephedra mixtures: 2.5 to 3.0 L/kg (Gurley et al., 1998a,b).

Like its enantomers, ephedrine is eliminated in the urine largely as unchanged drug, with a half-life of about 3 to 6 hours. Peak concentrations for the other enantomers, specifically phenylpropanolamine and pseudoephedrine, are shorter (0.5 and 2 hours, respectively) than for ephedrine, but both drugs are extensively distributed into extravascular

sites, with apparent volumes of distribution that are greater than that of ephedrine (2.6 L/kg for phenylpropanolamine and 5.0 L/kg for pseudoephedrine). No protein-binding data in humans are available. Urinary excretion of all three enantomers is pH dependent. Excretion may be much more rapid in children, and a greater dosage may be required to achieve therapeutic effects. Unlike amphetamines, acidification of the urine has no effect on ephedrine excretion (Wilkinson and Beckett, 1968).

Patients with renal impairment are at special risk for toxicity (Kanfer et al., 1993), because ephedrine isomers may accumulate. None of the enantomers is easily removed by dialysis, and the only treatment is supportive, using pharmacologic antagonists to counter the α- and β-adrenergic effects of these drugs (Lyon and Turney, 1996). Because excretion is pH dependent, patients with renal tubular acidosis, a rare disorder, are also at particular risk (Brater et al., 1980).

Other pharmacologic effects are less well understood. *Ma huang* has traditionally been used to treat cough and respiratory infection. However, the latest studies suggest another reason for treating respiratory infections with ephedra: it contains a compound that, in the test tube at least, has antibiotic properties. This compound is a quinoline alkaloid (4-quinolone-2-carboxylic acid), isolated from the aerial part of *Ephedra transitoria* and called transtorine. It inhibits the growth of common bacteria, such as *Enterobacter cloacae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* (Al-Khalil et al., 1998). No clinical trials have been performed.

In addition to possessing antibiotic activity, extracts of *Ephedra sinica* cause a partial inhibition of serum complement activity, specifically inhibiting C2 complement (Ling et al., 1995). Traditional Chinese herbalists have always claimed that *ma huang* could be used to treat arthritis and, although Western-style clinical trials are still lacking, it appears that these claims could have a scientific foundation. One problem in establishing efficacy is that traditional herbalists usually combine ephedra with other herbs. *In vitro* studies have shown that an ephedrine-containing remedy called *shinpi-to*, which also contains *Prunus armeniaca*, *Magnolia obovata*, *Citrus unshiu*, *Glycyrrhiza uvalensis,* and *Bupleurum falcatan*, inhibits IgE-mediated leukotriene synthesis, another action that could prove to be effective in the treatment of arthritis (Hamasaki et al., 1997).

2.3.8 Toxicity by organ system

Complications from ephedrine use are decidedly rare. Judged by reports in the peer-reviewed literature, the most frequent complications of ephedrine abuse appear to be behavioral. However, in the general population of non-abusers taking ephedrine or its isomers in recommended dosages, case reports are simply too few to permit generalizations.

2.3.8.1 Neurologic disease

Ephedrine-induced psychosis has been reported with some regularity (Herridge and a'Brook, 1968; Roxanas and Spalding, 1977; Whitehouse and Duncan, 1987; Ishigooka et al., 1991; Capwell, 1995; Doyle and Kargin, 1996; Jacobs and Hirsch, 2000). Ephedrine psychosis closely resembles psychosis induced by the amphetamines: paranoia with delusions of persecution and auditory and visual hallucinations, even though consciousness remains unclouded. Typically, patients with ephedrine psychosis will have ingested more than a 1000 mg per day. Recovery is rapid after the drug is withdrawn (Kalix, 1991; Nakatani and Hara, 1998). The results of neurochemical studies suggest that the basis for ephedrine-induced behavioral changes may be altered dopamine metabolism. When ephedrine (Blandini et al., 1997) or pseudoephedrine (Kumarnsit et al., 1999) is injected into rats, there is

almost immediate induction of the early gene c-*fos* in the nucleus accumbens and striatum. Induction can be prevented by injecting the rats with D1 dopamine antagonists (Kumarnsit et al., 1999). Exactly the same thing happens when amphetamine is injected, suggesting shared behavioral actions and effects.

In a case report of a two-year-old who developed psychosis and ataxia after being overmedicated with a combination of pseudoephedrine and dextromethorphan (another drug that can cause psychosis), the plasma pseudoephedrine concentration was 220 ng/mL and the child made an uneventful recovery (Roberge et al., 1999). But, because the ephedrine content per serving of most food supplements is on the order of 10 to 20 mg, it is extremely unlikely that, taken in recommended doses, use of any commercial supplements or over-the-counter medications would lead to psychiatric symptoms. On the other hand, methylephedrine abuse accounts for a considerable number of transient psychotic episodes which occur in Japan and the Philippines (Tokunaga et al., 1989; Ishigooka et al., 1991).

Other types of neurologic complications are even rarer. Many adverse events attributed to ephedrine, particularly cases of stroke identified in the Adverse Events Reports (AERs) gathered by the Food and Drug Administration (FDA), have actually been due to ephedrine enantomers, particularly pseudoephedrine and phenylpropanolamine. Intracranial hemorrhage does occur, but almost always in association with drug overdose (Loizou et al., 1982; Wooten et al., 1983; Stoessl et al., 1985; Glick et al., 1987; Forman et al., 1989; Strand et al., 1991; Bruno et al., 1993). In general, the incidence of these complications appears to be much lower with ephedrine than with other agents, such as phenylpropanolamine. Only two peer-reviewed reports describe cerebral infarct in an individual who had not taken an overdose (Vahedi et al., 2000; du Boisgueheneuc et al., 2001). Few large studies have assessed risk factors for stroke in young people (ages 20 to 49). In a study from Poland, a country where ephedra-based products are widely used, nearly half the strokes in young people were associated with pre-existing hypertension; another 15% had hyperlipidemia, and 6% were diabetic (Jovanovic, 1996). None of the individuals studied was an ephedrine user. A follow-up study of over 100,000 pseudoephedrine users (for purposes of toxicity, the FDA considers all ephedrine isomers as equivalent) below age 65 years who had filled a total of 243,286 prescriptions for pseudoephedrine found no hospitalizations among users that could be attributed to the drug — specifically, no admissions within 15 days for cerebral hemorrhage, thrombotic stroke, or hypertensive crisis. A small number of hospitalizations for myocardial infarction, seizures, and neuropsychiatric disorders were reported, but the rate of such admissions among the pseudoephedrine users was close to the expected rate in the population at large (Porta et al., 1986).

2.3.8.2 Renal disorders

Chronic ephedrine use has occasionally been implicated as the cause of renal calculi (Schweisheimer, 1976; Powell et al., 1998). A large commercial laboratory that analyzes kidney stones found that 200 of 166,466 stones (0.064%) contained either ephedrine or pseudoephedrine (Blau, 1998). Unfortunately, the analytic technique utilized by that laboratory could not distinguish between ephedrine and pseudoephedrine. Because pseudoephedrine is used so much more widely than ephedrine, it is reasonable to suppose that most of the 200 stones were due to pseudoephedrine. Except for the possibility of renal stones, no direct effect on the kidney or altered renal function has ever been demonstrated, nor is there any evidence that ephedrine exerts diuretic effects. Urinary retention can occur as a consequence of drug overdose (Glidden and DiBona, 1977; Lindberg, 1988) but has not been reported when recommended doses are consumed.

2.3.8.3 *Cardiovascular disorders*

The difficulty in relating ephedrine use to heart disease is that with so many people taking ephedrine-based products, it is inevitable that some ephedrine users will become sick or even die. Some may even have pre-existing cardiac malformations or pre-existing, undiagnosed coronary artery disease. Ephedrine and pseudoephedrine share properties with cocaine and with the amphetamines because they: (1) stimulate β receptors directly, and (2) cause the increased release of epinephrine from the adrenal glands. Chronic exposure to abnormally high levels of circulating catecholamines can damage the heart. This is certainly the case with cocaine and methamphetamine (Karch et al., 1995, 1999) and is probably true for ephedrine as well.

Scattered reports of severe hypertension have been published (To and Rampling, 1980; Gaulteri, 1996), but mostly in relation to pseudoephedrine use (Lyon and Turney, 1996), and several studies have shown that, taken in recommended doses (as opposed to overdose), the ephedrine contained in cough and cold remedies has a negligible effect on blood pressure (Bright et al., 1981; Gurley et al., 1998a,b; Mores et al., 1999; Rosene et al., 1999). In cases of drug overdose, either of ephedrine or its enantiomers, hypertensive emergency can occur (Hedetoft et al., 1999) but, apparently, only when very large doses of ephedrine have been consumed. A 1992 case report describes the clinical course of a 29-year-old woman who ingested 17,500 mg of ephedrine. Her blood pressure was 168/106 upon arrival in the emergency department but returned to normal 5 minutes after intravenous propanolol was administered (Burkhardt, 1992).

One case of alleged ephedrine-related hypersensitivity myocarditis has been reported (Zaacks et al., 1999), but because the individual affected was also taking other drugs, the diagnosis is not certain. Cases of ephedra-related coronary artery spasm are problematic. At least three such cases have been described (Menegakis and Amstey, 1991; Hirabayashi et al., 1996), but they all occurred during surgery in anesthetized patients after multiple other agents had been given. Two cases of coronary spasm leading to infarction have been documented in pseudoephedrine users (Wiener et al., 1990; Derreza et al., 1997).

Three case reports describe heart failure in ephedrine users; one was a 35-year-old asthmatic taking 4000 mg of ephedrine per day and "liberal doses of prednisolone" for 14 years. Another involved a woman who had been abusing ephedrine (300 to 600 mg/day) for 10 years, and a third case involved a 28-year-old, cigarette-smoking, 321-pound woman taking 2000 mg of ephedrine every day for 8 years (To and Rampling, 1980; Gaulteri, 1996; Schafers et al., 1998). The difficulty in interpreting these reports is that histologic findings were not described and angiography was not performed, making the diagnosis of cardiomyopathy virtually impossible to establish. Similar considerations apply to the possible relationship (if any) between myocardial infarction and ephedrine use.

Another case report describes a 25-year-old man who injected himself intravenously with an unknown amount of what he believed was amphetamine. It was, in fact, ephedrine, and he sustained a posterior wall infarction. Blood ephedrine concentrations were not determined (Cockings and Brown, 1997). No case reports in the peer-reviewed literature link the use of ephedra-containing food supplements or the ephedrine–caffeine combinations used to promote weight loss (these generally contain 20- to 50-mg doses of ephedra and are taken 2 to 3 times per day) to actual clinical episodes of myocardial infarction. That is not the case, however, for ephedrine isomers. Myocardial necrosis and arrhythmias have been reported both in humans and experimental animals after administration of phenylpropanolamine (Pentel et al., 1982, 1987) and, more rarely, after pseudoephedrine (Wiener et al., 1990). The relative paucity of ephedrine-related infarcts, but

the much more common occurrence of infarction with the other ephedrine isomers, may be explained by the fact that the latter are both more effective α agonists than ephedrine.

Cardiac arrhythmia is a known complication of catecholamine excess (Lerman et al., 1999), and chronic exposure to high levels of catecholamines can induce a type of myocardial fibrosis that favors arrhythmias. Nonetheless, a linkage between ephedrine and its isomers and arrhythmias has never been convincingly demonstrated, nor has microfocal fibrosis been described in any animal or experimental study of ephedrine toxicity. One case report describes arrhythmias occurring in a 14-year-old who overdosed on cold medications, taking a total of 3300 mg of caffeine, 825 mg of phenylpropanolamine, and 412 mg of ephedrine. Clearly, massive doses of ephedrine and its enantiomers, well beyond those used in clinical practice, are capable of exerting toxicity (Weesner et al., 1982), but the clinical relevance of this observation is obscure.

2.3.8.4 Dermatologic disorders

Use of ephedrine (Catlin et al., 1993; Villas Martinez et al., 1993) and its enantiomers is occasionally associated with the occurrence of nonpigmented fixed drug eruptions (Abramowitz and Noun, 1933; Brownstein, 1968; Tomb et al., 1991; Garcia Ortiz et al., 1997; Anibarro and Seoane, 1998; Vega et al., 1998). The lesions have no unique features and, given the great frequency with which these drugs are consumed in food supplements and over-the-counter medications, the occurrence rate must be low. Similar eruptions have been reported in cocaine users (Hofbauer et al., 1999).

2.3.8.5 Weight loss

Appetite control is impaired in the obese, especially when diets are fat rich and energy dense. Many obese people have a lower than expected resting metabolic rate, a deficiency that may be genetically controlled. Agents that stimulate adrenergic neurons inhibit hunger and stimulate energy expenditure, lipolysis, and fat oxidation, which is why combinations of ephedrine and caffeine have been evaluated in clinical trials.

In most of the trials, the caffeine–ephedra combinations have induced weight loss (Astrup and Lundsgaard, 1998; Ramsey et al., 1998; Molnar et al., 2000; Boozer et al., 2001). The mechanism by which this reduction occurs is, again, unknown. It appears that stimulation of some β receptors may also lead to production of proteins (called uncoupling proteins [UCPs] 1, 2, and 3) that uncouple adenosine triphosphate (ATP) production from mitochondrial respiration, favoring the dissipation of energy as heat. Studies with Pima Indians have shown that the greater the degree of UCP3 expression, the lower the body mass index (Schrauwen et al., 1999). Ephedra also acts directly on β_1 and β_2 receptors to cause increased heat production, with much the same result as UCP3 production; calories are dissipated as heat. Another observation that may have relevance is that both lean and obese rhesus monkeys treated with an ephedrine–caffeine mixture lost weight over a seven-week period, and plasma leptin concentrations decreased in both groups (Ramsey et al., 1998).

2.3.8.6 Sexual dysfunction

The results of one study suggest that ephedrine might have a role in treating female sexual dysfunction. In a study published in 1998, sexual responses to erotic stimuli were measured (vaginal photoplethysmography) in 20 sexually functional women. A double-blind, randomized, cross-over protocol was used such that each woman received either 50 mg of ephedrine sulfate or placebo. The latter had no effect, but ephedrine treatment resulted in significantly increased arousal and increased vaginal pulse-amplitude response (Meston and Heiman, 1998).

2.3.8.7 *Drug testing*

The IOC, while not entirely banning ephedrine consumption, has ruled that urine levels of over 500 ng/mL indicate abuse and are grounds for disqualification. The 500-ng/mL level set by the IOC is probably unrealistically low, although IOC rules consider each of the ephedrine enantiomers separately. For ephedrine, cathine, and methylephedrine, the definition of a "positive" is a concentration in urine greater than 5 μg/mL. For phenylpropanolamine and pseudoephedrine, the definition of a "positive" is a urine concentration in urine greater than 10 μg/mL. If more than one isomer is present, but the concentrations are below their respective thresholds, the concentrations are added together and considered positive if they are greater than 1000 ng/mL. In a recent study, healthy volunteers given realistic doses of ephedrine-containing nasal spray (roughly 14 mg) were found to have urine levels ranging from 0.09 to 1.65 μg/mL (Lefebvre et al., 1992).

Occasionally, innocent non-abusers may find themselves falsely accused of ephedra use. A Dutch professional cyclist who thought he was using a perfectly legal, ephedra-containing food supplement found to his surprise that he was taking cathine, a weak stimulant present in both khat and ephedra (Ros et al., 1999). In fact, a mixture of some 15 different herbs, including "ephedra," was present in the product. When tested after a competition, the bicyclist's urine was found to contain 20.2 μg/mL of norpseudoephedrine (cathine). No species of ephedra contains more norpseudoephedrine than ephedrine, and most contain substantially less. Obviously, the makers of the supplement had been spiking their product with norpseudoephedrine. Whether or not ignorance of the law is a sufficient excuse for the IOC is an open question, but competitive athletes need to realize that, since the passage of the Dietary Supplement Health Education Act (DSHEA) in 1994, production of these supplements is minimally regulated.

This could also be an issue for individuals subject to workplace drug testing, particularly if the testing is unregulated or done with an on-site immunoassay device. Depending on the source of the antibody being used in the device, ephedrine or one of its isomers might cause a false-positive test for methamphetamine. Under regulated testing schemes, confirmatory testing would disclose which drug was really present, but not all testing is regulated.

2.3.9 *Postmortem tissue measurements*

Some autopsy measurements have been published, but in every case other drugs were also present, and pharmacokinetic interactions, not to mention synergistic toxicity, cannot be ruled out. Baselt and Cravey (1995) mention the case of a young woman who died several hours after ingesting 2.1 g of ephedrine combined with 7.0 g of caffeine, but tissue findings were not described. The blood ephedrine concentration was 5 mg/L, while the concentration in the liver was 15 mg/kg (Baselt and Cravey, 1995). Garriott et al. (1985) reported on five individuals who died after taking "look-alike" diet pills that resembled commercially produced amphetamine capsules but which contained caffeine and ephedrine. Three of the individuals had taken caffeine–ephedrine combinations, and two had taken caffeine only. Blood caffeine concentrations were extremely high (130 to 344 mg/L), while ephedrine concentrations ranged from 3.5 to 20.5 mg/L. A 1997 case report described the findings in a young woman who committed suicide by taking an undetermined number of ephedrine tablets. The ephedrine level in the blood was 11 mg/L; in the liver, 24 mg/kg; in the kidney, 14 mg/kg; and in the brain, 8.9 mg/kg. Amitriptyline was also present, with a blood concentration of 0.33 mg/kg and a liver concentration of 7.8 mg/kg (Backer et al., 1997).

Blood and tissue concentrations in pure methylephedrine-related deaths have never been reported. However, Levin et al. (1986) described the case of a 19-year-old man who committed suicide by taking BRON. The methylephedrine concentration was 5.6 mg/mL; chlorpheniramine, 2.6; dihydrocodieine, 4.7; salicylate, 150; and verapamil, 6.0. It is doubtful whether anything can be inferred about the specific toxicity of methylephedrine from cases where so many other drugs are involved. In three cases where methylephedrine was an incidental finding at autopsy, blood concentrations ranged from 120 to 250 ng/mL (Kunsman et al., 1998).

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2.4 Khat

2.4.1 Incidence and epidemiology

Khat is native to the sub-Sahara and is cultivated on the mountain slopes of Yemen, where its use is endemic. However, the plant also grows well in California and the desert Southwest, where its popularity seems to be increasing. There is, however, no evidence to suggest that the practice of khat-leaf chewing is spilling over into the U.S. population, and khat is not even mentioned in the Annual Household Survey or in the DAWN reports. According to some estimates, 5 to 10 million people around the world chew khat on a daily basis (Balint et al., 1991).

2.4.2 Cultivation and manufacture

Outside of Africa, California appears to be the only area where khat is grown (Wallace, 1998), but most of the khat consumed in the U.S. is illegally imported. In 1999, U.S. Customs officers confiscated 49,000 lbs of khat, compared to more than 1.2 million lbs of marijuana (Hays, 2000).

2.4.3 History

Khat is an evergreen that grows at high altitudes in East Africa and on the Arabian peninsula. Its leaves contain a naturally occurring psychostimulant closely related in structure to both ephedrine and amphetamine. Khat first came to the notice of Europeans in 1762, when the botanist Peter Forskal found it growing on the mountain slopes in Yemen (Pantelis et al., 1989a,b). The habit of chewing khat leaves, however, is much older. Historical references go as far back as the thirteenth century, when the Arab physician Naguib Ad-Din gave khat leaves to soldiers to relieve fatigue (Giannini et al., 1986). Ad-Din might not have been the first ever to give soldiers psychostimulants, but he was certainly one of the earliest to experiment with performance-enhancing drugs. Since Ad-Din's pioneering experiments, the practice has been repeated many times. Aschenbrant gave cocaine to Prussian recruits during the Franco-Prussian war, while Japan and the Allies issued amphetamines to their troops during World War II (Karch, 1998).

In 1852, James Vaughn, an English surgeon, published illustrations and an account of khat chewing in the *Pharmaceutical Gazette* (Vaughn, 1852). Figure 2.4.3.1 is from Vaughn's paper. Vaughn speculated that the principal reason for the popularity of khat was the fact that, unlike alcohol, its use was not forbidden by the Koran. Khat chewing is usually a social event, with sessions often lasting for hours. In some areas of Africa where khat chewing is still popular (the World Health Organization estimates that there are still millions of khat users), houses often have a special room, called a *muffraj*, just for khat chewing.

The normal dose consumed is 100 to 200 g of leaves and stems chewed over a 3- to 4-hour period (Max, 1991). An occasional solitary individual will chew to increase his work capacity. Users describe increased feelings of alertness and an improved ability to concentrate. Use is also said to make people friendlier and improve the flow of ideas (Kennedy et al., 1980). Nonetheless, use of this material conforms to most definitions of

Figure 2.4.3.1 **Khat leaves.** This drawing from 1852, published in the *Pharmaceutical Journal* of London, was the first illustration of khat to appear in the English literature. Khat abuse is still a problem in Africa, where some of the gratuitous violence in areas such as Somalia is attributed to khat abuse.

addiction. Chewers attempting to secure their daily supply of leaves will do so to the exclusion of all other activities. In Yemen, 4% of all arable land is used to grow khat, and 10% of the revenues in Djibouti are derived from taxes on khat (Max, 1991). Anecdotal reports from Somalia suggest that soldiers from warring clans dose themselves liberally with khat before going into combat.

2.4.4 Chemistry

Cathinone is (s)-2-amino-1-phenyl-1-propanone. Its formula is $C_9H_{11}NO$, with a molecular weight of 165.23. It is composed of 72.5% carbon, 7.4% hydrogen, 9.4% nitrogen, and 10.7%

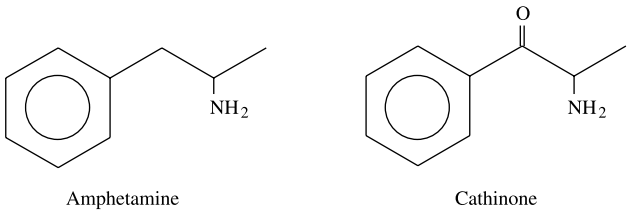

Figure 2.4.4.1 **Cathinone molecule.** Many of the effects of khat are similar to those produced by amphetamine. The structures of both molecules bear a strong resemblance to each other.

oxygen. The hydrochloride crystals ($C_9H_{11}ClNO$) have a melting point of 189 to 190°C (Budavari et al., 1996).

If many of the mood alterations induced by khat resemble those produced by amphetamine, it is not by chance. The active ingredient, cathinone, has the same basic configuration as amphetamine (Figure 2.4.4.1). A second active component, cathine, is much less active because its lipid solubility is much lower than that of cathinone. With the passage of time, cathinone is rapidly converted to cathine, and the result is a considerable loss of potency. Only fresh leaves have any commercial value, and the fragile nature of the product probably explains why it is not more widely distributed (Giannini et al., 1986; Critchlow and Seifert, 1987).

Analysis of khat leaves seized in Switzerland showed they contained, on average, 1 mg of cathinone, 0.86 mg of norpseudoephedrine, and 0.47 mg of norephedrine per gram of leaf (Widler et al., 1994). Absorption of cathinone from the leaves is a slow process. When volunteers were given leaf containing a total of 0.8 mg cathinone per kilogram body weight, maximal plasma concentrations (127 ± 53 ng/mL) were not reached until more than 2 hours after the subjects started to chew the leaves (127 minutes). The elimination half-life was on the order of 4.5 hours (206 ± 102 minutes). Peak norephedrine levels were 110 ± 51 ng/mL; for norpseudoephedrine, 89 ± 49 ng/mL (Widler et al., 1994).

Urine levels were measured in six volunteers 2, 4, 6, and 8 hours after taking 0.5 mg/kg of optically pure (S)-(–)-cathinone. Resultant levels were from 0.2–3.8 μg/mL for the parent compound, 7.2–46 μg/mL for (R,S)-(–)-norephedrine, and 0.5–2.5 μg/L for (R,R)-(–)-norpseudoephedrine (Brenneisen et al., 1986). It is not known if the normal antibody-based screening tests for amphetamine would be sufficiently cross-reactive to detect this compound, but it seems unlikely.

2.4.5 *Clinical studies*

Khat chewing produces symptoms consistent with sympathetic activation and has positive inotropic and chronotropic effects. Chewing khat causes elevations in blood pressure, temperature, and respiratory rate, with inconsistent effects on heart rate. In isolated heart preparations, cathinone causes increased release of norepinephrine (Wagner et al., 1982; Hassan et al., 2000). Khat also causes chronic constipation and reduced milk production in nursing mothers (Makonnen, 2000). Most of these effects are transient. It has been reported that in some parts of Saudi Arabia the only patients seen with oral cancers are those with long histories of khat chewing (Soufi et al., 1991).

Papers in the older literature described cerebral hemorrhage, myocardial ischemia, and pulmonary edema (Halbach, 1972). Animal studies have shown that cathinone releases

dopamine and, at very high concentrations, blocks dopamine uptake (Wagner et al., 1982). Rabbits treated daily with 6- to 10-mg oral doses of khat showed evidence for adrenocortical stimulation, with increased urinary 17-hydroxycorticosteroids and increased plasma free fatty acids (Ahmed and el-Qirbi, 1993). Cathinone has never been evaluated for neurotoxicity in animals and, lacking autopsy information, the situation in humans remains unclear; however, at least one report describes khat-related leucoencephalopathy, clinically identical to the syndrome seen in heroin smokers (see Section 5.8.6.3.4).

The cardiovascular effects of khat appear to be catecholamine related, but plasma catecholamines in khat users have not been measured, although urinary catecholamine excretion is increased after khat chewing. Unlike acute cocaine abuse, where prolactin levels are depressed, and in spite of reports of decreased lactation, khat chewing seems not to affect prolactin levels (Nencini and Ahmed, 1989). Because the absorption of cathinone from chewed leaves is relatively slow, and because the breakdown of cathinone to cathine is relatively rapid, blood concentrations tend to plateau, which may explain why episodes of florid toxicity seem to be uncommon (Max, 1991). Like watercress, khat is a member of the Celastraceae family, which means that the metacercaiae of *Fasciola hepatica* may grow on the leaves; a recent case report described a woman from London who contracted fascioliasis after chewing imported leaves (Doherty et al., 1995).

Khat rapidly loses its potency, so its use is not widespread; however, air transport is possible and home cultivation is not very difficult. Possession of khat leaves is legal in the U.K., which no doubt explains sporadic reports of khat-associated psychosis in that country. Samples have been confiscated on both coasts of the U.S., and importation seems to be increasingly common. The popularity of khat is somewhat surprising, as for all physiologic and pathologic purposes, the effects of khat are basically those of amphetamine, and amphetamine is both abundant and inexpensive.

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chapter three

Synthetic stimulants

3.1 Amphetamine and methamphetamine

3.1.1 Incidence

The Medical Examiner's component of the 1998 Drug Abuse Warning Network (DAWN) reported 501 methamphetamine-related deaths. By 1999, that number had risen to 690, accounting for not quite 6% of all drug-related deaths reported and moving methamphetamine from being the ninth most common cause of drug-related death to the number six position, just after diazepam (811 cases), and just ahead of marijuana-related deaths (670 cases) (Kissin and Ball, 2000).

3.1.2 Epidemiology

According to the Emergency Room component of the 1999 DAWN report, methamphetamine, at least when compared to cocaine and heroin, accounts for a small, but growing percentage of drug-related emergency department visits. In 1998, the estimated number of persons who had tried methamphetamine in their lifetime was 4.7 million (2.1% of the population). The 1998 estimate was similar to the 1997 estimate (2.5%) and the 1994 estimate (1.8%) (Kissin et al., 2000b). However, other data sources indicate a substantial increase in methamphetamine use during the 1990s. For example, based on the Treatment Episode Data Set of the Substance Abuse and Mental Health Services Administration (SAMHSA), methamphetamine-related admissions to publicly funded treatment programs rose from 14,000 in 1992 to 53,000 in 1997.

The National Household Survey on Drug Abuse continues to reflect the aging of the drug-using population (Greene et al., 2000). Methamphetamine users who were teenagers and young adults in the 1960s and 1970s are now older. Most no longer use drugs, but a significant number continue with their habits, which explains why the number of users ages 35 and older, as reported by the National Household Survey, continues to increase and account for an ever larger proportion of drug-related deaths (from 10% of users in 1979 to 32% of users in 1998). Projections indicate that the number of people ages 50 and older needing treatment for a drug problem will increase fivefold in the next 20 years (Gfroerer and Epstein, 1999). Similar trends seem to be emerging in the Medical Examiner component of the 1999 DAWN report. Methamphetamine was found in 6 to 8% of deaths involving decedents ages 6 to 54, and in 2% of deaths of individuals ages 55 and older (Kissin and Ball, 2000).

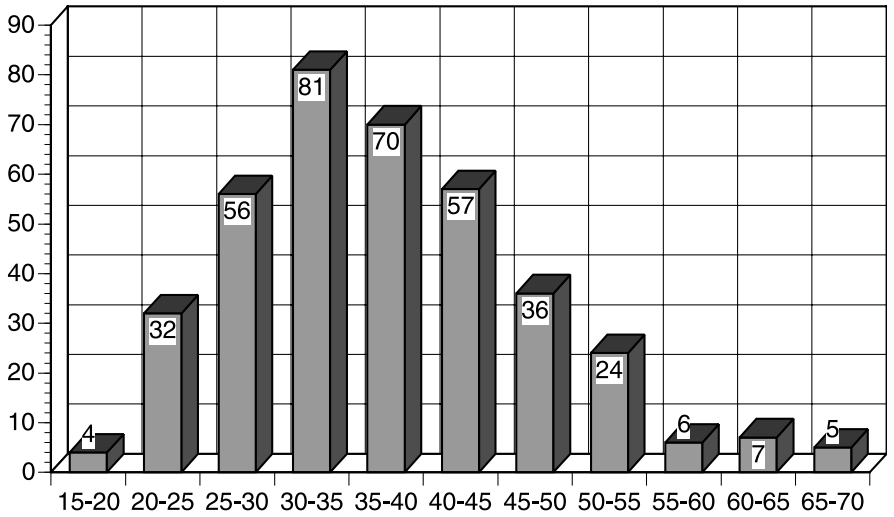

Figure 3.1.2.1 **An analysis of 413 methamphetamine-related deaths in San Francisco (1985–1996).** The mean age at death was 36.8 years. Three quarters were under the age of 43, 10% were over the age of 50, and some of the deceased were in their 60s and 70s.

In the single largest autopsy series published to date, a study of 413 cases in San Francisco (Figure 3.1.2.1), the mean age of the decedents was 36.8 years. Three-quarters of the decedents were under age 43, but 10% were over the age of 50, and some were in their 60s (Karch et al., 1999). In cases where methamphetamine was the cause of death, as opposed to cases where the drug was merely an incidental finding, the decedents were significantly older (38 years) than decedents incidentally found to be methamphetamine positive (35 years). In addition, the decedents were overwhelmingly male (86%) and Caucasian (75%). African-Americans accounted for 14% of the cases, and Asians 4.3% of the cases. Hispanics accounted for less than 2%. These results very much mirror those of the 1999 DAWN survey, where methamphetamine-related decedents were also predominately white (77%), male (80%), and over age 35 (53%) (Kissin et al., 2000a).

3.1.3 History

In the 1920s, concerns that the supply of naturally occurring ephedrine might not be sufficient to meet the needs of asthma sufferers prompted laboratories around the world to attempt the synthesis of ephedrine. A graduate student at the University of California at Los Angeles (UCLA), Gordon Alles, was assigned the task as his thesis project. Alles reviewed the older literature and discovered previous research carried out by an Italian chemist named Edeleano, who had synthesized the basic phenylisopropylamine molecule in 1887. Alles took the phenylisopropylamine molecule as a starting point from which to synthesize ephedrine. Alles never succeeded, at least not in his attempts to produce ephedrine. He did, however, produce a molecule called phenylisopropylamine, later named dextroamphetamine. He gave samples to laboratory animals, and when he saw little evidence of toxicity he tried it on himself. The mood-altering properties of this novel molecule quickly became apparent. A Japanese chemist, named Ogata, had also been trying to synthesize ephedrine, but Ogata ended up producing a different amphetamine, *d*-phenyl-isopropylmethylamine hydrochloride, later known as methamphetamine.

Ephedrine was finally synthesized by Hermann Emde in 1929, but the anticipated ephedrine shortage never occurred.

Ogata licensed his process for making methamphetamine to the Burroughs Wellcome Company, which sold methamphetamine in the U.S. under the brand name Methedrine® until it was taken off the market in 1968. In 1932, the Smith Kline & French Company sold a nasal inhaler containing Benzedrine®, their patented name for racemic β-phenylisopropylamine (*d*,*l*-amphetamine). The inhaler effectively relieved nasal congestion as well as drowsiness and fatigue. The latter qualities, along with exaggerated claims by both drug manufacturers and the popular press, led to widespread interest and even more widespread abuse.

The medical community responded to the introduction of amphetamine in almost exactly the same way it had responded to the introduction of cocaine 50 years earlier. Amphetamines were recommended for the same assortment of unrelated conditions that had been treated with cocaine when it was first introduced. Given what is known today, some of the earlier recommended uses for the amphetamines appear bizarre. For example, amphetamine was recommended as a "valuable adjunct" in the treatment of seizures and schizophrenia. Bearing in mind that amphetamine-induced psychosis is thought, by some (Janowsky and Risch, 1979; Machiyama, 1992; Sato et al., 1992) to be a useful model for the study of schizophrenia, it is difficult to imagine what type of improvement clinicians were observing!

Amphetamines were also said to be useful in treating barbiturate overdose, "caffeine mania," smoking, multiple sclerosis, myasthenia, head injuries, cerebral palsy, migraine, urticaria, seasickness, dysmenorrhea, ureteral colic, obesity (Figure 3.1.3.1), irritable colon, radiation sickness, Ekbom's syndrome, and other seemingly unrelated conditions — even impotence and loss of libido (Bett, 1946). It should come as no surprise that amphetamine was even recommended for use in the treatment of morphine addiction. By the time amphetamine arrived on the scene, Freud's disastrous cocaine experiments of 1885 apparently had been completely forgotten (Wax, 1997).

Moderate doses of *d*-amphetamine increase the ability to sustain attention over prolonged periods of time, especially when performing monotonous tasks. Like cocaine, *d*-amphetamine improves performance on auditory and visual reaction time tests, and on the digit symbol substitution test (DSST), a measure of psychomotor skills and attention (Heishman and Karch, 2000). These actions were recognized very soon after amphetamine became commercially available, which probably explains why, during World War II, troops of both the Allied and Axis forces were supplied with amphetamines.

Soon after World War II, laws limiting amphetamine distribution were enacted, but a regulatory lapse allowed the continued sale of the Smith Kline & French's nasal inhaler. Inside each inhaler were eight folded paper sections impregnated with 250 mg of amphetamine. Abusers opened the inhaler and chewed the papers. Friends mailed the strips to prison inmates, and abuse within the prison system became a problem (Monroe and Drell, 1947). In an escalating battle with would-be abusers, amphetamine manufacturers tried adding denaturants such as emetine and picric acid to the strips, but abusers found ways to extract the amphetamine, or simply put up with the transient side effects produced by the denaturants.

The Benzedrine® inhaler was reformulated in 1949, and the product name was changed to Benzedrex®. The new formulation contained propylhexedrine, also a potent vasoconstrictor, but with only 1/12 the central nervous system (CNS) stimulant potency of amphetamine. Smith Kline & French's patents expired in 1953, and almost immediately Wyeth, Rexall, Squibb, Eli Lilly, and W. S. Merrell brought competing products to market. Inhaler abuse continued until 1959, when the amphetamine inhaler was finally classified as a prescription item.

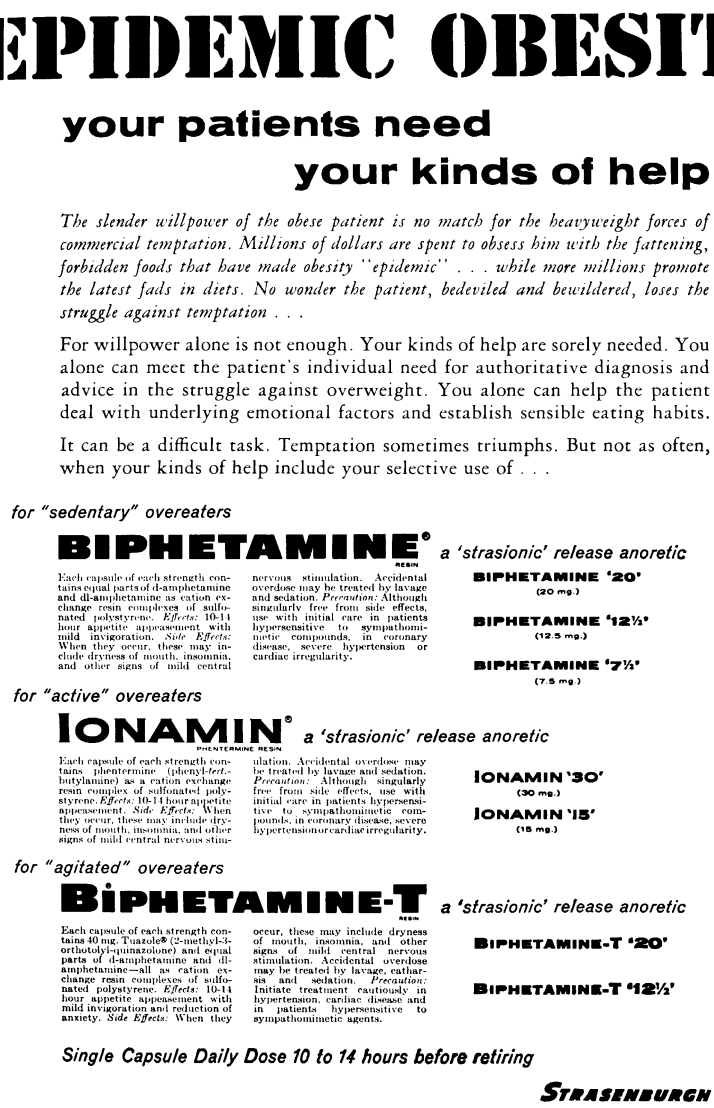

Figure 3.1.3.1 **Medical use of amphetamine.** For many years, amphetamine was promoted as a treatment for obesity. When first introduced to the market, amphetamine was claimed to be something of a wonder drug. The same claims were made for amphetamine as were made for cocaine when it was first introduced. This advertisement was published in a 1961 issue of *JAMA*.

The first amphetamine-related deaths were reported within a few years of the introduction of amphetamine. The serious complications associated with amphetamine abuse are essentially the same as for cocaine: arrhythmic sudden death, stroke, psychosis, and rhabdomyolysis. Most of the case reports are from the 1950s and 1960s. Mentions of toxicity were uncommon during the 1980s, when use was largely confined to the desert Southwest.

With the introduction of smokable "ice," a pure form of (+)-methamphetamine hydrochloride, interest in methamphetamine as a drug of abuse revived, and new case reports of toxicity began to appear (Cho and Wright, 1978). Methamphetamine becomes "ice" when it is crystallized out of a saturated solution. Depending on how methamphetamine is

initially prepared (a number of ways are possible; see Skinner, 1990), solvent is captured within the structure of the crystals. The type of solvent is a clue to which processes were used in the manufacture, and may also suggest where the illicit drug was made. The volatility of the solvent in which the methamphetamine is dissolved determines how large the resultant crystals will be. With very volatile solvents, such as freon, crystallization is rapid and only very small crystals form. With less volatile solvents, such as methanol, larger crystals are produced. No matter the size of the crystals, they are all equally smokable.

The first illicit "ice" laboratories were in Japan. The Japanese have referred to this particular form of methamphetamine by a number of different names, including *kaksonjae*, *hanyak*, *batu*, and *hiropon*. The use of the name *hiropon* is doubly ironic because that was the name the Japanese used for ephedrine during the epidemic of ephedrine abuse that swept Japan just after World War II. Today, ephedrine is the universally preferred starting material for making methamphetamine.

Large-scale "ice" production began in the early 1980s. Enforcement efforts by police convinced the illegal chemists to transfer their operations out of Japan to Korea. To this day, Korea remains the principal manufacturer of "ice." At first, the market for this form of amphetamine was confined to Taiwan, Japan, and the Philippine Islands. Japanese and Korean abusers took it intravenously, but the Filipinos began smoking it. The Filipinos were already used to smoking stimulants, having smoked *shabu* (a mixture of ephedrine and caffeine) for years. Demand within the Filipino community was also thought to be responsible for the introduction of "ice" into Hawaii (Skinner, 1990).

In the late 1980s, Korean chemists emigrated and established illicit laboratories in Portland, OR, and Los Angeles, CA. Most of their production was shipped back to the Philippines. In 1988, sporadic seizures of "ice" took place across the U.S., but no laboratories were seized in 1989. By 1990, the Drug Enforcement Agency (DEA) had seized seven laboratories in California alone. Impressive amounts of "ice" continue to be seized in China and Korea, but not in the U.S. No "ice" laboratories have been raided in the U.S. for several years, nor do any of the thousands of clandestine "meth" laboratories raided each year appear to be producing "ice." More recently, the Myamar Republic has begun mass production of methamphetamine, producing huge quantities of the drug, but mostly for local consumption. It is not clear what form — large crystals for smoking or small crystals for oral ingestion — is being produced.

Even though cocaine and amphetamine induce very similar behavioral effects, no real "ice" epidemic has ever occurred. A significant number of methamphetamine abusers also use cocaine. In the autopsy study of 413 methamphetamine-related deaths mentioned above, toxicologic testing disclosed that slightly more than 25% of the decedents were using both drugs simultaneously (Karch et al., 1999).

Considering the amount of illicit amphetamine produced and consumed in the U.S., episodes of toxicity are surprisingly uncommon, with only one methamphetamine-related death for every ten attributed to cocaine. Evidence indicates that, among pregnant women, methamphetamine abuse is more common than cocaine, especially in cigarette-smoking Caucasian women (Vega et al., 1993), but reports of methamphetamine-related pregnancy complications, in mother or child, are rare (Catanzarite and Stein, 1995; Plessinger and Woods, 1998).

3.1.4 Illicit manufacture

As legitimate medical indications for methamphetamine and amphetamine became fewer and fewer, and the dangers of long-term use more apparent, legal production fell off.

However, the recent dramatic rise in the number of illicit methamphetamine laboratories seized, which increased from only 263 in 1994 to 1627 in 1998 and 2252 in 1999, suggests a thriving market for the product (Tichacek and Napolitano, 1999). More clandestine laboratories are now seized in Missouri (371 in 1998) than in any other state, but most of these "laboratories" are small, with very modest production. In the mid-1990s, illegal Mexican laboratories operating in Southern California constructed "super labs" capable of processing 10-lb (and occasionally 100-lb) batches of methamphetamine (Tichacek and Napolitano, 1999).

Another fairly recent change in methamphetamine production is the entrance of new overseas illicit manufacturers. The Myamar Republic, in addition to being a major poppy grower and heroin manufacturer, has recently begun large-scale methamphetamine production. Ephedra is grown commercially in both India and Pakistan, sold to clandestine laboratories in Myamar (which produces mainly for export) and Thailand (which also produces mainly for local consumption). Occasional batches of methamphetamine from both countries have been confiscated by U.S. Customs, but the amount of methamphetamine being exported to the U.S. from Southeast Asia is not really known. Clandestine laboratories have also sprung up in the former Czech Republic, but the data are limited and the true magnitude of production there is not known (Board, 1999).

When phenyl-2-propanone (P2P) sales were not controlled, it was the precursor of choice for "meth cooks." Once P2P became a controlled substance, clandestine chemists in the U.S. were forced to first make P2P before they could make methamphetamine. P2P can be synthesized in several ways. The most frequently used approach starts with phenylacetic acid, acetic anhydride, and sodium acetate. P2P is then converted to methamphetamine by reductive amination (Puder et al., 1988; Skinner, 1990). Methylamine, aluminum foil, mercuric chloride, diethyl ether, and isopropanol are required. High yields can be obtained via this synthetic route. Formulas for production using readily available materials are easily found on the Internet. Legislation has been introduced in the U.S. Congress that would make the act of disseminating information about drug manufacture illegal.

In spite of strict controls in the U.S., massive amounts of P2P are still used in Europe. According to a report of the International Narcotics Control Board, more than 85,000 kg of P2P, enough to manufacture up to 40 tons of methamphetamine, were interdicted between 1994 and 1997. Part of the reason for the explosive rise in both European production and consumption is that many of the countries within the European Union are ill equipped to monitor shipments of P2P coming into their jurisdictions (Board, 1999).

Regardless of the source, methamphetamine made from P2P yields a racemic mixture. Because the (+) form of methamphetamine is five times as potent as the (–) isomer, the potency and yield of the final product can be variable. Not only can the potency vary, but an assortment of contaminants can also be introduced. Some of the contaminants have strong stimulant properties themselves (Soine, 1986), while others may be quite toxic, possibly more toxic than amphetamine. In the U.S., the P2P synthetic route has been entirely replaced by the "red phosphorus" route (Figure 3.1.4.1), and P2P toxicity is no longer an issue.

Both (–)-ephedrine and (+)-pseudoephedrine can be converted to methamphetamine by reductive dehalogenation using red phosphorus as a catalyst. If (–)-ephedrine is used as the starting point, the process generates (+)-methamphetamine. Pseudoephedrine also yields dextromethamphetamine. Regardless of the isomer produced, contaminants will be present. As is true with the P2P route, some of these contaminants, particularly 2-(phenylmethyl)phenethylamine, may also be toxic in their own right. Unfortunately, the subject has not been studied in any detail (Soine, 1989).

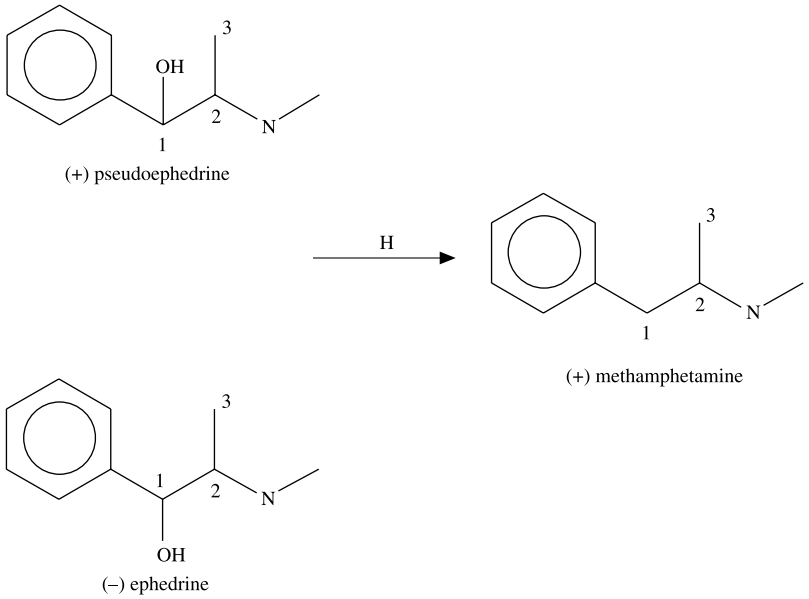

Figure 3.1.4.1 **Making methamphetamine.** The most popular formula for making methamphetamine starts with ephedrine and uses red phosphorus as a catalyst. Ephedrine used to be inexpensive and easily available, but now its sales are controlled and availability limited.

The popularity of the red phosphorus route has created an unprecedented demand for ephedrine. Until the red phosphorus synthetic route became popular, ephedrine was a nonprescription item, easily obtained from vitamin, dietary supplement, and organic food vendors. However, demand is now so great that many states have moved, or are moving, to restrict sales of ephedrine. The Mexican operators of the Southern California "super labs" illegally transport bulk quantities of ephedra from Mexico. California authorities reported seizing over 2.6 metric tons of ephedrine in 1993. More recent statistics are not available, but strict controls in California now make even the purchase of hydroiodic acid difficult. Hydroiodic acid can still be obtained in other states, but the price has risen to nearly $600 per gallon. Prices for iodine crystals, another essential ingredient, have soared. One chemical supplier reported that sales of iodine crystals rose from 161 lb in 1992 to almost 6 tons during the first 9 months of 1993 (Woodworth, Drug Enforcement Administration, 1999).

Occasionally, methamphetamine "cooks" have resorted to the use of assorted cold remedies in place of ephedrine. Mixtures of diphenhydramine, chlorpheniramine, dextromethorphan, doxylamine, and even guaifenesin have been used. All of these chemicals, except for chlorpheniramine, react with red phosphorus and hydroioditic acid to form an assortment of byproducts that may be detected in the finished product. Diphenhydramine is converted to diphenylmethane, but because it does not crystallize, at least not with the techniques used to crystallize methamphetamine, it is unlikely to appear in the final product. Other byproducts generated by the hydroiodic acid/red phosphorous reduction method include 1,3-dimethyl-2-phenylnaphthalene and 1-benzyl-3-methylnaphthalene (Lurie et al., 2000). Whether any of the other intermediates and byproducts produced in this fashion are toxic in their own right is not known.

3.1.5 Chemistry

Possible chemical designations for methamphetamine include *N*-α-dimethyl benzenethanamine, *d*-*N*-α-dimethylphen ethylamine, and *d*-deoxyephedrine. The drug has been sold under many proprietary names (Desoxyn, Hiropon, Isophen, Methedrine, to name just a few). Its formula is $C_{10}H_{15}N$, and its molecular weight is 149.2. It is 80.4% carbon, 10.13% hydrogen, and 9.39% nitrogen, with a melting point of 170 to 175°C. The low melting point permits it to be smoked, regardless of the crystal size (Sekine and Nakahara, 1987). Crystals have a bitter taste and are soluble in water, alcohol, chloroform, and freon. Methamphetamine is not soluble in ether. Manipulation of the phenyl ring of amphetamine yields fenfluramine, which, until recently, was a widely prescribed anorectic. Manipulation of the side chain yields a series of compounds with varying degrees of sympathomimetic activity.

3.1.6 Routes of administration

Methamphetamine can be swallowed, injected, smoked, or "snorted." In spite of the publicity accorded to "ice" smoking, most users still prefer to inject it intravenously or take it orally (Hall and Hando, 1993). An oral dose of 10 mg results in 30-ng/mL plasma concentrations 1 hour later (Lebish et al., 1970). Ten subjects given a 12.5-mg dose had peak plasma concentrations of 20 ng/mL at 2 hours, decreasing to 10 ng/mL at 24 hours (Lebish et al., 1970). Similar studies done with amphetamine have yielded comparable results, at least in terms of resultant blood levels.

The pharmacokinetics of smoked and intravenously injected methamphetamine have been compared in male volunteers acting as their own controls. The average dose smoked was 21.8 mg (bioavailability was >90%), and the dose injected intravenously was 15.5 mg. The mean plasma half-life was 11.1 hours for the smoked methamphetamine and 12.2 hours when the drug was injected. Peak methamphetamine blood levels after smoking and injecting were comparable, ranging from 50 to 100 ng/mL. Amphetamine concentrations were much lower, reaching peak values of only 4 ng/mL after 3.3 hours. Methamphetamine levels in saliva were very high after smoking, but saliva amphetamine levels were negligible (Cook et al., 1993). In other studies, larger doses of amphetamine have been given intravenously, again with comparable results. Volunteers given 160 to 200 mg of amphetamine intravenously had one-hour plasma concentration of 269 ± ng/mL (Änggård et al., 1970). In seven patients presenting at an emergency room with evidence of amphetamine toxicity, plasma concentrations were found to range from 105 to 560 ng/mL (Lebish et al., 1970).

3.1.7 Metabolism

Methamphetamine has a long half-life, between 11 and 12 hours. It is cleared from the blood by multiple routes. Approximately 20% is *N*-demethylated to form amphetamine and ephedrine derivatives which are also psychoactive (Figure 3.1.7.1) (Caldwell et al., 1972). These compounds are further metabolized by a combination of deamination, hydroxylation, and conjugation. The results of several clinical studies and of one large autopsy series suggest that 10 to 20% of a given dose of methamphetamine is converted to amphetamine (Karch et al., 1999). It appears that all phenylisopropylamines, including methamphetamine and amphetamine, are competitive inhibitors of CYP2D6 in human liver microsomes. Modifications of the basic phenylisopropylamine molecule at the 3,4 positions increase its affinity for CYP2D6 (Wu et al., 1997).

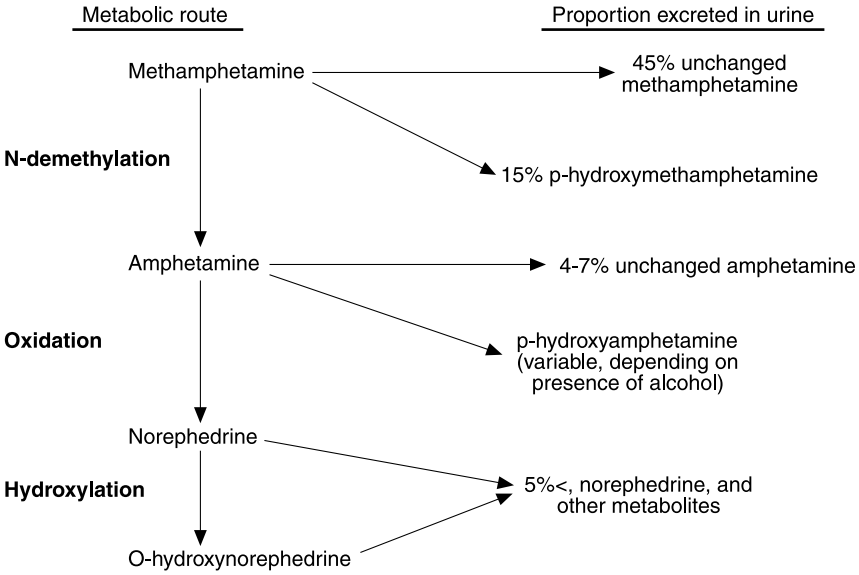

Figure 3.1.7.1 **Methamphetamine metabolism.** Methamphetamine is demethylated to produce amphetamine. Ephedrine and other analogs are not converted to amphetamine. Thus, the presence of amphetamine in a sample containing methamphetamine is proof that methamphetamine, and not some harmlesss analog, was taken.

When the National Institute on Drug Abuse (NIDA) discovered that the analytic process used by federally regulated laboratories caused the conversion of the legal drug/dietary supplement ephedrine to the illegal drug methamphetamine, new regulations were passed prohibiting the reporting of methamphetamine in a urine specimen unless: (1) the methamphetamine level is over 500 ng/mL, and (2) more than 200 ng/mL of amphetamine is also detected in the specimen. Ephedrine does not convert to amphetamine, so the presence of amphetamine confirms the act of methamphetamine ingestion, and rules out the possibility of innocent ephedrine ingestion.

Other factors besides methamphetamine ingestion may explain the presence of amphetamine in a urine or blood sample. One is that amphetamine may have been ingested at the same time as methamphetamine. Underground chemists have begun substituting phenylpropanolamine (PPA) for ephedrine as a precursor in methamphetamine production (Oulton and Skinner, 1999). The process is no more complicated than using ephedrine, and phenylpropanolamine may still be easier to acquire; however, the end product is dextroamphetamine, not methamphetamine. Producers unable to obtain adequate supplies of ephedrine have begun adding supplement phenylpropanolamine to the reaction mixture. The result is a product that contains a mixture of methamphetamine and amphetamine.

Because amphetamine may actually be present in clandestinely produced methamphetamine, the mere demonstration of amphetamine in hair or sweat samples does not necessarily prove that methamphetamine was ingested and demethylated to amphetamine within the body. Its presence could equally well be explained by contact (innocent or otherwise) and environmental contamination, such as might be found in a clandestine laboratory or in the home of a drug user or drug dealer. Of course, this would matter little for NIDA urine-testing purposes, but it could make a great deal of difference to probationers or those involved in child-custody lawsuits.

Over a period of several days, 35 to 45% of a given dose of methamphetamine is excreted unchanged in the urine (Cook et al., 1993). If the urine is acidic, that amount may increase to over 75%. On the other hand, when the urine is extremely alkaline the amount excreted unchanged may drop to as little as 2% (Beckett and Rowland, 1965). In C14 tracer studies of two volunteers, 23% was excreted in the urine within the first 24 hours. Other metabolites also appear in substantial quantities, including 4-hydroxymethamphetamine, norephedrine, and 4-hydroxynorephedrine (Caldwell et al., 1972). The (+) isomer of amphetamine is metabolized more rapidly than the (–) isomer and appears in the urine sooner.

Daily oral dosing with methamphetamine appears to have little effect on either metabolism or peak blood levels. When six volunteers were given 10 mg of methamphetamine per day for 2 weeks, no evidence of any change in the rate of metabolism or in peak blood levels, which remained between 25 and 50 ng/mL, could be found. Interestingly, saliva concentrations were much higher than concentrations measured in plasma, with an average saliva-to-plasma ratio of 7:8 (Cook et al., 1992). Other studies have shown that both the *d-* and *l-* forms of amphetamine appear in the saliva in concentrations that are two to three times higher than those measured in plasma. Detectable concentrations remain present for at least 48 hours (Wan et al., 1978). While methamphetamine does appear in saliva, its presence is unpredictable. In a different study of 25 methamphetamine abusers, methamphetamine was found in the hair of 73%, in the nails of 65%, in the sweat of 50%, but in the saliva of only 16% of the participants (Suzuki et al., 1989).

Evidently, the general public is quite unaware of the fact that acidification of the urine hastens methamphetamine excretion. The underground press recommends drinking vinegar as a way to foil urine drug testing. Obviously, acidifying the urine will increase the probability of being caught. If the urine is alkaline, the differences in metabolic rates among the methamphetamine enantiomers assume significance, because the (+) form is cleared about 5 hours more rapidly than the (–) isomer (17 hours vs. 12.7 hours) (Wan et al., 1978). Concomitant alcohol consumption appears to have relatively minor effects on methamphetamine pharmacokinetics, although evidence indicates that the simultaneous consumption of both drugs produces a more intense euphoria than either drug used alone (Mendelson et al., 1995; Hayase et al., 1999).

3.1.8 Tissue disposition

Rabbits sacrificed one hour after intravenous injection of methamphetamine had hepatic drug concentrations twice as high as blood concentrations. Amphetamine concentrations measured at the same time were eight times higher in the liver than in the blood. In the same rabbit model, skeletal muscle concentrations of both methamphetamine and amphetamine are equal to the concentration in the liver (Nagata et al., 1990). Histochemical studies of mice confirm the results of the rabbit studies. Amphetamine also localizes in the epithelial cells of the distal part of the renal tubule transitional epithelial cells of the bladder, liver parenchymal cells, epithelial cells of the striated duct of the salivary gland, parietal cells of the gastric gland, part of epithelial cells of the distal portion of the large intestine, secretory cells and part of the epithelial cells of the ductal portion of the sweat gland, alveolar cells of the mammary gland, secretory cells of the sebaceous gland and hair both in the medulla and cortex (Kajitani et al., 1989). The findings of a more recent study of drug distribution in humans suggest that skin and blood methamphetamine concentrations are comparable, and that methamphetamine may persist in the skin for some time. In the mammary gland, methamphetamine is combined with casein and excreted by exocytosis. Accumulation of methamphetamine in the hair is thought to be

the result of drug, derived from tissue fluid and sebum, penetrating the shaft of the hair. It could also be due to blood perfusing the hair follicle (Nakahara and Kikura, 1997).

The disposition kinetics of amphetamine is stereoselective, with significant differences in pharmacokinetic parameters for *d*- and *l*- forms (Hutchaleelaha et al., 1994). Whether or not the different isomers possess different toxicity in humans is not known. In a Japanese study of methamphetamine-related deaths, some cases were associated with the *l*- form and others with racemic mixtures (Mori et al., 1985). The metabolic conversion of methamphetamine to amphetamine is stereo specific; *d*- and *l*-methamphetamine are converted to *d*- and *l*-amphetamine, so the mixture of amphetamine forms detected in the urine will simply reflect the mixture of the methamphetamine that was ingested. If *l*-methamphetamine is detected in the urine, then *l*-methamphetamine had to have been the compound originally ingested (e.g., the donor was using a Vicks® inhaler). The presence of both isomers in the urine proves that the psychoactive *d*- form methamphetamine was taken (Hornbeck et al., 1993; Cooke, 1994).

Methamphetamine concentrates in breast milk. In milk from one amphetamine-using woman, tested 10 and 42 days after delivery, amphetamine concentrations were much higher than in her plasma (Steiner et al., 1984). There is very little evidence that either amphetamine use during pregnancy or excretion of amphetamine into breast milk directly harms the fetus. One study found evidence for prematurity and lower birth weight (Oro and Dixon, 1987). However, a number of other case reports have described women who took methamphetamine, either for narcolepsy or as abusers, throughout pregnancy and while nursing and produced no detectable ill effects in their children (Briggs et al., 1975; Milkovich and van der Berg, 1977; Eriksson et al., 1978; Little et al., 1988a,b; Joffe and Kasnic, 1994). Nonetheless, at least one methamphetamine-using mother has been convicted of child abuse, after being unsuccessfully tried for murder for administering drugs by breastfeeding (Ariagno et al., 1995).

Few data on the disposition of amphetamines in the fetus are available, and what little is known has been derived from studies of pregnant ewes (125 days' gestation is the equivalent of a 34-week human pregnancy). In these animals, methamphetamine quickly crosses the placenta, appearing in fetal tissues 2.5 minutes after intravenous injection into the mother. The half-life of methamphetamine in ewes receiving 1.2 mg/kg is 39 minutes. Peak levels in the ewe of 10.2 mg/L, and in the fetus of 7.2 mg/L have been reported. Fetal half-life for methamphetamine is considerably longer than in the mother. Two hours after injection, levels are higher in the fetus than in the ewe. In this same study, tissue levels measured at two hours were, in every instance, higher than blood levels. The highest concentrations, both in ewe and fetus, were found in the intestine and lung, while the lowest concentrations were found in the brain and heart (Burchfield et al., 1991). This is exactly the opposite of the pattern observed with cocaine. Other studies using this same model have demonstrated short-term increases in catecholamine concentrations, with secondary increases in pulse, blood pressure, blood sugar, and insulin levels (Stek et al., 1993; Dickinson et al., 1994). The long-term effects of these changes, if any, have not been studied.

The findings reported in two human cases are consistent with the findings in the sheep model. One case involved a 24-year-old chronic amphetamine abuser who delivered a premature, low-Apgar-score, 2-lb, 7.5-ounce child who expired at 4 hours. Autopsy findings were consistent with intrauterine anoxia. Both methamphetamine and amphetamine levels were quite low (0.246–0.857 μg/g and 0.030–0.120 μg/g, respectively). Methamphetamine concentration was highest in the lungs and lowest in the liver. The concentration in the lungs was nearly three times that in the blood (Garriott and Spruill, 1973). In a

second case, an amphetamine-abusing mother, who had intravenously injected amphetamine a few hours prior to delivery, gave birth to twins that died one to two hours later. The highest concentrations were in the kidney and liver, and the lowest levels were in the blood and brain. Methamphetamine concentrations ranged from 4.53 to 11.0 mg/kg. Amphetamine concentrations were less than 15% of the methamphetamine concentrations, which ranged from 0.18 to 1.40 mg/kg (Stek et al., 1993).

Steward and Meeker (1997) described the toxicologic findings in eight cases of fetal and infant death where methamphetamine was detected, though drug toxicity had not been deemed to be the cause of death in any of the cases. The mean fetal blood concentration of methamphetamine was 0.36 μg/mL (range, 0.03 to 1.20 μg/mL), and the mean concentration of amphetamine was 0.05 μg/mL (range, 0 to 0.08 μg/mL). In two instances, concentrations were also measured in the mother. Maternal and fetal methamphetamine concentrations, respectively, of the two mothers were 0.21 and 0.40 μg/mL and 0.18 and 1.20 μg/mL.

As the ability to detect nanogram quantities of drugs improves, drugs are being detected in more and more sick children (Kharasch et al., 1991; Smith and Kidwell, 1996; James et al., 1998; Lustbader et al., 1998). The mere presence of these drugs, however, is not sufficient reason to implicate them as a cause of illness or death, either in adults or in children. In order to prove that death was the result of drug toxicity, there should be some plausible explanation of how the toxic effect was exerted and, preferably, anatomic or histologic evidence of toxicity. In the case of methamphetamine and cocaine, such evidence may be provided by the presence of infarction, cardiac enlargement, myocardial fibrosis, or contraction band necrosis. Absent all anatomic lesions, it is unreasonable, and quite probably misleading, to attribute death to the presence of an abused drug that is present in concentrations of only a few nanograms per milliliter.

Interpretation is particularly difficult in the case of neonates and infants, as there is good reason to suppose that the fetus may be more resistant to drug effects than the mother. The birthing process is associated with a massive surge of catecholamines (partly to facilitate the mobilization of brown fat), and yet the hearts of newborns never display any histologic evidence of catecholamine toxicity, probably because at birth the adrenergic receptors in the heart have been downregulated (Robinson, 1996; Hata et al., 1997; Lustbader et al., 1998). If adrenergic receptors are downregulated, then it becomes increasingly difficult to imagine how such amphetamine toxicity is exerted.

Maternal drug use is not the only possible explanation for the presence of methamphetamine in newborn tissues. The environment is massively contaminated with drugs (Oyler et al., 1996), and if drugs are in the mother's milieu then the possibility exists that some drug will make the transition from maternal to fetal circulation. Such a scenario has already been demonstrated for the children of cocaine users (Smith and Kidwell, 1996), and similar mechanisms could easily account for the presence of methamphetamine in low concentrations.

Postmortem methamphetamine measurements have been reported in two large autopsy series (Logan et al., 1998; Karch et al., 1999). However, the occurrence of tolerance (McLeman et al., 2000), postmortem redistribution (Prouty and Anderson, 1990; Moriya and Hashimoto, 1999), and polydrug use (Greene et al., 2000) make the value of such measurements questionable at best.

In the largest autopsy series reported to date, drug concentrations were compared in a group of 132 decedents for whom methamphetamine toxicity was not the cause of death, and 232 patients for whom methamphetamine was the cause of death (Karch et al., 1999). Of the cases in both groups, 75% had blood methamphetamine concentrations

of less than 1.32 mg/L. The mean blood methamphetamine concentration was 1.84 mg/L in the first group, and 2.11 mg/L in the second. Blood amphetamine concentration was 0.24 mg/L in the incidental finding group, and 0.161 mg/L in those dying of drug toxicity. Concentrations in the two groups were not significantly different. In other words, blood concentrations, taken in isolation, did not identify those cases where methamphetamine was the cause of death and those where it was not. Measurement of urine methamphetamine and amphetamine concentrations revealed similar overlap; no difference was observed between cases in which methamphetamine was the cause of death and cases where it was not (38.6 vs. 27.5 for methamphetamine and 8.0 vs. 4.5 mg/L for amphetamine). Ethanol was present in one quarter of all the cases, and cocaine or cocaine metabolite in 24% of the decedents. However, the drug most often used in combination with methamphetamine was morphine, which was present in nearly one third of the cases (Karch et al., 1999).

Comparable results were also reported from a second autopsy series in Seattle, WA. Methamphetamine was detected in 146 cases. In 52 of the cases, death was a consequence of methamphetamine. In the remaining 92 cases, methamphetamine was an incidental finding. Overall, a very broad range of concentrations was observed (0.05 to 9.30 mg/L, median concentration of 0.42 mg/L). In spite of the wide range, blood concentrations were less than 2.20 mg/L in 90% of the cases with a substantial overlap in methamphetamine concentration between drug-related deaths and non-drug-caused deaths (Logan et al., 1998).

Though unlikely to be a factor in pregnant women, the presence of methamphetamine can also be explained by the conversion of certain drugs, such as selegiline (Eldepryl®, Deprenyl®), a monoamine oxidase (MAO) inhibitor used in the treatment of Parkinsonism. It is a derivative of phenethylamine, and two of its principal metabolites are amphetamine and methamphetamine. Both may accumulate in substantial amounts in patients receiving anti-Parkinson therapy. In such cases, the clinical history will be necessary to make the correct diagnosis. Other drugs that can be converted to methamphetamine include benzphetamine, clobenzorex, deprenyl, dimethylamphetamine, ethylamphetamine, famprofazone, fencamine, fenethylline, fenproporex, furfenorex, mefenorex, mesocarb, and prenylamine (Musshoff, 2000).

3.1.9 Interpreting amphetamine levels

In most methamphetamine-related deaths, blood concentrations fall between 0.5 and 2 mg/L; however, methamphetamine concentrations alone cannot be used to determine the cause of death. Long-term methamphetamine abuse sets in motion a complicated series of interactions affecting both physiologic and behavioral responses. As is true for cocaine, death from methamphetamine may be associated with very low or very high postmortem blood concentrations (Karch et al., 1998; Jenkins et al., 1999). Tolerance to stimulant drugs cannot be assessed at autopsy except, perhaps, by the measurement of brain receptor concentrations, a diagnostic modality not likely to be available to many medical examiners. Without knowing the degree of tolerance, it is not possible to attribute any significance to isolated high-concentration measurements. Low concentrations are equally difficult to interpret. If significant methamphetamine-related heart disease is present, and there is a documented history of long-term methamphetamine abuse, death could be attributed to methamphetamine even when blood drug concentrations are low or nonexistent.

The results of animal studies suggest that, over the long term, methamphetamine and amphetamine are stable in most tissues, no matter the degree of environmental exposure.

Nagata et al. (1990) found that concentrations of both drugs in whole blood, liver, and skeletal muscle were nearly unchanged after two years of storage in sealed tubes, and that concentrations only decreased by half in samples of bone exposed to the air over a two-year period. The amphetamine content of marrow submerged in tap water for two years barely decreased from baseline. Levels in blood and urine stains do decrease significantly with storage, but not to below detectable levels.

At autopsy, concentrations measured in left-heart blood may be many times higher than concentrations measured in right-heart blood. Concentrations in samples collected from other sites also differ. Diffusion of methamphetamine out of lung tissue into the pulmonary circulation occurs more rapidly than diffusion from the liver into the vena cava. As a consequence, methamphetamine concentrations in blood from the pulmonary artery (Nagata et al., 1990) and left ventricle may be many times higher than in blood collected from the right side of the heart (Moriya and Hashimoto, 1999). On the other hand, the ratio of methamphetamine to amphetamine appears to be the same, regardless of where the specimen is obtained.

In the living, testing for methamphetamine is often problematic. Under federally regulated workplace testing programs, a urine test is not considered to be positive for methamphetamine unless immunologic screening tests demonstrate that the specimen contains amphetamine or methamphetamine in concentrations of 1000 ng/mL or more, and subsequent gas chromatography/mass spectrometry (GC/MS) analysis shows a concentration of at least 500 ng/mL. First-generation amphetamine screening tests often cross-reacted with compounds such as ephedrine, phenylpropanolamine (Aoki and Kuroiwa, 1985; Smith-Kielland et al., 1995), and diet pills such as phentermine (Wayamine®), phenmetrazine (Preludin®), and fenfluramine (Pondimin®). The Vicks® decongestant inhaler contains the levo-rotatory isomer of methamphetamine (Poklis et al., 1993). This isomer has minimal CNS activity but, unless special precautions are taken, it may give false-positive test results for methamphetamine during both screening and confirmatory testing.

Newer generation screening tests, such as the EMIT® d.a.u. monoclonal immunoassay, seemed to have solved this particular problem, but not all laboratories use this methodology, and false-positive screening tests still can occur. Agents structurally dissimilar to the amphetamines, such as chlorpromazine and brompheniramine, and agents not so dissimilar, such as doxepin, famprofazone, clobenzorex, and trimethobenzamide, have been noted to cause positive reactions (Colbert, 1994; Tarver, 1994; Yoo et al., 1994). Manufacturers do extensive premarketing tests to rule out cross-reactivity of their reagents with other compounds, but they are unable to test all of the possible metabolites. For that reason, among others, the results of screening tests can never be accepted without a confirmatory test that utilizes a different technology.

False positives due to the presence of ephedrine have been a perpetual problem. In the past, specimens containing high levels of ephedrine were incorrectly analyzed as containing methamphetamine (Yoo et al., 1994). As a result, the federal government issued a regulation requiring that, even if GC/MS showed that more than 500 ng/mL of methamphetamine were present, specimens could not be reported as positive unless amphetamine was also detected in the sample. The reasons for the confusion relate to the analytic process itself. In some instances, contaminants in a derivitizing agent (heptaflurobutyric anhydride, also referred to as HFBA) can be responsible for the confusion, while in other cases the temperature at which samples are injected into the chromatograph can play a role (Wu et al., 1992; Hornbeck et al., 1993).

Whatever the cause for the error, humans do not metabolize ephedrine to amphetamine, so the presence of amphetamine in a specimen is additional proof that methamphetamine,

and not ephedrine, is responsible for the positive test result (DHHS/NIDA, 1990). Considerable care must still be exercised during specimen preparation, because periodate degradation, the process used to rid urine samples of innocent compounds such as ephedrine and phenylpropanolamine, can generate small amounts of amphetamine. This could be falsely interpreted as confirmatory evidence that the specimen actually came from a methamphetamine abuser (Paul et al., 1994). The situation is likely to become more confusing in the near future, when workplace testing rules are liberalized to allow for the detection of "designer amphetamines" and other stimulants such as Ritalin®. New immunoassay screen tests will be required to cross-react with a broad range of substances, not just the old "NIDA 5." As a consequence, much more confirmatory GC/MS testing will be required.

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3.1.10 Toxicity by organ system

Considering the large number of individuals who use and abuse methamphetamine, the number of reported deaths and medical complications remains surprisingly low. The explanation may be that the most important complications are cardiovascular, and that the production of cardiovascular damage takes time. Exact figures are not known, but many more people experiment with methamphetamine than use it on a regular basis, and intermittent use probably does not result in the anatomic changes associated with long-term abuse. Table 3.1.10.1 shows the 10 most frequently seen disorders in the autopsy study of 413 methamphetamine-related deaths. Liver disease, ranging from steatosis to cirrhosis, was present in nearly 40% of the cases, followed by heart and lung disease.

Table 3.1.10.1 Top Ten Abnormalities in Methamphetamine Abusers at Autopsy

Abnormality	Percent (%)
1. Fatty liver	16.2
2. Moderate coronary artery disease	10.3
3. Cirrhosis	9.0
4. Pneumonia	8.2
5. Myocardial fibrosis	6.7
6. Triaditis	6.1
7. Severe coronary artery disease	6.1
8. AIDS	5.4
9. Emphysema	5.1
10. Hepatitis	4.1

Source: From Karch, S. B. et al., *J. Forensic Sci.,* 44(2), 359–368, 1999. With permission.

3.1.10.1 Cardiovascular system

Methamphetamine and cocaine cause the same types of vascular toxicity. The hearts of stimulant abusers are likely to be slightly heavier than predicted, with areas of fibrosis and contraction band necrosis (CBN). The pattern of fibrosis is perimyocytic in distribution in both cocaine and methamphetamine users, and is usually accompanied by hypertrophy in adjacent myocytes. Stimulant abusers are also prone to accelerated coronary artery disease (CAD) and microvascular disease, making proper classification of the underlying disorder (ischemia? myopathic?) without a biopsy or autopsy problematic (Karch et al., 1999).

The underlying mechanism appears to be catecholamine excess. As Table 3.1.10.1 clearly illustrates, multivessel coronary artery disease occurs at a much higher rate in methamphetamine users than in age-matched controls, yet, surprisingly, reports of methamphetamine-related myocardial infarction remain so uncommon as to still be reportable. Recent advances in molecular biology may explain why; the rise in body temperature associated with amphetamine use leads to the increased production of myocardial heat-shock proteins (Maulik et al., 1995). Cells produce these proteins in response to stressors such as ischemia and cellular injury (Lindquist, 1986), and animals pretreated with amphetamine are resistant to ischemia. If the same set of responses occurs in humans, that would explain the apparent difference in cardiotoxicity between methamphetamine and cocaine, and why cocaine-related infarction is common, but methamphetamine-related infarction is not.

Cocaine and the amphetamines both cause norepinephrine to accumulate in the synaptic cleft and overflow into the circulation, but amphetamines exert additional effects. Amphetamine is also transported into the presynaptic terminal, where it inhibits MAO and prevents further storage of catecholamines within the nerve ending (Figure 3.1.10.1.1) (Lindquist, 1986). These actions, taken together, lead to increased sympathetic stimulation and increased circulating levels of catecholamines in the periphery (Fukunaga et al., 1987).

High circulating catecholamine levels are cardiotoxic, regardless of their origin. The very same morphologic alterations produced by amphetamine abuse have been seen in patients with pheochromocytoma (Szakacs and Cannon, 1958; Szakacs et al., 1959) and

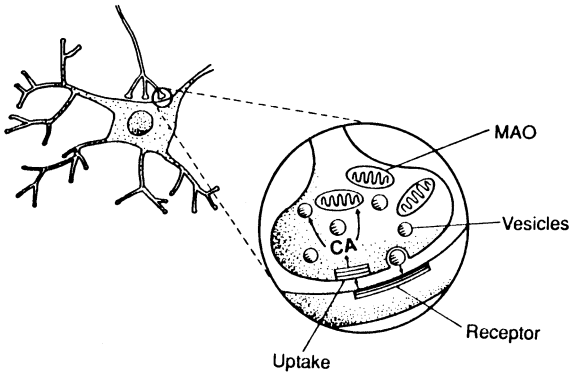


Figure 3.1.10.1.1 **Effects of amphetamine on nerve endings.** The effects of amphetamine on catecholamine metabolism are more complex than those of cocaine. In addition to blocking re-uptake, amphetamine also causes increased release of neurotransmitters. (Courtesy of Dr. Arthur K. Cho, Department of Pharmacology, UCLA School of Medicine.)

cocaine abusers (Tazelaar et al., 1987) and are easily reproduced in experimental animals by infusing catecholamines (Rona, 1985; Todd et al., 1985a,b). Changes typical of catecholamine toxicity were first described in methamphetamine-related fatalities by Japanese researchers in the early 1980s (Matoba, 1986). In Japan, where methamphetamine abuse has been a problem since the drug was first invented, methamphetamine-induced arrhythmic sudden death is a recognized entity. Myocardial alterations in the decedents include focal subendocardial hemorrhage, usually surrounding areas of myocytes disruption, sometimes with lymphocytic infiltrates (Tazelaar et al., 1987; Fukunaga et al., 1987a,b). Interstitial fibrosis with myocyte hypertrophy is the pattern commonly seen.

Medial hypertrophy of myocardial arterioles has also been described (Matoba et al., 1986). Until recently, the significance of this microvascular change was not recognized. It is now apparent that the combination of microvascular disease and myocyte hypertrophy almost certainly provides the underlying substrate necessary for arrhythmic sudden death. The most recent experimental evidence suggests that, given the pre-existing anatomic changes, elevated concentrations of catecholamines provide the trigger for these arrhythmias.

It seems likely that all phenylisopropylamines are capable of producing catecholamine-mediated cardiotoxicity. Phenylpropanolamine given to rats produces a pattern of injury indistinguishable from the pattern seen after infusions of isoproterenol or norepinephrine (Pentel et al., 1987). Unanesthetized dogs given 10 mg/kg of amphetamine and autopsied 1.5 to 22 hours later were found to have subendocardial hemorrhages. In some cases, the hemorrhages were extensive enough to disrupt the conduction system. In addition, obvious myocardial fiber necrosis was scattered throughout both ventricles, and many of the myocytes appeared eosinophilic and granular. In short, all the features associated with catecholamine toxicity were reproduced. In more extreme cases, hemorrhage into the mitral valve leaflets and in the papillary muscles can occur (Zalis et al., 1967). Nearly the exact same lesions can be induced by infusing large amounts of norepinephrine. The connection was first recognized over 30 years ago (Szakacs and Cannon, 1958; Szakacs et al., 1959).

Myocardial infarction has been reported after "snorting" methamphetamine (Furst et al., 1990; Huang et al., 1993), after intravenous injection (Carson et al., 1987; Lam and Goldschlager, 1988; Packe et al., 1990), and after the oral use of various amphetamine

analogs, including propylhexedrine (Marsden and Sheldon, 1972), dextrofenfluramine (Evrard and Allaz, 1990), and pseudoephedrine (Wiener et al., 1990; Derreza et al., 1997). None of these case reports has included histological findings, but in several instances angiography was performed and found to be normal. The absence of fixed lesions suggests that the infarcts were due to coronary spasm, but the underlying mechanism has never been proven.

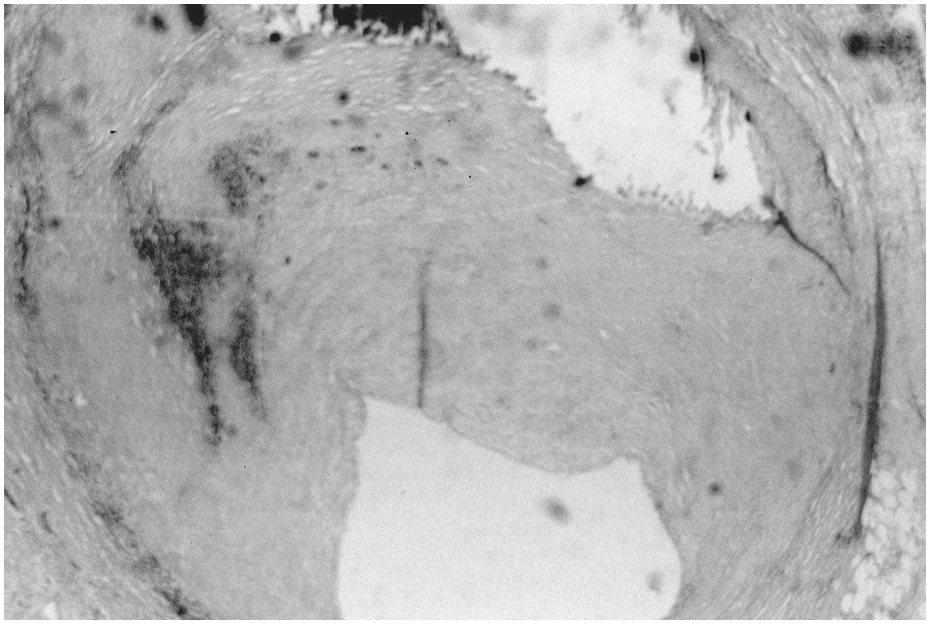
Even though reports of myocardial infarction in methamphetamine users remain uncommon, postmortem studies indicate that methamphetamine abusers are prone to accelerated, multivessel coronary artery disease. In the one published large autopsy series (Karch et al., 1999), coronary artery disease, ranging from minimal to severe multivessel, was identified in nearly 20% of the methamphetamine users but in only 5% of the controls ($p < .001$). A number of cases of aortic dissection also occurred, and aortic dissection is now a well-recognized complication of methamphetamine abuse.

The mechanisms for coronary artery disease and aortic dissection in methamphetamine abusers (Figure 3.1.10.1.2) are not known, but methamphetamine abuse is associated with elevated plasma and tissue concentrations of catecholamines, and catecholamine excess is associated with free-radical generation. Physiological oxidation products of catecholamines, called *o*-quinones, contribute to redox cycling, toxicity, and apoptosis. Cyclized *o*-quinones, including aminochrome, dopachrome, adrenochrome, and noradrenochrome (formed from dopamine, dopa, adrenaline, and noradrenaline, respectively), are all highly reactive compounds capable of producing damage to the endothelium of large and small vessels, not to mention the destruction of neurons (Baez et al., 1997).

Cardiomyopathy in methamphetamine abusers has also been reported but this disorder is much more commonly associated with cocaine abuse than with abuse of any of the other stimulants (Smith et al., 1976; Call et al., 1982; Jacobs, 1989). "Reversible" cardiomyopathy has been described as a complication of both amphetamine and cocaine use (Call et al., 1982; Chokshi et al., 1989; Jacobs, 1989; Henzlova et al., 1991). In every instance, the acute onset of heart failure is associated with decreased cardiac output and increased wedge pressure that eventually resolved with medical therapy. Because the patients survived, the underlying morphologic changes, if any, remain uncharacterized. Pathologists reserve the term "cardiomyopathy" for only those patients with normal coronary arteries and specific myocyte changes demonstrable on biopsy or autopsy, and the term should not be applied in the absence of a normal arteriogram.

Nonetheless, true cardiomyopathy has been reported in association with methamphetamine abuse (Matoba et al., 1986; Hong et al., 1991), propylhexedrine abuse (Croft et al., 1982), and methylphenidate abuse (Stecyk et al., 1985), although methylphenidate appears to produce morphologic changes in the heart dissimilar to those associated with the use of other stimulant drugs (Henderson and Fischer, 1995). Endomyocardial biopsy of a methamphetamine abuser with heart failure disclosed patchy interstitial fibrosis along with the presence of scattered mononuclear cells (Jacobs, 1989). Another report described autopsy findings in a 45-year-old female abuser of oral amphetamine who died of heart failure. Her heart was enlarged (530 g) but the coronary arteries were widely patent. Widespread interstitial edema, with scattered lymphocytic and histiocytic infiltrates, was evident, along with degeneration of individual fibers and patchy myocardial fibrosis. In another case, patchy myocardial fibrosis, without infiltrates, was the principal finding in a young "ice" smoker who died of an acute posterior wall infarct (Smith et al., 1976). The pattern described in all of these cases is very much like the pattern produced by catecholamine toxicity in general and by cocaine in particular. Similar lesions have been observed in experimental animals treated with methamphetamine (Smith et al., 1976).

a



b

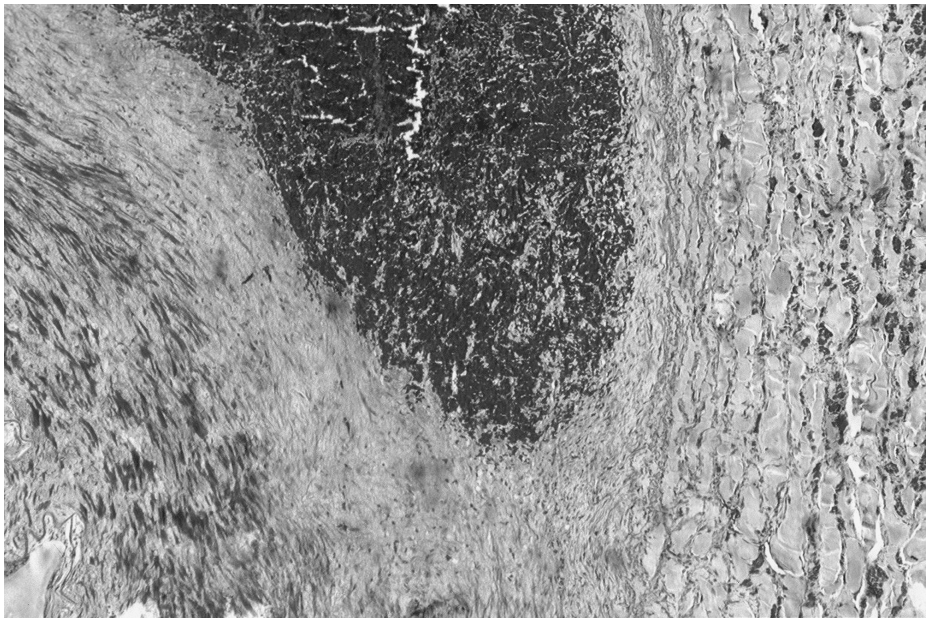


Figure 3.1.10.1.2 (a) Cross section of left anterior descending coronary artery in a gunshot wound victim, where methamphetamine abuse was unrelated to the cause of death. Extensive coronary artery disease is common among methamphetamine abusers and occurs at a much younger age than coronary artery disease in the general population. **(b) Dissecting femoral artery aneurysm in a methamphetamine abuser.** Aortic dissection is a recognized complication of methamphetamine abuse, although the mechanism is not known. Special staining procedures are unrevealing, and none of the reported cases has involved individuals with Marfan's syndrome. (From the office of the San Francisco Medical Examiner.)

Electron microscopic studies of autopsy material from a chronic amphetamine abuser were first carried out more than a quarter century ago; myofilament rupture and disarray could be seen, and the mitochondria contained many large electron-dense granules (Smith et al., 1976). The later finding is a marker for mitochondrial calcium overload, the typical response seen in myocytes after ischemia and/or excessive catecholamine stimulation.

A different type of process has been observed in methylphenidate abusers. Lamellated ultrastructural lesions have been observed in the heart of a patient treated with methylphenidate (Ritalin®) hydrochloride, and a causal relationship suggested. Similar lesions have been produced in rats injected with methylphenidate, with the accumulations of membranes and lamellations that stain positively for sarcoplasmic reticulum. Lesions persist for more than three months after the drug has been withdrawn, raising the possibility of long-term myocardial damage (Henderson and Fischer, 1995). Arguing against that possibility is the near total absence of case reports describing heart failure in children treated for attention deficit hyperactivity disorder (ADHD).

3.1.10.2 Pulmonary toxicity

In the only large autopsy series of methamphetamine-related deaths, pulmonary edema was present in over 70%, pneumonia in 8%, and emphysema in 5% of all cases. Birefringent crystals were noted in 11% (Karch et al., 1999). When drug tablets are crushed and injected intravenously, the insoluble fillers (microcrystalline cellulose, corn starch, or cotton fibers) contained in the tablet become trapped in the pulmonary microvasculature, where they are easily visualized as birefringent crystals. If the process is repeated enough times, the smaller vessels become thrombosed, and foreign body granulomas form. Eventually, some of the foreign material will work its way into the perivascular spaces, leading to further granuloma formation and more fibrosis (Tomashefski and Hirsch, 1980; Tomashefski et al., 1981).

Repeated injections result in a net reduction in the size of the pulmonary vascular bed and an increase in pulmonary vascular resistance. At autopsy, organizing and recanalizing thrombi will be seen, along with easily identifiable birefringent material (Rajs et al., 1984; Kringsholm and Christoffersen, 1987). Histologically, this type of pulmonary hypertension can be distinguished from the much rarer primary variety by the presence of plexiform lesions at branching points of the obstructed small arteries (Pietra and Ruttner, 1987; Pietra et al., 1989). This complication seems to be associated more with some abused drugs than with others. In general, heroin abusers are much more prone to thromboembolic arteriopathy than stimulant abusers.

In addition to pulmonary hypertension, the repeated injection of tablets intended for oral consumption may result in symptoms and findings indistinguishable from pulmonary amyloid, with bilateral pulmonary nodules apparent on x-ray. Immunocompromised hosts, such as HIV-infected heroin addicts, may be misdiagnosed as suffering from pulmonary amyloid, but the presence of focal birefringent material and foreign body giant cell reactions is usually sufficient to make the diagnosis (Shah et al., 1998).

Of the commonly abused stimulants, methylphenidate (Ritalin®) is the agent most often associated with pulmonary complications, particularly pulmonary talcosis (Hopkins and Taylor, 1970; Schmidt et al., 1991). As methylphenidate has become more widely used to treat ADHD, considerable quantities of the drug have been diverted to the black market, and the incidence of talcosis, from injection of the crushed pills, is increasing. The diagnosis can often be made by computed tomography (CT) scan. Typical findings consist of a fine micronodular pattern with a ground-glass appearance, and panacinar emphysema, particularly of lower lobes (Padley et al., 1993; Stern et al., 1994; Ward et al., 2000).

3.1.10.3 Central nervous system

With the exception of ADHD, the only other legitimate use for drugs in this group is appetite suppression. Amphetamine and phentermine are anorectic drugs by virtue of their ability to cause the release and/or prevent the re-uptake of noradrenaline and dopamine. Other drugs used for appetite suppression seem to operate via different mechanisms. Phenylpropanolamine and its isomer, dexfenfluramine, are active by virtue of their ability to directly stimulate a variety of serotonin receptors (Samanin and Garattini, 1993). Ephedrine (see Chapter 2) is thought to promote weight loss by virtue of its ability to simulate β3 receptors (Astrup and Lundsgaard, 1998; Ramsey et al., 1998).

In drug abusers (as opposed to individuals taking pharmacologic doses of methamphetamine), the most obvious manifestations of toxicity are psychosis and stroke. Large doses of methamphetamine (10 to 15 mg/kg) given to experimental animals quickly alter the serotonergic and dopaminergic systems of the brain. Tyrosine hydroxylase activity, the rate-limiting enzyme in the synthesis of dopamine and norepinephrine, decreases in a dose-related fashion, and so does the content of dopamine and homovanillic acid in the brain (Koda and Gibb, 1973). The pattern of injury associated with chronic amphetamine treatment is similar to that seen with methamphetamine, though less severe (Ellison and Switzer, 1993).

In contrast to the animal studies, little is known about methamphetamine neurotoxicity in humans. Magnetic resonance imaging (MRI) studies of abstinent methamphetamine abusers show that, when compared to non-drug-using controls, concentrations of *N*-acetylaspartate, a neuronal marker, are significantly reduced in the basal ganglia and frontal white matter, and that the reduction in the frontal white matter correlates inversely with the logarithm of lifetime methamphetamine use, findings indicative of long-term neuronal damage (Ernst et al., 2000). However, gross neuroanatomic lesions have never been identified, either in humans or experimental animals. Even though grossly demonstrable lesions have not been demonstrated in humans, the results of animal studies suggest that dopamine depletion resulting from striatal damage may be a factor in some cases of lethal methamphetamine-related hyperthermia (Bowyer et al., 1994).

The possibility that methamphetamine-related CNS injuries do occur in humans is reinforced by the observation that patients with methamphetamine-related psychosis may remain in that state for months after the drug has been discontinued (Young and Scoville, 1938). Amphetamine-related psychotic reactions were recognized soon after the drug was first introduced, with the first paper on the subject appearing in 1938 (Iwanami et al., 1994). A 1958 paper reviewed 36 cases from the world's literature and concluded that there were striking similarities between the symptoms of amphetamine-induced psychosis and schizophrenia (Connell, 1958), and at one time, large numbers of amphetamine abusers were admitted to mental hospitals with the mistaken diagnosis of schizophrenia.

The reason amphetamine-related psychosis seems to be more common than psychosis in cocaine abusers may be a function of the affinity of methamphetamine for sigma receptors. The ability to bind sigma receptors is related to the occurrence of psychosis. In animal studies, chronic methamphetamine administration leads to upregulation of sigma receptors in the substantia nigra, frontal cortex, and cerebellum (Connell, 1958); enhances catecholamine-related, cortical-event-related potentials (Takeuchi et al., 1999); and even leads to the expression of some early genes (c-*fos*) (Namima et al., 1999). Cultural determinants may also have some bearing on the psychiatric manifestations of amphetamine abuse; even though methamphetamine psychosis is responsible for large numbers of psychiatric hospitalizations in Japan (Iwanami et al., 1994), disease on a similar scale has never occurred in the U.S.

Even if they do not become psychotic, amphetamine users may be restless, tense, and fearful. Some develop delusions of persecution and ideas of reference. They may also have auditory, tactile, and visual hallucinations. Strangely, most are not disoriented and will act appropriately, given their paranoid state. The frequency with which hallucinations are visual, and the relative preservation of orientation in amphetamine users, are believed by some researchers to differentiate amphetamine psychosis from true schizophrenia (Iwanami et al., 1994). Amphetamine toxicity in animals is associated with stereotyped, compulsive behavior such as grooming and pacing. Similar stereotypical behavior may be apparent in intoxicated humans. Generally, all of these symptoms disappear within a day or two of drug cessation, although depression can be marked for some time afterwards. The syndrome of excited delirium, known to occur in conjunction with cocaine use, has also been reported in amphetamine abusers (O'Halloran and Lewman, 1993; Karch et al., 1999).

Hemorrhagic and ischemic strokes occur in association with methamphetamine smoking (Rothrock et al., 1988; Yen et al., 1994; Perez et al., 1999), oral ingestion (Delaney and Estes, 1980; Yu et al., 1983), and intravenous injection (D'Souza and Shraberg, 1981; Caplan et al., 1982; Lukes, 1983; Lessing and Hyman, 1989; Imanse and Vanneste, 1990; Yen et al., 1994; Goplen et al., 1995; O'Brien, 1998; Petitti et al., 1998; Bakheit, 1999). The mechanism for stroke in these patients is not always clear. No experimental histologic studies have been done, and only a handful of autopsies of stroke victims have been reported (Bostwick, 1981).

Amphetamine-related hemorrhages are more often intracerebral, or simultaneously intracerebral and subarachnoid, than pure subarachnoid. Hemorrhage is most often confined to the frontal lobes, though it occasionally involves the basal ganglia. This distribution is in contrast with the pattern seen in hypertensive hemorrhages which usually involves the basal ganglia and hypothalamus. The pattern is, however, almost exactly the same as that seen in cocaine abuse where the frontal lobes are most often involved.

Rarely, the etiology may be embolic (Imanishi et al., 1997), and occasionally there is evidence for vasculitis. Amphetamine-related vasculitis was first described by Citron in 1970 (Citron et al., 1970). The histological appearance, in the cases described by Citron, was identical to that seen in polyarteritis nodosa, with fibrinoid necrosis of the intima and media, and mixed cellular infiltrates. With longer periods of survival, intimal proliferation and marked luminal narrowing, especially at the bifurcation of vessels, occurred. Characteristically, giant cells were absent and the veins spared. Other reports described involvement of smaller (Stafford et al., 1975) and larger vessels (Bostwick, 1981; Shibata et al., 1991).

In the case described by Shibata et al. (1991), the smaller vessels were spared but virtually all of the other major vessels were necrotic, with destruction of the smooth muscle layer and scarring of the elastic layer. No leukocytic infiltration of the vessels was seen, but additional reports have been uncommon. A possible explanation for the apparent decline in the number of cases is that the process may have been the result of some contaminants or adulterants introduced during the manufacture of methamphetamine. Vasculitis has also been reported in association with the use of oral methylphenidate (Trugman, 1988; Schteinschnaider et al., 2000), fenfluramine (Derby et al., 1999), phenylpropanolamine (Ryu and Lin, 1995), and ephedrine (Mourand et al., 1999).

Treatment with beta blockers and calcium channel blockers seems to ameliorate signs of cocaine-induced CNS toxicity, but treatment with the calcium channel blocker nimodipine actually elevates blood and brain concentrations of both amphetamine and methamphetamine (Elkins et al., 1993). In the absence of clinical trials, such treatment might best be avoided.

3.1.10.4 Genitourinary tract

Except for episodes of rhabdomyolysis, involvement of the kidney is secondary to disease elsewhere. Renal complications of amphetamine and methamphetamine abuse are uncommon. In the series of 413 methamphetamine-related deaths reported from San Francisco, the incidence of renal disease was less than 2%. When renal disease was detected, most often it was comprised of the typical nephrosclerotic lesions considered to be indicative of hypertension (Luke, 1999; Meggs and Kodali, 1999). Without experimental models, there is no way to determine whether nephrosclerosis in these individuals is a consequence of methamphetamine abuse, or untreated hypertension. The first report linking amphetamine ingestion and reversible renal failure was published in 1970 (Ginsberg et al., 1970); few additional mentions have appeared since then. Most of the recently reported cases have involved the use of "designer" amphetamines, particularly MDMA (3,4-methylenedioxymethamphetamine, also known as Ecstasy) (Sultana and Byrne, 1996), and PMA (paramethoxyamphetamine) (Byard et al., 1998). Nonetheless, methamphetamine abuse is becoming an increasingly common cause of rhabdomyolysis. In a recent retrospective review of 367 emergency room patients with rhabdomyolysis, nearly half were found to be methamphetamine users (Richards et al., 1999), often with hyperthermia.

Hyperthermia in amphetamine users can occur for a number of reasons. Increased motor activity, even without seizures, raises body temperature, especially when heat loss from the skin is inhibited because of catecholamine-induced vasoconstriction. Altered thermoregulation may also be the result of the direct actions of amphetamine on the hypothalamic temperature centers. However, a number of other unrelated insults can lead to rhabdomyolysis, as well; alcoholism, drug toxicity, hypokalemia, muscle ischemia, hypotension, and prolonged immobilization have all been implicated as possible factors (Scandling and Spital, 1982; Terada et al., 1988). When rhabdomyolysis does occur, myoglobin, potassium, and phosphorus are released into the plasma. The presence of these substances in the plasma sets into motion a series of metabolic derangements and fluid shifts. The resultant damage to the kidneys can be indirect, resulting from hypotension and renal ischemia, or direct, as when myoglobin or its decomposition products cause tubular obstruction. Much of the damage may be mediated by free-radical formation (Odeh, 1991).

Another possible explanation is that amphetamines themselves are myotoxic. Prolonged elevations in creatine phosphokinase occur, even in patients who did not go on to develop full-blown rhabdomyolysis (Williams and Unwin, 1997). In the retrospective review of Richards et al. (1999), individuals with methamphetamine-related rhabdomyolysis had much higher initial mean concentrations of creatinine phosphokinase than individuals with rhabdomyolysis from other causes (12,439 vs. 5678 U/L (p = 0.02). How amphetamine interacts with muscle sarcolemma to release cell contents is not known.

3.1.10.5 Gastrointestinal tract

Chronic methamphetamine abuse is associated with liver damage. In the study by Karch et al. (1999), fatty liver was evident in 15.4% of all cases, cirrhosis in nearly 9%, cellular infiltrates of the portal triads ("triaditis") in 6%, and hepatitis in 5%. Hepatitis and infiltration of the portal triads are both common findings in intravenous drug users, and their occurrence in methamphetamine drug users probably is coincidental, having nothing to do with the basic pharmacologic properties of methamphetamine. On the other hand, excessive α_2-adrenergic stimulation, such as would occur in methamphetamine users, is inherently hepatotoxic (Roberts et al., 1994a,b, 1997).

Two amphetamine analogs, pemoline and Ritalin® (2-1-amino-5-phenyl 4-oxazolidinone and methylphenidate, respectively) have rarely been implicated as hepatotoxins

(Mehta et al., 1984; Patterson, 1984; Nehra et al., 1990; Roberts et al., 1994a,b, 1997). In one review of 100 alleged cases of pemoline-associated hepatotoxicity, only 43 of the cases had sufficient data to analyze. Based on the results of enzyme measurements and the findings in one autopsy, the injury pattern is said to be hepatocellular in nature, probably due to an idiosyncratic reaction (Nehra et al., 1990). An 11-year-old taking pemoline for ADHD developed frank liver failure, and open-liver biopsy demonstrated submassive hepatic necrosis with extensive fibrovascular replacement (Pratt and Dubois, 1990). Instances of hepatotoxicity in children treated for ADHD with either pemoline or methylphenidate are rare. This is in marked contrast to the relatively frequent reports of hepatic injury as a consequence of MDMA misuse (Chenard-Neu et al., 1996; Brauer et al., 1997; Andreu et al., 1998; Varela-Rey et al., 1999) (see Chapter 4). The difference suggests that liver damage in MDMA users may be a consequence of some adulterant and not the drug itself.

A relationship between gastrointestinal ulcers, particularly of the duodenum, and methamphetamine appears to exist, but the connection is not nearly so striking as that seen with cocaine abuse, nor does the incidence of this complication appear to be increasing as much as might be expected given the increasing popularity of methamphetamine abuse (Pecha et al., 1996). Presumably, the same mechanisms are operative with both cocaine and methamphetamine: vasospastic ischemia leading to ulceration. Unfortunately, no animal studies of the process have been done.

Hemorrhagic pancreatitis occurs in chronic methamphetamine abusers (Pecha et al., 1996), and the same condition has been reproduced in experimental animals. Rats injected daily with methamphetamine eventually develop regional hemorrhage, partial acinal cell necrosis, destruction of the acinal cells, neutrophilic infiltration, interstitial vessel dilatation, interstitial edema, and fatty cell invasion (Ito et al., 1997). No further case reports or studies have been published, suggesting that the incidence of this complication is not very high.

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3.2 Methylphenidate (Ritalin®)

3.2.1 Incidence and epidemiology

Methylphenidate (Ritalin®) is used extensively for the treatment of ADHD (Robison et al., 1999). No clandestinely produced methylphenidate has ever been encountered. Because

Ritalin® is so widely available, diversion and illicit sales do occur, mostly to teenagers and young people. Based on the findings of the DAWN report, the amount of drug diverted to the black market cannot be very great. Twelve methylphenidate deaths were reported in the Medical Examiner's component of the 1999 DAWN report (0.01% of all drug-related deaths), but no mentions were found in the Emergency Department component of the same DAWN report or in the National Household Survey (Greene et al., 2000). On the other hand, prescribing methylphenidate for adults with persistent symptoms of ADHD is increasing. Some feel this is cause for concern given the increased risk for substance abuse disorders in this subgroup of patients (Levin et al., 1999).

3.2.2 Names and drug constants

Methylphenidate ([*d*,*l*]-threo-α-phenyl-2-piperidine acetic acid methyl ester) has two chiral centers, but the drug used in therapy comprises only the threo pair of enantiomers. *d*-threo-methylphenidate is more potent than the *l*- enantiomers. Methylphenidate is administered as a racemic mixture that undergoes stereoselective clearance (Kimko et al., 1999), and the different isomers have profoundly different tissue distributions (Thai et al., 1999). In the U.S., it is only sold under the brand name Ritalin®, either as immediate or time-release tablets.

3.2.3 Routes of administration

Like the other amphetamines, methylphenidate is rapidly absorbed after oral administration, reaching peak levels between 1 and 3 hours after ingestion (Wargin et al., 1983; Volkow et al., 1995). In cases of methylphenidate abuse, ground tablets are injected (Levine et al., 1986; Fulton and Yates, 1988; Parran and Jasinski, 1991) or occasionally snorted (Jaffe, 1991; Garland, 1998). Neither the transnasal bioavailability nor the resultant blood concentrations have ever been determined.

3.2.4 Metabolism and pharmacokinetics

The reinforcing effects of methylphenidate are a consequence of its ability to block dopamine transporters. Even though cocaine and methylphenidate have similar *in vitro* affinities for the dopamine transporter, abuse of methylphenidate is extremely uncommon, at least when compared to cocaine. It has been suggested that the difference has to do with the persistence of methylphenidate within the striatum. Unlike cocaine, which is washed out in a matter of minutes, methylphenidate remains localized in the striatum for several hours (Volkow et al., 1995). Similarly, even though cocaine and methylphenidate cause comparable increases in heart rate and blood pressure, these increases persist for much longer with methylphenidate than cocaine (Volkow et al., 1999).

Methylphenidate has a much shorter half-life, two to four hours on average, than other amphetamines. First-pass hydrolysis to ritalinic acid occurs in the intestine, and 80% is excreted in the urine as ritalinic acid. Peak plasma levels of both methylphenidate and ritalinic acid occur at the same time. *In vitro* studies indicate that methylphenidate metabolism is not P-450 dependent (DeVane et al., 2000), which suggests minimal intra-individual variation in rates of metabolism.

A range of values have been reported for the pharmacokinetic parameters of methylphenidate. In one controlled study, after giving a 15-mg dose of immediate-release drug to 35 healthy volunteer adults, the mean average peak concentration (C_{max}) was 4.17 ± 1.0

ng/mL, reached at 6.5 ± 1.8 hours (T_{max}). The observed half-life ($T_{1/2}$) was 3.0 ± 0.5 hours (Modi et al., 2000). Somewhat different results were obtained in a second study where 40-mg doses of immediate-release drug were given to 26 healthy volunteers; very substantial differences were observed between the *d*- and *l*- isomers, with the *l*- isomer eliminated at nearly three times the rate of the *d*- isomer (Wong et al., 1998).

	d- isomer (n = 21)	*l*- isomer (n = 5)
C_{max}	17.8 ng	.821 ng
T_{max}	1.5 hr (range, 1–3)	.5 hr (range, 0.5–1.0)
$T_{1/2}$	2.8 ± 0.38 hr	1.09 ± .19 hr

When methylphenidate and ethanol are co-ingested, a new, active metabolite, ethylphenidate (ritalinic acid ethyl ester), is formed by a mechanism analogous to the one responsible for production of cocaethylene: hepatic-carboxylesterase-dependent transesterification. Only very small amounts of ethylphenidate are produced after clinically relevant doses and, unlike cocaethylene, which has a much longer apparent half-life than cocaine, the half-life of ethylphenidate is much shorter than that of the parent compound (Markowitz et al., 2000).

3.2.5 Methylphenidate blood concentrations

In therapeutic settings, peak concentrations of methylphenidate may reach 0.07 mg/L (Gualtieri et al., 1984), but treatment is not generally guided by plasma drug concentrations. Interestingly, in studies designed to determine whether differences in plasma concentration of the *d*- and *l*-threo enantiomers had any bearing on clinical response, researchers found that nonresponders (based on electrophysiological testing) had significantly higher plasma concentrations of both isomers than responders, and that plasma concentrations of the *d*- enantiomers were always higher than the *l*- enantiomers, regardless of the response (Jonkman et al., 1998).

3.2.6 Methylphenidate tissue disposition

Tissue disposition in humans has been poorly studied. In rats, after doses of 1 mg/kg (Kotaki et al., 1988), 10 mg/kg (Thai et al., 1999), or 20 mg/kg (Patrick et al., 1984), the tissue distribution was the same: kidney > lung > brain > heart > liver.

3.2.7 Postmortem measurements

Data on the tissue disposition of the amphetamine analogs are sparse. A woman who died after injecting 40 mg of methylphenidate intravenously had a blood concentration of 2.8 mg/L (Levine et al., 1986). In that same case, the concentration in the liver was 2.1 mg/kg, while the bile contained 5.7 mg/L and the kidneys 3.0 mg/kg. Little accumulation of methylphenidate occurs in the body. The blood level of a woman who died during a Cesarean section, who presumably had not had any drug for a number of hours, was only 9 ng/mL (Lundquest et al., 1987). A paper published in 1999 described the findings in two individuals who had died after intentional methylphenidate overdose. Ethanol had also been consumed and, as a consequence, ethylphenidate was also detected, although in extremely small quantities (8 ng/mL and 1 ng/mL) (Markowitz et al., 1999).

3.2.8 Toxicity by organ system

3.2.8.1 Overview

Information about methylphenidate toxicity is confined to anecdotal case reports. These can be divided into two separate groups: (1) complications related to catecholamine toxicity, and (2) complications related to the intravenous injection of talc-containing pills meant for oral consumption. The lungs and eyes bear the brunt of the latter insult, and, except in the case of drug abusers, medical complications are rare.

3.2.8.2 Integument

Occasionally, drug users will grind up methylphenidate tablets and inject them subcutaneously (Zumwalt and Franz, 1983). Superficial skin abscesses are the result, but they appear to be no different than the type of infection produced by "skin popping" heroin or cocaine.

3.2.8.3 Cardiovascular system

A recent case report described the cardiac findings in a 19-year-old who died after snorting powder methylphenidate tablets. The myocardium displayed foci of localized, microfocal necrosis with infiltration by histocytes and polymorphonuclear leukocytes — typical changes associated with catecholamine toxicity (Massello and Carpenter, 1999).

3.2.8.4 Pulmonary system

Granuloma formation and pulmonary fibrosis have been recognized as complications of methylphenidate abuse for many years (Hahn et al., 1969; Waller et al., 1980; Levine et al., 1986). If anything is unique about the histopathology of methylphenidate abuse, it remains to be identified. Presumably, the deposition of birefringent material contained in the methylphenidate preparations is followed by a granulomatous inflammatory reaction and focal thrombosis (Byers et al., 1975). The situation has never been studied experimentally, and nothing has been found to distinguish granuloma formation in stimulant abusers from the same alterations seen in opiate addicts.

Panacinar emphysema, more pronounced in the lower lung fields, has been described in a group of young intravenous methylphenidate Ritalin® abusers who died of severe obstructive lung disease (Sherman et al., 1987; Schmidt et al., 1991), and repeatedly confirmed in a series of case reports. Autopsy findings included variable degrees of vascular involvement by talc granulomas, but no interstitial fibrosis. X-rays of these individuals show a distinctive picture with prominent, or even massive, fibrosis in the upper lobes and with translucence and bullae formation in the lower lobes (Pare et al., 1989). In most respects, the clinical and pathologic findings are the same as those associated with α_1-antitrypsin deficiency, though tests for that disorder are negative. Obstructive lung disease is an uncommon complication of intravenous drug abuse, regardless of the type, and its mechanism remains to be evaluated (Groth et al., 1972; Vevaina et al., 1974; Ward et al., 2000). It is unclear whether the apparent connection of lung disease with methylphenidate has to do with the drug itself or with the way it is compounded.

3.2.8.5 Gastrointestinal tract

Methylphenidate-associated hepatocellular injuries, unlike those reported in pemoline users, have mostly involved intravenous abuse (Mehta et al., 1984; Lundquest et al., 1987). In the case described by Mehta et al., portal inflammation with hepatocellular disarray was diagnosed in the liver biopsy of an intravenous abuser who survived a bout of liver

failure. In a second case, the autopsy findings in a polydrug user who died of amniotic fluid embolus included biventricular hypertrophy and multiple granulomas in the liver and lungs. Autopsy findings in a third polydrug abuser, known to have repeatedly injected methylphenidate and hydromorphone, are best explained by the injection of tablets meant for oral use, and probably have nothing to do with the pharmacologic effects of either drug. Pulmonary hypertension is the expected outcome of this practice but, because this particular individual had a patent foramen ovale, the elevated pulmonary pressure caused a right-to-left shunt. Talc granulomas were found throughout the body, including the brain and kidneys (Lundquest et al., 1987).

3.2.8.6 Nervous system

Psychosis occurs, even in nonabusers. In one recent study, 6 of 98 children diagnosed with ADHD and treated with stimulant drugs developed psychotic or mood-congruent psychotic symptoms during treatment (Cherland and Fitzpatrick, 1999).

Individuals who injected ground tablets of methylphenidate may experience ophthalmologic complications. The pills are compounded with talc (magnesium silicate) and cornstarch. When they are crushed and injected they lodge in the pulmonary bed, obstructing flow and ultimately causing pulmonary hypertension. Elevated pressure, in turn, leads to collateralization of blood vessels, allowing part of the venous return to bypass the lung and directly enter the left side of the heart. Once the talc particles have gained access to the left heart, they are then distributed in the arterial circulation throughout the body. Particles entering the retinal circulation usually settle out in the posterior pole, the portion of the globe with the richest supply of capillaries. These particles are easily visualized on routine fundoscopic examination (Lederer and Sabates, 1982). The presence of retinal talc emboli occasionally leads to the process of neovascularization, depriving the retina of its normal blood supply and leading to vasoproliferation. The underlying mechanism and the appearance of the retina are much the same as seen in patients with sickle cell disease (Schatz and Drake, 1979).

In contrast to methamphetamine, which is an increasingly common cause of stroke in young people, stroke in methylphenidate users is exceedingly rare and, in fact, has only been reported once. The case involved an 8-year-old boy being treated for ADHD. Arteriography showed no congenital malformations, but did show evidence of cerebral vasculitis. An extensive hematologic evaluation failed to disclose any coagulation abnormalities (Schteinschnaider et al., 2000). Because only one such case has been reported and millions of children take methylphenidate, it would appear that the associated risk is exceedingly low and, in fact, there may not be any connection at all.

3.3 Phenylpropanolamine

3.3.1 Historical considerations

Phenylpropanolamine (PPA) is an ephedrine isomer, (±)-norephedrine, but virtually all of the PPA formerly sold in the U.S. was chemically synthesized, not extracted from ephedra plants. In late 2000, because of an alleged link between PPA and hemorrhagic stroke in young women, PPA was withdrawn from the market (Kernan et al., 2000). At the time, PPA was a component in over 100 different over-the-counter remedies sold in the U.S., with an estimated 5 billion doses of PPA consumed annually (Kernan et al., 2000). Most of the PPA sold in the U.S. was used to make cough and cold products, but in 1979 the Food and Drug Administration (FDA) published a monograph declaring that

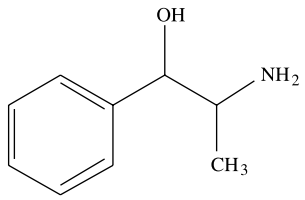

Figure 3.3.2.1 The phenylpropanolamine molecule.

PPA was safe and effective when used as an anorectic. Afterward, increasing amounts were used to produce over-the-counter diet pills. During the early 1980s, PPA was a key component of "look-alike" stimulants, pills made to resemble methamphetamine but which contained variable mixtures of ephedrine, caffeine, and phenylpropanolamine (Kernan et al., 2000).

3.3.2 Chemistry

Phenylpropanolamine (PPA) (Figure 3.3.2.1) is α-(1-aminoethyl)benzene methanol hydrochloride. Its formula is $C_9H_{14}ClNO$, with a molecular weight of 187.67. It is composed of 57.6% carbon, 7.5% hydrogen, 18.9% chloride, 7.5% nitrogen, and 8.5% oxygen. Crystals composed of racemic forms have a melting point of 194 to 199°C (Budavari et al., 1996).

3.3.3 Metabolism

Phenylpropanolamine is an ephedrine isomer. Ephedrine contains two asymmetric carbon atoms, allowing it to exist as four different isomers designated as 1R,2S- and 1S,2R-ephedrine and 1R,2R- and 1S,2S-pseudoephedrine (PE). The only two isomers that occur naturally, as plant alkaloids, are 1R,2S-ephedrine and 1S,2S-pseudoephedrine. Ephedrine and its isomers, including phenylpropanolamine, exert their effects both by preventing the re-uptake of norepinephrine and by activating adrenergic receptors directly. Human β receptors have been cloned and can be expressed in tissue culture, and the relative potency of each isomer against each type of human β receptor (β_1, β_2, and β_3) has been measured (Vansal and Feller, 1999). Naturally occurring 1R,2S-ephedrine has twice the activity at the β_1 and β_2 receptors as synthetic pseudoephedrine. The 1R,2S form was the only form to bind the β_3 receptors — the receptors thought to be responsible for fat mobilization (one of the justifications for taking ephedrine) (Bravo, 1988), which may explain why the results of some clinical trials show that treatment with ephedrine promotes weight loss (Boozer et al., 2001).

The same structural features that give ephedrine greater affinity for β receptors also give it less affinity for α receptors. In general, the larger the group attached to the amino terminal group of the basic phenethylamine molecule, the greater the affinity for β receptors and the less the affinity for α receptors (Mukai et al., 1999; Waugh et al., 2000). Phenylpropanolamine has much more marked affinity for α than for β receptors and therefore is likely to cause much greater elevation in blood pressure than either PE or ephedrine. The various ephedra isomers also vary in metabolism, tissue disposition, and excretion. PPA increases caffeine plasma levels and decreases theophylline clearance, but no evidence indicates that this effect is exerted by the other isomers (Kanfer et al., 1993). Modest amounts (less than 15%) of both ephedrine and PE are demethylated to form PPA and norpseudoephedrine, but in humans PPA is hardly metabolized at all. Excretion times vary as well. Urinary excretion of PPA is pH dependent.

Table 3.2.1.1 Peak PPA Blood Levels in Five Volunteers after Different Oral Doses

Dosage (mg)	Range of peak blood levels (ng/mL)
25	67–185.3
50	147.7–190.1
100	290.6–480.6

Note: Except for modest increases in systolic blood pressure with 50- and 100-mg doses, these individuals were otherwise asymptomatic.

Source: From Dowse, R. et al., *Int. J. Clin. Pharmacol. Ther. Toxicol.,* 28(5), 205–210, 1990. With permission.

Phenylpropanolamine is mainly an α-adrenergic agonist, but it also possesses some β activity; as a result, toxic reactions can occur. The standard PPA dose of 50 to 75 mg is not associated with significant increases in levels of circulating catecholamines (Lake et al., 1990), but doses of 85 to 100 mg have been implicated as the cause of severe hypertensive reactions (Pentel, 1984).

3.3.4 Pharmacokinetics and toxicokinetics

Peak concentrations of PPA occur between 0.67 and 2.5 hours after oral dosing. Regardless of the dose taken, the half-life is on the order of 1.5 hours, although in some individuals it may be much shorter. Almost all PPA is excreted unchanged in the urine (Sever et al., 1975). Table 3.2.1.1 shows the peak concentrations produced after different dosing regimens (Dowse et al., 1990).

Toxic blood and tissue concentrations are poorly characterized (Pentel et al., 1987). Postmortem blood from a woman who sustained a cardiac arrest after taking an unspecified number of cold pills had a concentration of 2 mg/L (Baselt and Cravey, 1995). A 20-year-old suicide victim described as taking a "large overdose" had a postmortem blood (unspecified site) concentration of 48 mg/L, and hepatic concentrations that were 10 times higher than those of the blood, while the concentration in the brain was twice that in the blood (Baselt and Cravey, 1995). Because this concentration is hundreds of times higher than the therapeutic concentration, or even previously reported toxic levels, its relevance is open to some question. Blood concentrations (site of origin again unspecified) in 12 pediatric deaths reported to the National Association of Medical Examiners Pediatric Toxicology Registry ranged from as low as 0.04 mg/L to as high as 0.84 mg/L (Hanzlick and Davis, 1992).

Phenylpropanolamine increases plasma caffeine levels, and when the two agents are taken at the same time the resultant blood pressure increases are greater than those observed when either drug is taken alone. Test subjects given 400 mg of caffeine with 75 mg of PPA at the same time had peak plasma caffeine concentrations (8.0 ± 2.2 μg/mL), almost four times higher than observed when the same amount of caffeine was given alone (Hanzlick and Davis, 1992). Caffeine is a competitive inhibitor of adenosine receptors, and adenosine

causes blood vessels to dilate (Benowitz, 1990). The net effect of blocking adenosine vasodilation is elevation of blood pressure. Another caffeine–adenosine interaction involves adenosine inhibition of catecholamine release from nerve endings. In the presence of caffeine, more norepinephrine will be released from nerve terminals, and this effect may explain why the increased incidence of adverse reactions when phenylpropanolamine is taken together with caffeine and/or ephedrine.

3.3.5 Toxicity by organ system

3.3.5.1 Cardiovascular system

Electrocardiogram changes, arrhythmias, chest pain, and myocardial infarction and/or necrosis have all been reported (Chouinard et al., 1978; Pentel et al., 1982; Clark and Simon, 1983; Conway et al., 1989; Leo et al., 1996; Oosterbaan and Burns, 2000). Typical catecholamine-type lesions can easily be produced in rats treated with PPA, but only at dosages that produce blood concentrations four to six times higher than normal clinical regimens (Pentel et al., 1987). Therapeutic doses, given to healthy volunteers, increase pulse rate, blood pressure, and peripheral resistance (Thomas et al., 1991). Individuals with preexisting but asymptomatic coronary artery lesions might well become symptomatic. Arrhythmic sudden death has been described (Dietz, 1981; Bernstein and Diskant, 1982), but no autopsy findings have been reported.

In experimental animals, PPA produces exactly the same constellation of lesions classically associated with catecholamine toxicity: myocardial necrosis with contraction bands, eosinophilia, and occasional infiltrates (Pentel et al., 1987). Injury patterns of this type heal by fibrosis, and the presence of microfocal fibrosis could well account for the arrhythmias that have been described in PPA users (Karch and Billingham, 1986). Based on the number of published case reports, phenylpropanolamine seems to be more toxic to the cerebral than the coronary vasculature. The difference is unexplained but may be a function of differing receptor distribution and regulation.

3.3.5.2 Pulmonary system

There is no convincing evidence that PPA use is associated with pulmonary disease and, in fact, only two case reports have suggested such a connection. In one case, a 15-year-old who died 32 hours after taking 400 mg of phenylpropanolamine was found to have changes consistent with the diagnosis of acute respiratory distress syndrome (ARDS) (Logie and Scott, 1984). In a second case, where death resulted from a 600-mg overdose, multiple pulmonary emboli were found, along with changes consistent with ARDS (Patterson, 1980). Blood and tissue levels were not reported for either case.

3.3.5.3 Nervous system

The most commonly encountered complications of PPA use are neurologic. Frank episodes of psychosis can occur even after using therapeutic doses of phenylpropanolamine-containing decongestants (Wharton, 1970; Norvenius et al., 1979; Traynelis and Brick, 1986; Dewsnap and Libby, 1992; Stroe et al., 1995; Goodhue et al., 2000). The mechanism for psychosis in these individuals is not known, but certain factors do predispose to the emergence of psychosis, including the symptoms or history of mood spectrum disorder or psychosis and a family history of psychiatric disorder. Women appear to be at much greater risk than men (Marshall and Douglas, 1994).

Seizures also occur (Howrie and Wolfson, 1983; Cornelius et al., 1984; Goodhue et al., 2000), and stroke has been reported with some frequency (Edwards et al., 1987; Kase et al., 1987; Montalban et al., 1989; Lake et al., 1990; Sloan et al., 1991; Kokkinos and Levine, 1993; Ryu and Lin, 1995). Angiograms of these patients usually, but not always, show changes consistent with vasospasm or angiitis. Many of these patients were normotensive when they first came to medical attention, and almost all were women. However, in some cases, hypertension is a factor. Doses greater than 50 mg are associated with significant blood pressure increases (Lake et al., 1991). As is the case with cocaine and amphetamine, most of the PPA-associated stroke patients are quite young, usually in their late 20s or early 30s (Kernan et al., 2000).

3.3.5.4 Genitourinary tract

Phenylpropanolamine can induce acute myoglobinuria renal failure (Swenson et al., 1982), and one case of biopsy-proven interstitial nephritis has been reported (Swenson et al., 1982). Another case report describes a patient with fever, myalgia, episcleritis, hemoptysis, pleurisy, eosinophilia, and renal impairment. Renal biopsy revealed granulomatous interstitial nephritis, which resolved without specific treatment. As the individual in question was taking multiple drugs, it is impossible to say which drug was responsible (Singer et al., 1988).

3.3.5.5 Gastrointestinal tract

Phenylpropanolamine has never been shown to produce liver disease, but like methamphetamine (Roberts et al., 1994) and like other sympathomimetic agents active at the α_2 receptor, PPA enhances the amount of necrosis produced when carbon tetrachloride is given to mice. The mechanism for this change has yet to be identified (Roberts et al., 1997). In experimental models, pretreatment with PPA (200 mg/kg, i.p.) markedly worsens acetaminophen hepatotoxicity. The synergistic effect is due to depletion of hepatic glutathione, brought about by previous treatment with any α-adrenergic agent (James et al., 1993).

3.4 Fenfluramine

3.4.1 Historical considerations

Racemic fenfluramine (Ponderax®, Pondimin®) was first sold as an anorectic in 1963 (Pondimin®, Wyeth-Ayerst Laboratories). After many years of use in Europe, the dextro isomer was introduced into the U.S. market in 1996 (Redux®, Wyeth-Ayerst Laboratories). In 1992, a paper was published showing that fenfluramine, when combined with phentermine, produced greater weight loss with fewer side effects than either drug taken alone (Weintraub, 1992), and the combination became immensely popular. However, a paper published in August 1997 described a group of 24 fenfluramine–phentermine users with valvular heart disease (Connolly et al., 1997). The 24 cases described had been culled from an indefinite number of echocardiography studies of patients taking the combination for varying periods of time. Thus, it was not possible to estimate the true incidence of the reported abnormalities. In 1998, safety considerations (not to mention legal concerns) led manufacturers to withdraw both isomers of fenfluramine from the market. A closely related compound, aminorex fumarate, a popular appetite suppressant during the early 1960s, was also withdrawn from the market when it became apparent that users were developing pulmonary hypertension (Follath et al., 1971).

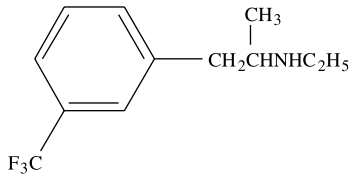

Figure 3.4.2.1 **The fenfluramine molecule.**

3.4.2 Chemistry

Fenfluramine is *N*-ethyl-α-methyl-3 (triflurомethyl) benzenethanamine (Figure 3.4.2.1). Its formula is $C_{12}H_{16}F_3N$, with a molecular weight of 231.27. It is composed of 62.3% carbon, 7% hydrogen, 24.7% fluorine, and 6.1% nitrogen. Crystals of the racemic mixture have a melting point of 108 to 112°C. Until the introduction of *d*-fenfluramine, commercial fenfluramine was supplied as a racemic mixture.

3.4.3 Mechanism of action

Dexfenfluramine causes anorexia by altering serotonin metabolism. The parent compound causes serotonin to be released from presynaptic neurons while at the same time preventing its re-uptake. The principal metabolite of dexfenfluramine, *d*-norfenfluramine, binds to type 2C serotonin receptors (5-HT2) located on postsynaptic brainstem neurons, and treatment with dexfenfluramine increases serotonergic tone (Spedding et al., 1996). In experimental animals, fenfluramine induces large, rapid decreases in brain serotonin and 5-hydroxyindoleacetic acid, and also decreases tryptophan hydroxylase activity (5-HIAA) (Steranka and Sanders-Bush, 1979; Spedding et al., 1996). These changes persist for more than one month after a single dose of drug (Steranka and Sanders-Bush, 1979).

3.4.4 Metabolism

Following a single oral dose of 60 mg, fenfluramine is slowly, but completely, absorbed from the gastrointestinal track. Peak plasma concentrations of 0.05 to 0.07 mg/L occur two to three hours later. The parent drug has a very long half-life (on the order of 17 hours), and patients tend to maintain consistent steady-state concentrations (average of 0.16 mg/L) when therapeutic doses are regularly taken (Cheymol et al., 1995). The half-life of the principal metabolite, *d*-norfenfluramine, is substantially longer (over 30 hours) than the parent compound, and in stabilized patients norfenfluramine concentrations are about half as high as those of the parent compound (Innes et al., 1977). Like the other amphetamines, the excretion of fenfluramine depends on the urinary pH. Almost 20% of fenfluramine is excreted unchanged in the urine, and another 20% appears in the urine as the *N*-dealkylation product norfenfluramine (Beckett et al., 1972).

3.4.5 Blood and tissue concentrations

An adult who survived a 1600-mg fenfluramine overdose had peak plasma concentrations of 0.85 mg/L (Richards, 1969), and a 2-year-old child who ingested 440 mg had a peak level of 0.78 mg/L, with 0.17 mg/L of norfenfluramine (Richards, 1969). Clinical reports suggest that overdose with fenfluramine produces a syndrome indistinguishable from that produced by other amphetamines (Genne et al., 1994; LoVecchio and Curry, 1998; Koury

et al., 1999). Hyperpyrexia is usually a factor in fatal cases (Haines and Shoenberg, 1972). Blood concentrations in cases of suicide may be extremely high. Kintz and Magnin (1992) reported blood concentrations of 7.46 mg/L in a 36-year-old woman who, as demonstrated by high hair drug concentrations, had been taking fenfluramine for some time. Concentrations in the brain were only 0.48 mg/L, while the concentration of fenfluramine in the liver was over 155 mg/L. Fenfluramine blood concentrations in three children who died after ingesting up to 1200 mg ranged from 6.5 to 16 mg/L. Hepatic concentrations in these same children were four to nine times higher (24–136 mg/kg) (Gold et al., 1969; Simpson and McKinaly, 1975). Similar concentrations were seen in a teenager who died 3.5 hours after taking 2 g of fenfluramine. Both liver and brain had fenfluramine concentrations nine times as high as those measured in blood (6.5 mg/L) (Fleisher and Campbell, 1969).

3.4.6 Toxicity by organ system

3.4.6.1 Cardiovascular system

In addition to the secondary cardiac changes expected as a consequence of pulmonary hypertension, evidence indicates that fenfluramine is cardiotoxic, and that toxicity is exerted through several different mechanisms. *In vitro* studies have shown that fenfluramine produces electrophysiologic changes favoring arrhythmias, including concentration-dependent tonic blockade of sodium channels, and shortening of the action potential duration in papillary muscles and Purkinje fibers (Rajamani et al., 2000).

Fenfluramine was removed from the market because of concerns about valvular damage. Since the initial warnings raised by Conolly et al. in 1997, six additional studies have been published, all suggesting an association between use of fenfluramine, or fenfluramine and phentermine in combination, and valvular incompetence. Reported estimates of prevalence have been highly variable, with the risk placed at anywhere from less than 6% to more than 33% (Jick et al., 1998; Weissman et al., 1998; Gardin et al., 2000; Teramae et al., 2000). While many dispute the results of the original reports, a very large number of patients has now been studied, and the evidence for fenfluramine-related valvular injury is substantial.

The length of treatment with fenfluramine–phentermine correlates with the prevalence of valvular abnormalities. Aortic regurgitation is the most common lesion, but it only occurs in individuals who have taken the combination for more than six months (Jollis et al., 2000). However, the degree of regurgitation is usually minor. Symptoms and signs other than a murmur and mild dyspnea are generally lacking.

3.4.6.2 Pulmonary system

Fenfluramine, even in recommended doses, can cause pulmonary hypertension. The first two patients with fenfluramine-associated pulmonary hypertension were reported in 1981. Both were women who had been taking the medication for more than eight months. In both cases, pulmonary hypertension was due to greatly increased vascular resistance (Fleisher and Campbell, 1969) that did not decrease (McMurray et al., 1986; Fotiadis et al., 1991) when the drug was discontinued (Fotiadis et al., 1991; Atanassoff et al., 1992). Since the index reports were published, many additional new reports have appeared, primarily in the European literature (Ferrari et al., 1994; Maesen et al., 1994; Weitzenblum et al., 1996; Dillon et al., 1997; Mark et al., 1997; Olschewski, 1997; Delcroix et al., 1998; Simonneau et al., 1998).

In a study from a European referral center specializing in the treatment of primary pulmonary hypertension, 15 out of 73 patients referred for treatment were discovered to

have been fenfluramine users (Brenot et al., 1993). Autopsies performed in several of the cases revealed the classic findings of plexogenic arteriopathy (Brenot et al., 1993). Similar findings were also seen in the more recent case of a 39-year-old woman with rapidly progressing fatal pulmonary hypertension following the use of a fenfluramine–phentermine combination. Autopsy was remarkable for complex pulmonary vascular lesions that were thought to be most consistent with thrombotic arteriopathy (Strother et al., 1999).

The occurrence of pulmonary hypertension in some individuals using therapeutic doses of fenfluramine and closely related compounds, such as propylhexedrine or phenformin, is difficult to explain (Fahlen et al., 1973; Douglas et al., 1981; Gaul et al., 1982; McMurray et al., 1986; Pouwels et al., 1990; Strother et al., 1999). While the histologic changes are well characterized, the underlying mechanism is not. All drugs suspected of causing primary pulmonary hypertension block the re-uptake and/or metabolism of serotonin, while at the same time causing increased release of serotonin from nerve endings and platelets. High concentrations of serotonin cause pulmonary artery contraction in humans (Boe and Simonsson, 1980), and also favor proliferation of vascular smooth muscle (Nemecek et al., 1986). Patients with primary pulmonary hypertension have abnormally high circulating concentrations of serotonin (Herve et al., 1995), suggesting that pulmonary hypertension in these individuals is a consequence of serotonin toxicity (Egermayer et al., 1999). Other explanations are possible. Patients with chronic heart failure and pulmonary hypertension also have increased plasma concentrations of endothelin-1 (ET-1). Concentrations of ET-1 correlate very strongly with pulmonary artery pressures and pulmonary vascular resistance (Givertz et al., 2000).

The principal lesion seen in the aminorex fumarate-related cases, either at autopsy or in biopsies, was medial hypertrophy with widening of the arterial media to occupy more than 10% of the cross sections of the vessel. One third of the cases showed evidence of eccentric intimal fibrosis with cushion-like thickening of the arterial intima (Givertz et al., 2000). These lesions are reminiscent of those produced by Szakacs in his experimental studies of catecholamine toxicity, nearly half a century ago (Szakacs and Cannon, 1958; Szakacs et al., 1959). The same type of medial hypertrophy has also been observed in the small coronary arteries of cocaine users and methamphetamine users, although the pulmonary vessels have not been studied (Majid et al., 1990).

3.4.6.3 Nervous system

Neurotoxicity can be induced in laboratory animals (Molliver and Molliver, 1990; Thakkar et al., 1990), but evidence for such an occurrence comes entirely from *in vitro* or animal studies, where *d*-fenfluramine was found to be cytotoxic to serotonin transporter expressed in human placental choriocarcinoma cells. It also caused DNA fragmentation and apoptosis, which could be blocked by fluoxetine, indicating that intact serotonin transporter function is required for *d*-fenfluramine to induce programmed cell death. Whether these effects are actually relevant to humans is not known (Bengel et al., 1998).

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chapter four

Hallucinogens

4.1 Introduction

Criteria for membership in this group are difficult to define. Hallucinogens are said to share five common features: (1) changes in mood and perception dominate in proportion to any other effects such drugs might exert, (2) minimal memory or intellectual impairment occurs, (3) use is not associated with either stupor or excessive agitation, (4) side-effects from autonomic nervous system stimulation are minimal, and (5) craving and addiction do not occur (Hollister, 1967). Traditionally, hallucinogens have been divided into two groups: phenylalkylamines (drugs such as mescaline, DOM, DOB) and the indoylalkylamines (psilocybin, bufoteine, LSD, harmaline). Dissociative anesthetics, including GHB, phencyclidine, and ketamine, do not meet these criteria, and so are included in a separate chapter.

4.2 Incidence

Hallucinogenic drugs are not tracked as a separate component in the annual Drug Abuse Warning Network (DAWN) Emergency Department survey, although individual drugs such as LSD are. Only 641 LSD-related emergency department visits were recorded for all of 1999 (compared to 311 in 1990). In 1999, the MDMA-related visits were too rare to rate a separate mention, but use of MDMA in conjunction with marijuana is tracked by the system and appears to have undergone a very striking increase. In 1990, only eight cases of combined marijuana–MDMA use were reported. By 1999, that number had risen almost 10,000% to 796 cases. The number of people developing medical difficulties after combining marijuana with psilocybin has also increased; 23 cases were reported in 1990, but by 1999 that number had risen to 3990, an increase of 1565% (Garfield et al., 2000a). The increasing number of emergency room visits is not reflected in the Medical Examiner component of the 1999 DAWN survey. For all of the 1999 reporting period, only 71 deaths were related to the use of hallucinogens, and 95% of those (68/71) were attributed to phencyclidine. If any MDMA-related deaths were reported to the government in 1999, they were too few for a separate mention (Garfield et al., 2000b).

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4.3 Phenylethylamine derivatives

The most popular hallucinogens are mescaline derivatives, and MDMA is by far the most widely used mescaline analog. Mounting evidence indicates that these compounds may be more toxic than had previously been appreciated, but to date this evidence has not been corroborated by an increase in the reported number of deaths.

4.3.1 Mescaline

4.3.1.1 History

Mescaline comes from the cactus referred to as either *Lophora williamsii* or *Anhalonium lewinii*. (Dr. Louis Lewin was one of the first to systematically study this group of plants and their active principle, mescaline.) This small cactus can be found growing in dry places and rocky slopes throughout the southwestern U.S. (Figure 4.3.1.1.1). It grows singly or in clusters. It is an inconspicuous plant that can be difficult to find. Unless it is in flower, it tends to look like a small rock. The dried tops of the plants, known as peyote buttons, have been used by Indian shamans for centuries. In the early 1800s, the Apaches, Kiowas, and Commanches of the Great Plains began to chew the buttons and incorporate them into their religious rites. The practice quickly spread among the Plains Indians, who combined its use with elements of Christianity. Today, their ceremonies still begin with the chewing of peyote buttons, followed by nights of prayers and singing. The sect is now

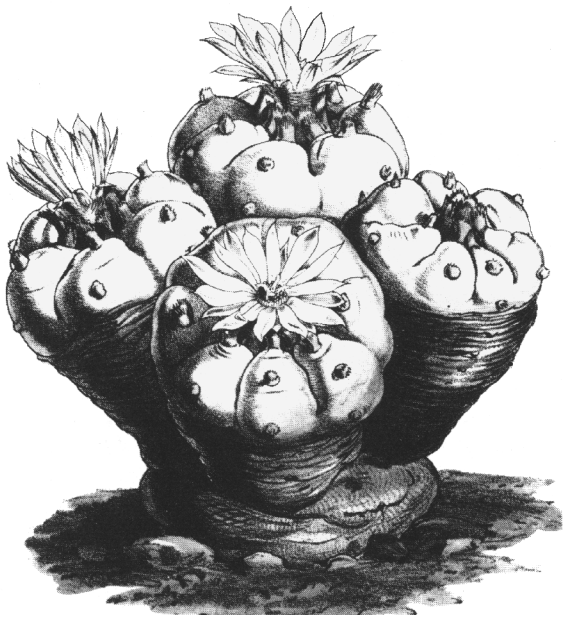

Figure 4.3.1.1.1 **Peyote cactus.** Even though it grows wild throughout the American Southwest, it can be very difficult to find. Except when it is in bloom, it tends to resemble a small rock.

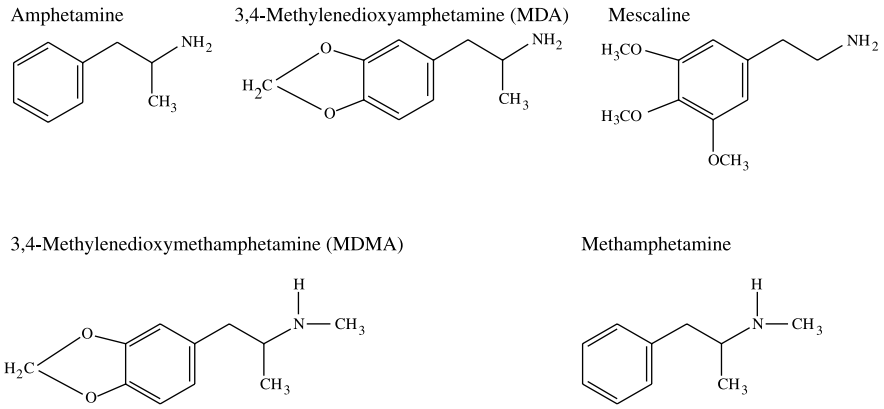

Figure 4.3.1.2.1 **Mescaline and the "designer" amphetamines.** Whether small recreational doses of these drugs are hallucinogenic is difficult to say, but all of these agents can impair judgment, and their use occasionally leads to fatal accidents.

known as the Native American Church, with more than 200,000 members (Barron et al., 1964). Mescaline, or 3,4,5-trimethoxy-β-phenethylamine, is the active principle found in peyote cactus. The average mescaline content is 6%. No mescaline-related deaths or emergency room visits were reported in the 1999 DAWN surveys (Garfield et al., 2000a,b).

The first systematic chemical and pharmacologic studies were reported by Lewin and Henning in 1888 (Lewin and Henning, 1888). Lewin's work attracted the attention of the famous American neurologist, S. Weir Mitchell (Prentiss and Morgan, 1895). Mitchell, who was a prolific writer and a pioneer in the study of peripheral nerve injuries, was also interested in toxicology and psychiatry (Metzer, 1989). He obtained some peyote buttons and used them himself. Mitchell then published an account of his experiences in the *British Medical Journal* (Mitchell, 1896). He believed that the plant might be of great value in the study of psychological disorders, but he also warned of the abuse potential. The famous sexologist Havelock Ellis also dabbled with mescaline and described the many benefits to be derived from its use (Mitchell, 1896). Neither the benefits nor the epidemic of abuse ever really materialized. Similar claims are now being made for MDMA.

4.3.1.2 Drug constants and drug preparations

Mescaline is 3,4,5-trimethoxybenzeneethanamine or 3,4,5-trimethoxyphenethylamine (Figure 4.3.1.2.1). Its formula is $C_{11}H_{17}NO_3$, and it has a molecular weight of 211.23. It is composed of 62.5% carbon, 8.1% hydrogen, 6.6% nitrogen, and 22.7% oxygen. Mescaline crystals have a melting point of 35 to 36°C. Pure mescaline will combine with carbon dioxide in the air to form crystalline carbonates. The hydrochloride form of mescaline, $C_{11}H_{18}ClNO_3$, forms colorless, needle-like crystals with a melting point of 181°C (Budavari et al., 1996).

Mescaline is extracted from the cactus by first drying and then grinding the plant tops. The ground material is then soaked in methanol for a day, filtered, and acidified. After the alcohol has evaporated, the solution is neutralized and the mescaline extracted with chloroform. Less sophisticated chemists "cook" the cactus in a pressure cooker, producing a tarry material that can be formed into small pills. Some clandestine producers may even apply an enteric coating or place the tarry material in gelatin capsules with the hope of reducing the nausea induced by mescaline use.

4.3.1.3 *Metabolism and tissue levels*

In one case report, where accidental death was a consequence of a mescaline-induced confusional state (Reynolds and Jindrich, 1985), the mescaline blood concentration was 9.7 mg/L, with a urine concentration of 1163 mg/L. Most of the published metabolic studies were performed nearly 30 years ago, using techniques that are now considered obsolete. The hallucinogenic dose is said to be on the order of 200 to 500 mg. In tracer studies with healthy volunteers, plasma concentrations peaked at of 3.88 mg/L two hours after a 500-mg dose. A 350-mg dose given intravenously produced a peak blood concentration of 14.8 mg/L at 15 minutes, declining to 2.1 mg/L at two hours. The half-life of mescaline is on the order of six hours. Mescaline is mainly excreted in the urine. Approximately 60% is excreted unchanged, and 30% excreted as 3,4,5-trimethoxyphenylacetic acid. Smaller amounts of other inactive metabolites also appear (Charalampous et al., 1966; Charalampous, 1971). Unlike the other phenylisopropylamine amphetamine analogs, mescaline does not interact with the CYP2D6 cytochrome (Wu et al., 1997).

When dogs are injected subcutaneously with mescaline, the highest concentrations are found in the liver and kidneys. Concentrations in the liver, spleen, and kidneys are three to six times the concentration found in the bloodstream. Brain levels tend to parallel the blood levels (Kapadia and Fayez, 1970). But, because animals metabolize mescaline differently than humans, it may be that tissue concentrations vary as well. Human tissue levels have been measured at autopsy in only one case: a mescaline user who died of a head injury had a blood concentration of 9.7 mg/L, a concentration eight times higher than that in the liver (Reynolds and Jindrich, 1985).

4.3.1.4 *Clinical syndromes*

Healthy volunteers given a .5-mg dose exhibited symptoms of psychosis indistinguishable from the symptoms of acute schizophrenia. Neuropsychologic measurements made during mescaline intoxication suggest that the behavioral changes are due to right-hemispheric striato-limbic hyperactivity, with associated left-hemispheric dysfunction (Oepen et al., 1989). Single photon emission computed tomography (SPECT) imaging of human volunteers during mescaline-induced psychosis shows increased regional flow in the frontal lobes bilaterally (Hermle et al., 1992; Hermle et al., 1998); the symptoms otherwise associated with mescaline abuse are mostly those of sympathetic nervous system stimulation. Transient rises in pulse, blood pressure, and temperature may occur (Kapadia and Fayez, 1970), but episodes of clinically significant hyperthermia and/or excited delirium have not been reported. Laboratory studies on the cardiovascular effects of mescaline have yielded inconsistent results.

4.3.1.5 *Pathologic findings*

Lethal overdoses of mescaline have never been reported, nor have there been any reports of medical complications associated with its use. The deaths that have been reported have been accidental, usually as a result of drug-induced confusion (Reynolds and Jindrich, 1985).

4.3.2 *Other phenethylamine derivatives*

Many of the drugs in this class are mescaline analogs that have been substituted at the 4 position (e.g., escaline, proscaline, buscaline) and are, on a weight-for-weight basis, much more potent than mescaline. Alkoxylated mescaline homologs (e.g., metaescaline, metaproscaline) are less potent. A series of thiomescaline analogs have also been synthesized, with substitutions at both the 3 and 4 positions. The clinical effects of these agents have

never been systematically studied, and virtually nothing is known about their pharmacology, either in humans or animals.

4.4 Substituted amphetamines (phenylisopropylamines)

Since 1947, when researchers produced the first psychoactive mescaline analog (TMA), molecular manipulations have been used to produce a long list of psychoactive derivatives. Except for MDMA, considerably more is known about the confirmation chemistry of these molecules (Kovar, 1998) than about their clinical effects.

4.4.1 TMA

2,4,5-Trimethoxyamphetamine (TMA) has twice the psychoactive potency of mescaline (Shulgin, 1973). It was first synthesized in 1933 but was not used as a psychedelic until 1962. It produces all the same effects as mescaline but is said to have a lower therapeutic index. The amount required to cause hallucinatory or psychedelic experiences is not very different from the amount needed to produce toxicity (Chesher, 1990).

4.4.2 DOM

Methyl-2,5-dimethoxyamphetamine (DOM) was first synthesized in 1963, shortly after TMA (Shulgin, 1977). The first reports of abuse appeared in 1967. DOM was also referred to as STP ("serenity, tranquillity, and peace"). It is a white solid, soluble in most organic solvents, and has a melting point of 60 to 61°C. The melting point for the hydrochloride salt is 190 to 191°C. In doses of less than 3 mg, the effects of DOM are said to be similar to mescaline. Higher doses cause hallucinations and unpleasant side-effects that may last for as long as eight hours (Snyder et al., 1967). DOM disappeared rather quickly from the street, probably because when used in excessively high doses it produced very unpleasant feelings. Regardless of the dose, approximately 20% appears unchanged in the urine with peak excretion occurring at between three and six hours, the period when intoxication is most intense. Hallucinations produced by higher doses are associated with nausea, diaphoresis, and tremor. Moderate elevations in pulse and systolic, but not diastolic, pressure occur. Blood and tissue levels have never been determined, and the pathologic changes associated with its use, if any, are unknown.

4.4.3 PMA

Paramethoxyamphetamine (PMA) is a potent hallucinogen with sympathomimetic properties. The first PMA-related deaths were reported in Canada in the mid-1970s (Cimbura, 1974), followed not too long thereafter by a series of fatalities in Australia (Byard et al., 1998; Felgate et al., 1998; James and Dinan, 1998). The first PMA-related death in the U.S. was reported in the summer of 2000. The evidence suggests that many decedents think they are taking MDMA but have purchased drugs adulterated with PMA (Byard et al., 1998).

Animal studies from the early 1960s suggested that the hallucinogenic potency of PMA is nearly as great as that of LSD (Byard et al., 1998), but, unlike LSD, PMA may cause instances of marked hypertension and hyperthermia. Most of the reported fatalities have been as a consequence of extreme temperature elevation. Decedents are always young, usually in their mid-20s, but, unlike other abuse drugs, PMA fatalities are just as likely to be female as male.

In six fatalities reported from Australia, femoral blood PMA concentrations ranged from 0.24 to 4.9 mg/L (mean, 2.3 mg/L), while liver PMA levels ranged from 1.4 to 21 mg/kg (mean, 8.9 mg/kg). Other amphetamines were found in five of the six cases, confirming the impression that, when PMA is detected, it is probably present as an adulterant. Blood PMA concentrations in nonfatal cases are usually less than 0.5 mg/L (Felgate et al., 1998).

4.4.4 DOB (bromo-DMA)

4-Bromo-2,5-dimethoxyamphetamine (DOB, also called bromo-DMA) is a potent hallucinogenic and sympathomimetic. Compared to MDMA (and most of the other mescaline derivatives), it is longer lasting and more likely to produce toxicity. Reports of DOB abuse are rare in the U.S. and Europe but, like PMA, DOB may occasionally be sold as MDMA or be found as an adulterant in MDMA tablets. Because it is so potent, DOB can be absorbed into blotter paper and misrepresented as LSD (Shulgin, 1981). The problem with this method of distribution, other than the fact that DOB is considerably more toxic than LSD, is that during preparation the drug may migrate to the corners or bottom of the sheet. Users buying squares from the center of the sheet often receive less DOB than they paid for, while those buying squares from the margins of the sheet often get more than they bargained for. This may explain why so many bad experiences have been associated with use of the drug (Delliou, 1980, 1983).

Symptoms of intoxication occur 3 to 4 hours after ingestion and may take 24 hours to resolve. Pupillary dilitation, increased pulse, blood pressure, and increased temperature may be present. Human pharmacokinetics have not been studied, but the effective dose is said to be between 2 and 3 mg. DOB is associated with more morbidity than other mescaline analogs (Winek et al., 1981; Buhrich et al., 1983). Diffuse vascular spasm, identical to the classic picture of ergotism, has been reported after DOB use (Bowen et al., 1983), and grand mal seizures have also been described (Delliou, 1983). This syndrome has not been reported in conjunction with other "designer" amphetamines, but it is a well-known complication of LSD use. Scant autopsy information about DOB is available. In one reported case (Winek et al., 1981), a 21-year-old woman was found dead at the wheel of her parked car. Gross autopsy findings included cerebral edema with uncial herniation. The lungs were minimally congested. Microscopic findings were not reported. Blood and tissue concentrations are shown in Table 4.4.4.1.

Table 4.4.4.1 Blood Levels in a Case of Fatal DOB Intoxication

Tissue	Concentration (mg/L)
Blood	0.90
Bile	0.64
Vitreous	0.51
Brain	0.25
Liver	9.00
Kidney	1.10

Source: Winek, C. L., Collom, W. D. et al., *Clin. Toxicol.*, 18(3), 267–271, 1981. With permission.

4.4.5 Nexus (2-C-B, bromo, toonies)

In Texas in 1979, the Drug Enforcement Agency (DEA) first encountered 4-bromo-2,5-dimethoxyphenethylamine (also known as 2-C-B, bromo, or toonies; for a time this drug was popularly known as Nexus). Since that time, 4-bromo-2,5-dimethoxyphenethylamine has been found in material seized in California, Arizona, Louisiana, Pennsylvania, Iowa, Oregon, Georgia, Tennessee, and Florida. Nexus-producing clandestine laboratories were seized in California in 1986 and in Arizona in 1992, but no further reports have been published. Illegally sold and produced Nexus was usually represented as 3,4-methylene-dioxy-methamphetamine or sold in sugar cubes as LSD (Anon., 1994).

Nexus shares structural and behavioral characteristics with older, more familiar, designer amphetamines such as STP and DOM. It is said to produce euphoria and sensory enhancement with effects lasting six to eight hours, but otherwise little is actually known, and no controlled studies have been done. A typical oral dose is thought to be 10 to 20 mg of the hydrochloride salt; however, Nexus can also be snorted. The recreational dose is thought to be 0.1–0.2 mg/kg, and the effects are said to last for six to eight hours. Frightening hallucinations can occur at higher dosage levels. Because Nexus is effective at relatively low doses, it can also be impregnated in sugar cubes or even sold as blotter tabs. No animal studies have been published, the human pharmacokinetics is unknown, and no fatalities have been reported (Anon., 1994).

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4.4.6 MDMA

4.4.6.1 Chemical constants

3,4-Methylenedioxymethamphetamine (MDMA) is *N*-α-dimethyl-1,3-benzodiaoxole-5-ethanamine or 3,4-methylenedioxymethamphetamine. Other names include XTC, Adam, MDM. The formula is $C_{11}H_{15}NO_2$, and it has a molecular weight of 193.25. Hydrochloride crystals have a melting point of 147 to 148°C (Budavari et al., 1996).

4.4.6.2 History

MDMA is said to be an empathy-enhancing compound (Eisner, 1989), or "empathogen" or "entactogen," from the Greek *en* meaning "inside" and *gen* meaning "to produce" and the Latin term *tactus* for touch (Nichols, 1986). It is immensely popular in Europe, where the number of MDMA tablets seized has increased from less than 500,000 in 1997 to more than 30 million tablets in the year 2000 (Hauschild, 2001).

Merck was issued a patent for MDMA in 1914, but the toxicology of this compound was not systematically studied until the early 1950s when the U.S. Army contracted with a group at the University of Michigan to study the toxicity of MDMA. The results of the Michigan study remained classified until 1973. When the study results were finally released, they showed that MDMA was somewhat less toxic than MDA but more toxic than mescaline (Hardman et al., 1973). MDMA was classified as a Schedule I drug in 1985.

4.4.6.3 Incidence and epidemiology

No MDMA-related deaths are listed in the DAWN report for 1999 (Garfield et al., 2000). The total number of deaths reported from France, where MDMA has been immensely popular for more than a decade, is fewer than 10 (Kintz, 2001). If the patterns of use observed in Europe are the same as in the U.S., then 80% of MDMA users will be found to have used other drugs and the more often MDMA is used, the more likely it is that the individual will be a polydrug abuser. As a consequence, any fatality observed will almost certainly involve polypharmacy. The pattern of multiple drug use seems to follow a fixed order; an initial dose of MDMA followed, approximately two hours later by a dose of methamphetamine followed by marijuana smoking (Bernahard, 2001).

4.4.6.4 Illicit production

Illicit production of this drug is relatively simple. Safrole, the active ingredient in nutmeg, can be used to prepare the starting ketone (3,4-(methylenedioxy)phenylpropanone) by oxidization with hydrogen peroxide in an acid medium. The resulting compound is then combined with methylamine in alcohol. Aluminum powder, freshly treated with mercuric chloride in ethanol, is added to the mixture, which is then boiled for several hours. MDMA is then distilled off under pressure (Verweij, 1991a,b). The final product is compressed into a tablet that is usually embossed with a logo. In Europe, the Mitsubishi logo is a common imprint, and tablets with similar markings have been confiscated in the U.S., occasionally contaminated with PMA. Logos often have whimsical themes, ranging from an imprint of McDonald's Golden Arches to the Rolex trademark symbol, the Mercedes symbol, and even a skull and crossbones.

Stamping of the pills with a recognized logo is no guarantee of quality or safety. PMA-containing tablets sold as MDMA (a much more dangerous drug than MDMA) have been confiscated in the U.S., and European officials have observed that clandestine laboratories sometimes resort to intentional adulteration, first producing a tablet containing large amounts of MDMA, but then later substituting less expensive methamphetamine and selling it under the same logo. Interpol officials also report that MDMA production in the former Soviet Union has accelerated, and that production may even be occurring in disused chemical factories under the supervision of experienced chemists (Hauschild, 2001).

4.4.6.5 Metabolism

The metabolism of MDMA in humans involves two different cytochrome systems and may be altered in cases of genetic polymorphism. MDMA first undergoes *N*-demethylation (P-450 CYP3A4) to form MDA. Both MDMA and MDA also undergo demethylenation (P-450 CYP2D6) to form 3,4-dihydroxymethamphetamine and 3,4-dihydroxyamphetamine, respectively. The latter two compounds are subject to glucuronide and sulfate conjugation, but the demethylenated molecules can also act as substrates for COMT-mediated *O*-methylation, with the formation of additional products that are also eventually converted to glucuronides and excreted in the urine. Seven to ten percent of Caucasian Europeans are CYP2D6 deficient and are classified as "poor metabolizers." This could, in theory, contribute

Table 4.4.6.5.1 MDMA Pharmacokinetics

MDMA dose (mg)	Peak concentration (C_{max}) (ng/mL)	Half-life ($T_{1/2}$) (hr)
50	51	2.7–5.1
75	126	7.7
100	190	5.8
125	229	8.6
150	485	6.9–7.2

to toxicity, but studies of MDMA users who have developed liver failure show that all are normal metabolizers (Kreth et al., 2000). The contribution of genetic polymorphism to toxicity remains unclear.

The pharmacokinetics of MDMA has been studied in groups of volunteers given oral doses of 50, 75, or 100 mg. Maximal plasma concentration occurs two to four hours later. As illustrated in Table 4.4.6.5.1, the MDMA pharmacokinetics is nonlinear. Small increases in the dose of MDMA result in disproportionate increases in the resultant plasma concentrations.

The half-life of MDMA is somewhere between four and seven hours, but the greater the dose administered, the longer the half-life. The half-life for MDA is substantially longer than that of the parent compound, with peak plasma concentrations that are only one tenth as great. MDA itself is psychoactive. Illicitly produced MDMA is a racemic mixture, and clinical evidence indicates that the different enantiomers are metabolized at different rates (Moore, 1996). Enantiomer effects on tissue distribution are not known.

4.4.6.6 Blood and tissue concentrations

Postmortem measurements have been reported in a handful of cases. As with all abused drugs, recreational and toxic levels tend to overlap, but drug concentrations in MDMA fatalities may be extremely high, as much as four or five times higher than the concentrations measured in controlled studies with doses of MDMA comparable to those used by "recreational" users. MDMA undergoes postmortem redistribution, and concentration measurements are site dependent. The cases reported by Bernahard (2001) (Table 4.4.6.6.1) are typical. In one case, the MDMA concentration in femoral blood was 2750 ng/mL, while the concentration measured at the same time in "heart" blood was 9100 ng/mL. Although not shown in the table, the concentrations in the brain were even higher: 10,000 ng/g in the medulla and 14,000 ng/mL in the cerebellum. However, in other case reports, evidence of site dependency has been lacking. This may be a consequence of either postmortem interval or sampling technique, neither of which is documented in the case reports.

Blood concentrations in recent reports seem to be higher than those described in reports from the early 1990s. MDMA concentrations in five patients who survived serious bouts of toxicity were from 200 to 970 ng/mL, while levels in five car-accident victims varied from 50 to 340 ng/mL (Henry et al., 1992). Plasma concentration measurements in driving while intoxicated (DWI) suspects have been reported by several authors. The concentration ranges reported are extremely wide, ranging from less than 50 ng/mL to nearly 600 ng/mL, and as high as 2140 ng/mL in one traffic fatality attributed to MDMA; it appears that in these cases MDMA was almost always co-ingested with other drugs.

Table 4.4.6.6.1 MDMA and MDA Concentrations in Femoral and Heart Blood

	Femoral blood (ng/mL)			Heart blood (ng/mL)		
	MDMA	MDA	MDEA	MDMA	MDA	MDEA
Case 1	2750	280	—	9100	830	—
Case 2	1564	43	—	417	37	—
Case 3	3370	—	—	3510	—	—
Case 4	5210	—	—	5380	—	—
Case 5	—	—	—	—	22,000	12,000

Note: MDMA = 3,4-methylenedioxymethamphetamine; MDA = 3,4-methylenedioxyamphetamine; MDEA = 3,4-methylenedioxyethamphetamine.

Of course, the presence of MDMA might just be an accidental finding. Dowling et al. (1987) described one asthmatic with a blood MDMA concentration of 1.1 mg/L, and autopsy findings showed severe chronic lung disease. MDMA users are very likely to be using more than one drug (see above); if death is to be attributed to MDMA, then at least some plausible mechanism, such as water intoxication, should be present.

4.4.6.7 Neurotoxicity

Like other amphetamines, MDMA acts on both the heart and the central nervous system, causing release of catecholamines (including serotonin) and preventing their re-uptake. Neurotoxicity in animals is manifested by damage to serotonergic neurons. In the rat model, even one dose of MDMA causes degeneration of serotonin-containing neurons, but animals treated with massive and repeated doses of MDMA eventually recover and at one year after treatment have no apparent lesions (Battaglia et al., 1987). Interspecies variation in the response to MDMA is considerable. The monkey is much more sensitive to the serotonin-depleting effects of MDMA than is the rat (Ricaurte et al., 1985). Animal models show no evidence of gliosis, an anatomic marker for tissue damage, and it remains a matter of some contention whether the findings in animal models can be extrapolated to human beings (Burgess et al., 2000; Curran, 2000; Turner and Parrott, 2000).

Brain lesions have not been demonstrated in humans, but chronic paranoid psychosis occurs, raising the possibility of underlying structural damage (Creighton et al., 1991; Schifano, 1991; Williams et al., 1993). The experience in Europe has been that MDMA abusers may present with a diverse group of psychiatric syndromes including, but not limited to, toxic psychosis (Morland, 2000). Nothing distinguishes the psychotic symptoms of MDMA users from symptoms seen in individuals with any other type of toxic psychosis.

A wealth of experimental evidence suggests that MDMA is toxic to serotenergic neurons, but there is no clinical evidence that humans ever develop the typical symptoms of serotonin depletion (disorders of sleep, mood, appetite). On the contrary, MDMA users are at risk for serotonin syndrome (Padkin, 1994), with severe hyperthermia, altered mental status, and autonomic dysfunction. Serotonin syndrome was first recognized in depressed patients who had been treated with combinations of monoamine oxidase (MAO) inhibitors and tryptophan. Some of these patients became confused and simultaneously developed ataxia, restlessness, lower extremity hyperreflexia, and diaphoresis — symptoms very much like those seen in individuals with MDMA toxicity (Ames and Wirshing, 1993; Bodner et al., 1995; Gillman, 1997; Naito, 1997; Mueller and Korey, 1998).

Users of MDMA are at increased risk for seizure activity. Whether this is a consequence of the flashing strobe lights used at some "rave" parties or water intoxication from drinking copious amounts of water or is due to MDMA-induced release of vasopressin is not clear. MDMA does cause increased release of vasopressin (Henry et al., 1998), and increased water consumption (a practice encouraged at all-night dance parties known as "raves") in the face of elevated concentrations of vasopressin could well result in water intoxication, with hyponatremia and potentially fatal cerebral edema (Milroy et al., 1996; Hall, 1997; Parr et al., 1997).

Intracranial hemorrhage has also been described (Gledhill et al., 1993; Hughes et al., 1993; Selmi et al., 1995; Bailly, 1999), usually as a consequence of a pre-existing, previously undiagnosed aneurysm or arteriovenous malformation. Several reports of cerebral infarction were published in the early 1990s (Manchanda and Connolly, 1993; Hanyu et al., 1995), but none has been published recently. Given the very great number of users today, and the absence of new case reports describing infarction, the connection with MDMA abuse is questionable. Similar considerations apply to the one report of MDMA-related spongiform encelopathy (Bertram et al., 1999).

4.4.6.8 Cardiovascular toxicity

Modest oral doses of MDMA cause increases in heart rate (increases of up to 30 beats per minute), blood pressure (average increase of 7 mm in diastolic pressure), and myocardial oxygen consumption. These increases are comparable to those induced by a dobutamine infusion of 20 to 40 μg/kg per minute. But, unlike dobutamine, MDMA has no measurable inotropic effects (Lester et al., 2000). Large autopsy studies have yet to be published. In the report by Milroy et al. (1996) describing the findings in seven MDMA-related fatalities, hepatic damage was the most frequent finding (see below), but one of the decedents, who was assumed to have suffered a sudden cardiac death, was found to have myocardial fibrosis, a very common finding in methamphetamine abusers (Figures 4.4.6.8.1 and 4.4.6.8 2).

Some of the published case reports have described patients with classic amphetamine/catecholamine toxicity with hyperadrenergic symptoms, including fever, tachycardia, and hypertension, as well as rhabdomyolysis, renal failure, and disseminated intravascular coagulation (Chadwick et al., 1991; Campkin and Davies, 1992). A report published in 1988 described an MDMA user, previously diagnosed with Wolff–Parkinson–White syndrome, who experienced sudden cardiac death. In addition to the presence of an aberrant pathway, myocardial fibrosis was present, so it is impossible to say whether it was pre-excitation or re-entry, or both, that led to the individual's demise (Suarez and Riemersma, 1988).

One case of aortic dissection in an MDMA user has been reported (Duflou and Mark, 2000). Dissection is a known, and not uncommon, complication of methamphetamine abuse, but the mechanism in such a case remains unknown. In such cases, special stains are generally unrewarding, and evidence of medial degeneration is conspicuously absent. Presumably, the MDMA-related cases and the methamphetamine-related cases share common mechanisms.

4.4.6.9 Hepatotoxicity

Reports from Europe continue to describe patients with severe hepatitis, sometimes even with fulminant liver failure (Brauer et al., 1997; Hellinger et al., 1997; Andreu et al., 1998; Friebe, 1998; Jones and Simpson, 1999). Multiple, unrelated mechanisms may be responsible for MDMA hepatotoxicity. In rats, acute doses of MDMA cause increased triglyceride

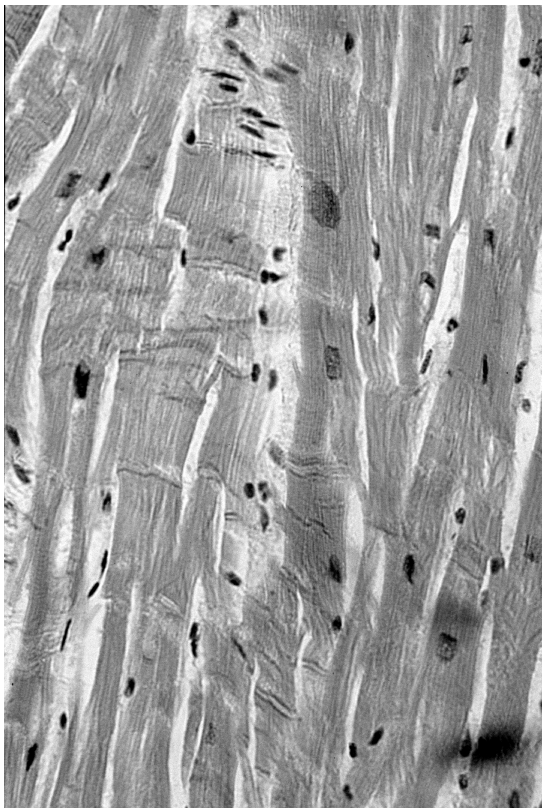

Figure 4.4.6.8.1 Myocardium for 28-year-old man with sudden cardiac death. He was thought to be a chronic MDMA user. Note areas of extremely intense contraction band necrosis. CNS is a common lesion in stimulant abusers, but lesions are rarely this severe (H & E stain). (Courtesy of Professor Chris Milroy, Sheffield Forensic Center, United Kingdom.)

and cholesterol concentrations and elevated hepatic enzymes within six hours of administration. A marked decrease in hepatocyte glycogen content is accompanied by a decrease in serum glucose levels; however, acute treatment with MDMA does not affect lipid peroxidation or hepatic glutathione (GSH) content. When multiple doses of MDMA are given, GSH content decreases and there is clear evidence of oxidative stress (Beitia et al., 2000). This mix of overlapping acute and chronic effects could account for the confusing histologic picture seen in cases of human toxicity.

Liver damage seems to be the result of an idiosyncratic reaction to MDMA or to some contaminant ingested along with it. In the cases that have been reported to date, all of the standard tests for hepatitis have been negative. A liver biopsy in one case showed florid changes with portal and lobular necrosis (Figure 4.4.6.9.1), an inflammatory infiltrate containing mostly monocytes, and substantial numbers of eosinophils. In a second case report, extensive necrosis was concentrated in the periportal areas (Shearman et al., 1992). The infiltrate was comprised of plasma cells and lymphocytes with only an occasional eosinophil. In a third case, there was acute cholestatic hepatitis, with canalicular bile casts evident throughout the lobule. Hepatocyte necrosis was evident in all three zones, and the portal tracts contained an inflammatory-cell infiltrate composed of many eosinophils and histiocytes.

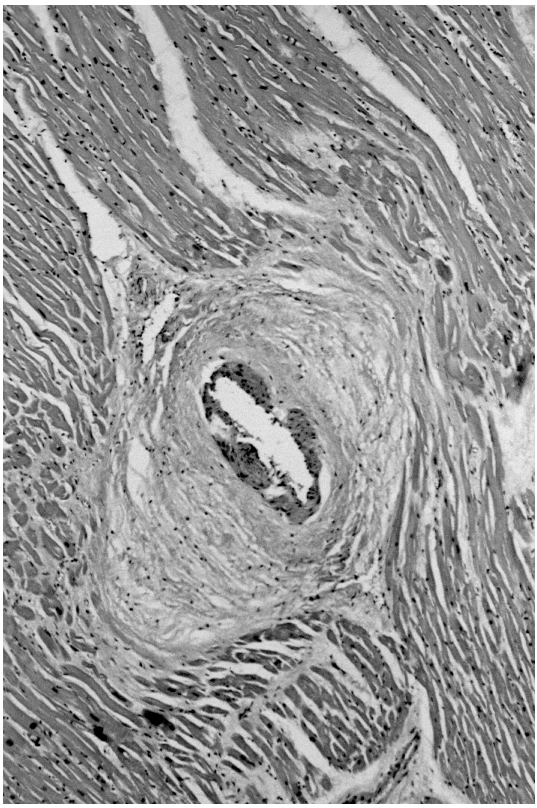

Figure 4.4.6.8.2 **Zone of perivascular fibrosis from the same heart showing contraction band necrosis in 4.4.6.8.1.** The combination of perivascular fibrosis, microvascular disease, and contraction band necrosis is nearly diagnostic for chronic exposure to high concentrations of catecholamines, which can only be explained by the presence of a pheochromocytoma or by a chronic stimulant abuser (H & E stain). (Courtesy of Professor Chris Milroy, Sheffield Forensic Center, United Kingdom.)

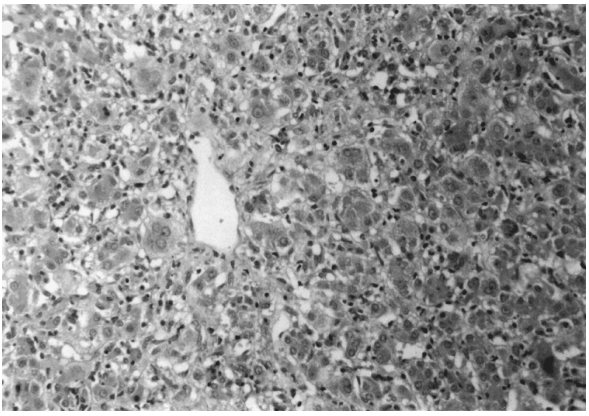

Figure 4.4.6.9.1 **MDMA hepatitis.** Florid hepatitis with inflammatory cell infiltrates and lobular disarray. The infiltrate is predominantly mononuclear, but eosinophils and neutrophils are present in the portal tracts. It is not clear whether these changes represent a reaction to MDMA or to some contaminant in the drug. (Courtesy of Dr. N. G. Ryley, John Radclyffe Hospital, Oxford.)

4.4.6.10 Miscellaneous MDMA-related illness

An assortment of disorders have been reported in conjunction with MDMA use, but their incidence is so low that causal relationships are difficult to establish. It appears that rhabdomyolysis, a common finding in MDMA users secondary to hyperthermia, may sometimes be the result of direct drug toxicity (Lehmann et al., 1995). Several cases of reversible aplastic anemia have also been described, further reinforcing the notion that MDMA, or some contaminant introduced during its production, is inherently toxic (Marsh et al., 1994; Clark and Butt, 1997). Urinary retention is a much less serious, but certainly distressing, disorder associated with MDMA use. Because MDMA is both an α- and β-adrenergic agonist, it may disrupt the innervation of the bladder neck and produce urinary retention (Bryden et al., 1995).

4.4.7 MDA (the "love drug")

3,4-Methylenedioxyamphetamine (MDA) was first synthesized in 1910 by two Merck chemists (Mannich and Jacobsohn, 1910). Even moderate doses of MDA can produce marked sympathetic stimulations, with resultant tachycardia and hypertension (Gunn et al., 1939). Gordon Alles, the inventor of amphetamine, tried MDA on himself in a series of experiments later described in Hoffer and Osmond's (1967) text on hallucinogenic drugs. MDA was patented as an anorectic agent and as an antitussive (Lukaszewski, 1979), but it never saw commercial distribution. Today it is important only because it a major metabolite of MDMA. No evidence indicates that MDA is currently synthesized or sold in the U.S. or Europe.

The effects of a 150-mg dose will peak at 1.5 hours and can last for as long as 8 hours, but the half-life of MDA is unknown and we have no human data on excretion. MDA undergoes oxidative cleavage of the methylenedioxy ring, producing methoxy and/or hydroxy metabolites which then undergo conjugation (Marquardt et al., 1978). In rats, the (d)-isomer of MDA is extremely arrhythmogenic, and even moderate doses can provoke ventricular tachycardia. This may explain some reported cases of MDA-associated sudden death. Illicitly manufactured MDA is always a racemic mixture (Marquardt et al., 1978), but the proportions of each isomer present may vary. Blood and tissue concentrations reported in several fatalities have ranged from 6 to 26 mg/L (Cimbura, 1972). The most recent fatalities to be reported occurred in 1990. The decedent was a 26-year-old individual whose clinical history suggested arrhythmia. At autopsy, fresh thrombosis was found in a severely obstructed (75%) left main coronary artery. Microscopic features were not described (Nichols et al., 1990).

4.4.8 MDEA (Eve)

3,4-Methylenedioxyethamphetamine (MDEA) is a rarely encountered hallucinogen closely related to MDMA and appears to have essentially clinical effects. Brain glucose utilization in human volunteers has been studied using functional magnetic resonance imaging (fMRI). Both MDMA and MDEA cause similar neurochemical alterations, most marked in the frontostriatocerebellar regions, an area implicated in the actions of most psychotropic drugs (Schreckenberger et al., 1999). One fatality in an individual with an enlarged heart and some nonspecific histologic changes has been reported. The subject's blood contained 2.0 mg/L of MDEA (Milroy et al., 1996). A second report described the findings in a 19-year-old who died after taking 10 tablets of pure MDEA. His symptoms progressed from apparent intoxication to profuse sweating, followed by aggressive behavior and

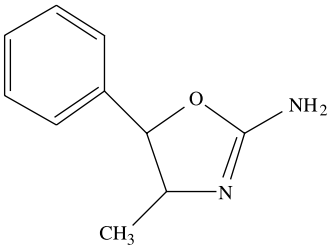

Figure 4.4.9.1 **Aminorex molecule.** 4-Methylaminorex differs from MDMA and other ring-substituted amphetamines. It is classified as an oxazoline and has a side-chain substitution that resembles pemoline, a potent stimulant.

hallucinations. Respiratory failure quickly supervened. The only significant autopsy finding was passive congestion. The serum MDEA was12 mg/L in femoral vein blood, 22 mg/L in "heart" blood, and 201 mg/L in the urine (Weinmann and Bohnert, 1998).

4.4.9 4-MAX (U4Euh, EU4EA, U4EA), aminorex

4-Methylaminorex (4-MAX) and aminorex belong to a group of compounds known as oxazolines (Figure 4.4.9.1). Aminorex was sold in Europe by McNeil Laboratories during the 1960s under the brand names Menocil® and Apiquel®. It was promoted for appetite suppression and weight reduction, but it had to be withdrawn from the market when its use was linked with the development of fatal pulmonary hypertension. The first reports of 4-methylaminorex abuse came from Florida during the mid-1980s. Since then, sporadic seizures have continued, but only rarely (Gaine et al., 2000). Instead of being sold under its own name, it was usually misrepresented as methamphetamine. Based largely on concerns that aminorex had the potential to become a low-cost substitute for cocaine or methamphetamine, aminorex was classified as a Schedule I substance in April 1989. No deaths or emergency room visits have been attributed to 4-MAX since then.

The *cis*-(+)-isomer is the form found in most clandestine drug laboratories. It is synthesized in a one-step reaction by condensing phenylpropanolamine with cyanogen bromide. It could also be produced starting with norpseudoephedrine. Both phenylpropanolamine and norpseudoephedrine are unrestricted and easily available. In laboratory experiments, 4-MAX produces the same effects as the other amphetamines, causing substantial increases in brain dopamine release, and decreases in tryptophan hydroxylase activity (Hanson et al., 1992). The discovery that aminorex could cause fatal pulmonary hypertension effectively stopped all further research on this substance (Seiler, 1975; Gurtner, 1985).

Pharmacokinetic studies of aminorex were done before sophisticated measurement techniques became available. Aminorex absorption is rapid; a single 15-mg oral dose produces peak plasma concentration of 40 μg/mL at 2 hours. Concentrations decline slowly after that, dropping to 5 μg/mL at 24 hours. The reported half-life for aminorex in humans is 7.7 hours. Studies have not been done on 4-MAX, but the similarities to aminorex are so great that it should behave in much the same way. Most of a given dose is eliminated unchanged in the urine (WHO, 1991).

Detecting 4-MAX in blood or body fluids is problematic. Neither aminorex nor 4-MAX is detectable with the routinely used screening tests. None of the currently available radioimmunoassays (RIA), fluorescence polarization assays (TDX), or enzyme multiplied immunoassays (EMIT) for amphetamines cross-reacts with the oxazolines. Detection with

chromatographic or spectrophotometric techniques is not a problem, but because most medical examiners, and all workplace testing programs, screen with immunoassays, the presence of the oxazolines is likely to go undetected. Blood and urine levels have been measured in one fatality; the 4-MAX concentration was 21 μg/mL in the blood and 12.3 μg/mL in the urine (WHO, 1991).

4.4.10 Other MDMA homologs

The 2-butanamine-2-homolog of MDMA (*N*-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine) has been produced by clandestine chemists in Germany. Use of the drug is said to result in a pleasant introspective state, devoid of hallucinogenic effects. Identification of the drug is straightforward, but nothing is known of its pharmacologic or metabolic effects (Rösner and Junge, 1994).

4.4.11 Kat, Jeff, Cat

"Kat" — 2-methylamino-1-phenylpropan-1-one ("Jeff"), 2-(methylamino)-propiophenone, α-(methylamino) propiophenone, α-N-methylaminopropiophenone, *N*-methylcathinone, methylcathinone, AL-464, AL-422, AL-463, UR1432 ("Cat") — was first discovered many years ago, but reports of abuse, initially from the former Soviet Union, only began to appear in the early 1990s. After a flurry of media coverage, this agent has all but disappeared from the scene. In the 1950s, the Parke-Davis company considered marketing methcathinone as an appetite suppressant, and in 1957 filed for a patent on the production process. In subsequent studies, Parke-Davis chemists discovered that only the *l*- form was active, but with storage, especially in basic solution, the pure *l*- form rapidly converted into a racemic mixture. Because of the limited shelf life of the active form, Parke-Davis never proceeded to human testing. In the early 1990s, clandestine chemists began using the synthetic route specified in the original Parke-Davis patent.

Kat is synthesized directly from ephedrine by oxidation with potassium permanganate. In the U.S., clandestine chemists have traditionally opted to reduce ephedrine and make methamphetamine, but the oxidative route is much simpler. The required chemicals (battery acid, sodium dichromate, lye, paint thinner, and Epsom salts) are much easier to come by without attracting notice, and cookbook recipes are being sold on the street and over the Internet.

Methcathinone has all of the characteristics of an amphetamine, including the ability to cause the release of dopamine from the rat caudate nucleus (Glennon et al., 1987). Many methacathinone-related deaths are said to have occurred in the former Soviet Union, but nothing is known of the pathology or clinical pharmacology of this agent (Zhingel et al., 1991). A nearly 10-year-old report described the clinical findings in four alleged cases treated in a midwestern hospital, but blood and urine levels were not measured (Emerson and Cisek, 1993). Symptoms in the four subjects were generally indistinguishable from those of amphetamine toxicity. In two cases, ephedrine was also detected, suggesting that the clandestine chemist responsible had not carried the reaction to completion.

Between June 1991 and August 1993, 27 clandestine methacathinone laboratories were seized, all in Michigan and Wisconsin. Since then, production has expanded, and seizures have been reported in the south and western portions of the U.S. Although it is occasionally passed off as methamphetamine, Kat is usually represented as a form of synthetic khat. Methcathinone has been classified as a Schedule I drug (Anon., 1993). Shortly following its placement in Schedule I, it disappeared from the scene. During the

last eight years, no new cases of methacathinone-related deaths or toxicity, and no further laboratory seizures have been reported.

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4.5 Phenylalkylamines

4.5.1 Simple tryptamines

4.5.1.1 DMT

N,*N*-dimethyltryptamine (DMT) is a component of South American hallucinogenic snuffs. It can be isolated from both Old and New World plants, and even European mushrooms. DMT is not active when taken orally and must be either smoked or injected. DMT is usually sold on the black market as a brownish solid material that smells like mothballs. Users cut off small pieces and smoke them by placing them at the end of a cigarette, often a marijuana cigarette. DMT is sometimes referred to as the "businessman's high" because a single inhalation will produce a 5- to 10-minute "trip" that is entirely gone in 30 minutes (Chamakura, 1993a).

Nothing is known about the toxicokinetics of smoked DMT; however, controlled double-blind studies with intravenously administered drug have been done with experienced hallucinogen users. With doses of 0.2 and 0.4 mg/kg (which are fully hallucinogenic), effects were experienced almost instantly, peaking within 2 minutes and disappearing in 20 to 30 minutes. Measured blood levels corresponded to the subjective effects of the drug. Peak levels varied widely from subject to subject and ranged from 32 to 204 ng after a 0.4 mg/kg dose. Hallucinogenic drugs such as DMT are serotonergic agonists, or at least partial agonists, and, in addition, have adrenergic and dopaminergic properties. DMT causes hormonal, autonomic, and cardiovascular effects. Pupils dilate, and levels of cortisol, prolactin, corticotropin, growth hormone, and β-endorphin all increase in a dose-dependent manner. Values returned to near baseline within 30 minutes. Increases were also observed for heart rate and blood pressure. Body temperature also rose, although that change lagged slightly behind the others (Strassman and Qualls, 1994; Strassman et al., 1994).

4.5.1.2 Bufotenine

5-Hydroxy-*N*,*N*-dimethyl-tryptamine (bufotenine) shares structural and mass spectral similarities with psilocybin and is a potent hallucinogen. The results of receptor binding studies suggest that bufotenine has approximately the same affinity for 5-HT2A and 5-HT2C receptors as LSD (McBride, 2000). It was the active ingredient in the South American hallucinogenic snuffs described by early Amazon explorers more than 400 years ago (Monardes, 1574). Under U.S. law it is a controlled substance, as are the related bufadienolides: resibufogenin, bufalin, and cinobufagin. Bufadienolides are derived from toad venom or toad skin secretions, although very closely related molecules have been found in the bulbs of some tropical plants (Krenn et al., 2000). The Chinese medication *Chan Su* and the West Indian "love stone" both contain bufadienolides, which are, in fact, cardiac glycosides. Taken in excess, these compounds can produce all the symptoms of digitalis poisoning and can be successfully treated with digoxin-specific Fab fragments (Brubacher et al., 1999).

Archaeologic evidence indicates that the use of bufotenine-containing snuff goes back several thousand years. In spite of its ancient origins, the drug received little attention until a California wildlife instructor was arrested in 1994 for the possession of bufotenine, which he had collected from four pet toads. At about the same time, police from Australia began to encounter people smoking the dried skin of the Australian cane toad. Occasional samples of bufotenine began appearing at crime laboratories in the early 1990s (Chamakura, 1993a). At the same time, "toad smoking" began to receive extensive publicity in the lay press (Gallagher, 1994).

Bufotenine is present in at least four different species of toads, and not just in their skin. The digitalis-like component of the poison can be detected in toad plasma and internal organs (Lichtstein et al., 1993). It can also be found in Asian herbal remedies prepared in China, from either dried toad skins or from milked parotid secretions. A medication that contains toad product is called *Chan Su* and is used topically to treat skin ailments. Toad products are also added, in minute amounts, to other Asian proprietary mixtures in hopes of strengthening the heart. *Chan Su* can be legally prescribed by herbalists practicing in the U.S.

Confiscated samples of bufotenine have been described as resinous, reddish brown cubes, reminiscent of root beer barrel candies that have been sucked on (Chamakura, 1993a). It is believed that abusers shave off some of the resin and smoke it at the end of a cigarette. The dose used is not known, and resultant blood levels have never been measured. A fairly extensive literature on the botany and chemistry of bufotenine now exists, but essentially nothing is known of its pharmacokinetics or pharmacodynamics.

Toad secretions contain at least two different pharmacologically active classes of compounds: bufogenins, a group of steroid derivatives, and bufotoxin. At least one of these glycosides is also a potent vasoconstrictor, and its effects are not entirely blocked by antidigoxin antibodies (Bagrov et al., 1993). A second group of basic components includes epinephrine, norepinephrine, serotonin, and bufotenine. Dogs poisoned with toad secretions develop drooling, seizure activity, cyanosis, and cardiac arrhythmias (Palumbo et al., 1975). The hemodynamic effects, at least, seem to be due to the combined effects of the glycosides and catecholamines (Ojiri et al., 1991).

Human toad poisoning does occur, although death is rare. A 1986 case report described a child who developed status epilepticus after mouthing a toad (Hitt and Ettinger, 1986). Profound drooling, seizure activity, arrhythmias, and cyanosis have all been described in *Chan Su* users (Chern et al., 1991; Kwan et al., 1992; Yei and Deng, 1993; Jan et al., 1997; Chi et al., 1998). Toxicity is reported to be common in dogs (Roberts et al., 2000).

4.5.1.3 Psilocybin

4.5.1.3.1 Chemistry. Psilocybin (4-phosphoryl-*N*,*N*-dimethyltryptamine) is 3-[2-(dimethylamino)ethyl]-1H-indol-4-ol dihydrogen phosphate ester (Figure 4.5.1.3.1.1). Its formula is $C_{12}H_{17}N_2O_4P$, and it has a molecular weight of 284.27. It is composed of 50.7% carbon, 6% hydrogen, 9.9% nitrogen, 22.5% oxygen, and 10.9% phosphorus. The melting point is variable, depending on how it was crystallized. Psilocin, the 4-hydroxyl analog of psilocybin, is formed by metabolic dephosphorylation. It is also contained in hallucinogenic mushrooms, but in much smaller amounts. Psilocin is the active form within the central nervous system and, on a weight-for-weight basis, is much more potent than

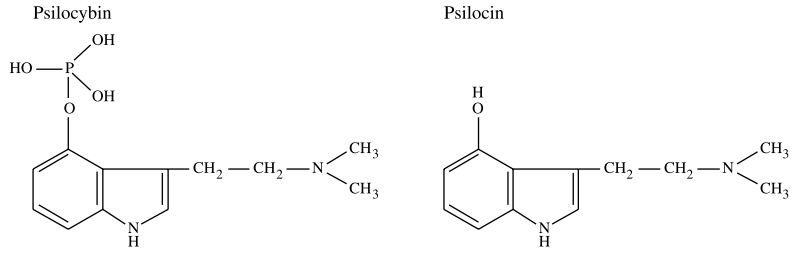

Figure 4.5.1.3.1.1 **Psilocybin and psilocin molecules.**

psilocybin. Its formula is $C_{11}H_{16}N_2O$, and it has a molecular weight of 204.27. It forms plate-like crystals and has a melting point of 173 to 176°C (Budavari et al., 1996).

4.5.1.3.2 History. Psilocybin-containing mushrooms were probably used by the Aztecs, but until the 1960s they aroused little interest outside of Mexico. The name *psilocybin* is derived from the Greek roots *psilo,* meaning "bald" and *cybe*, meaning "head," presumably because of the shape of the mushrooms from which the compounds are derived. The structure of the molecule was not established until 1958, when the active principle of these mushrooms was isolated by Albert Hoffman at Sandoz Pharmaceuticals. Hoffman had succeeded in synthesizing LSD just a few years earlier. For some time, Sandoz marketed pure psilocybin under the brand name Indocybin® (Stafford, 1982).

Psilocybin can be found in three different genera of mushrooms: *Psilocybe*, *Panelous*, and *Concybe*. All three varieties grow naturally in the northwestern and southeastern portions of the U.S. Related or identical forms grow wild in Central and South America, as well as in Southeast Asia and India. Large quantities are cultivated for illegal distribution. The most common species is *Psilocybe cubensis*. It grows wild in the manure of cattle, water buffalo, and other ruminants, including deer, and possibly kangaroos. In Southeast Asia, farmers collect droppings from these animals and systematically grow the fungi in disused rice paddies (Allen and Merlin, 1992).

All three genera contain the tryptophan derivatives psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine) and psilocin (4-hydroxyl-*N*,*N*-dimethyltryptamine). *Psilocybe cubensis* is generally the preferred cultivar and on average yields 10 mg of psilocybin per gram of fresh mushroom, which is equal to an average dose. Psilocin is 1.5 times more potent than psilocybin, but, because the latter oxidizes more slowly, both contribute almost equally to the effect of the mushroom (Leikin et al., 1989). During the early 1980s, growing kits complete with spores were advertised in magazines. They are now illegal (Schwartz and Smith, 1988).

Identifying wild *Psilocyba* is difficult and dangerous. Psilocybin-containing mushrooms grow side by side with the poisonous *Galerina autumnalis*. *Galerina* species have rust-brown-colored spores, while the spores of *Psilocybe* species are gray to lilac. Some, but not all, species can be distinguished from poisonous mushrooms by their reaction to room air; when *Psilocybe* mushrooms are cut, they oxidize and turn blue within 30 to 60 minutes. Unfortunately, some poisonous mushrooms can do the same thing. Pathologists are much more likely to encounter cases of mushroom poisoning than they are to encounter psilocybin-associated medical problems!

4.5.1.3.3 Physiologic and psychological effects. After oral doses of up to 15 mg, psilocyin produces no significant alterations in pulse, blood pressure, or neuroendocrine function, although profound psychological alterations occur (Gouzoulis-Mayfrank et al., 1999).

4.5.1.3.4 Pharmaco- and toxicokinetics. Studies in rats, which may or may not be relevant to humans, suggest that bioavailability from the stomach is only 50%, and that 65% of what is absorbed is eventually excreted in the urine, with another 20% appearing in the bile and stool. Most of the excretion occurs in the first eight hours, but in the rat, labeled drug may appear in the urine for as long as a week (Aboul-Enein, 1974). Fatalities are rare (fewer than half a dozen case reports have ever been published), and tissue levels in humans have not been studied. One case report from more than 40 years ago described a 6-year-old child who developed hyperthermia and status epilepticus after ingesting an undetermined number of mushrooms. No toxicologic studies were performed (McCawlley et al., 1962). A review of 27 patients with "magic mushroom" poisoning found that

mydriasis and hyperreflexia were common, but also noted that individuals recovered uneventfully (Peden et al., 1981). A 1983 study reviewed 318 psilocybin-related cases that had been reported to poison control centers in the U.S. and found no evidence of serious toxicity (Francis and Murray, 1983). Since then, only one additional case has been reported. It involved a young man with arrhythmias and a myocardial infarction, but because the individual also had underlying congenital heart disease (Wolff–Parkinson–White syndrome), causality is impossible to determine (Borowiak et al., 1998). It seems probable that any deaths that occur in association with psilocybin use are likely to be accidental, a result of drug-induced confusion. In times of shortage, dealers may misrepresent LSD or PCP as psilocybin, producing a puzzling picture that can only be clarified with extensive toxicologic testing.

4.5.2 β-Carbolines

4.5.2.1 Harmaline

Harmine and harmaline are indole alkaloids, the active ingredients in some of the hallucinogenic snuffs used by South American Indians. Both molecules are melatonin analogs structurally related to ibogane, an alkaloid currently under investigation as a treatment for opiate addiction (Mash et al., 2000; Xu et al., 2000). Harmine and harmaline are only two of many naturally occurring alkaloids found in *Peganum harmala*, also known as Syrian rue, the traditional source of the characteristic red dye used in Turkish carpets (Furst, 1985). *Peganum harmala* is a perennial herbaceous plant found not only in the Amazon basin but also in North Africa and the American Southwest (el Bahri and Chemli, 1991). *Peganum harmala* is just one of at least eight plant families, some Old World, some New, containing harmine and harmaline. They are β-carboline derivatives, thought to be tryptophan hydroxylase and MAO inhibitors. They are profoundly hallucinogenic. In the New World, *Banisteriopsis*, a malpighiaceous tropical genus, is the main source of the psychoactive snuff.

Very little is known about metabolism or potential toxicity. Analysis of a 200-mL sample of Daime, the ritual herbal potion used in the Amazon, disclosed the presence of 298 mg of harmine, 278 mg of tetrahydroharmine, and 106 mg of DMT (Liwszyc et al., 1992). Based on a limited number of animal studies, harmaline and its derivatives do not appear to be particularly toxic; the LD_{50} in rats is 120 mg/kg. Autopsies of cattle that consumed large amounts of harmaline-containing shrubs have disclosed only passive visceral congestion (Bailey, 1979). Studies in humans have not been reported. Harmaline is closely related to ibogaine, a compound thought to have potent anti-addictive properties. Preclinical trials with both harmaline and ibogane have shown that, in high doses, both compounds are capable of causing Purkinje cell degeneration, possibly due to the release of excitatory amino acids (O'Hearn and Molliver, 1993). However, the results of other studies indicate that, in experimental animals, harmaline protects against MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) neurotoxicity through a scavenging action on reactive oxygen species and by inhibiting MAO and thiol oxidation (Lee et al., 2000).

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4.5.3 α-Methyltryptamines

4.5.3.1 5-MeO-DMT

5-Methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) is a potent hallucinogen closely related to bufotenine (5-hydroxy-*N,N*-dimethyltryptamine). It is also found in some toad species (Weil and Davis, 1994). Other than the fact that it is a potent 5HT2 antagonist (Gudelsky et al., 1994) and the fact that it is only effective when smoked, virtually nothing is known about its toxicology in humans.

4.5.3.2 α-Ethyltryptamine

Also known as Etryptamine and Monase, α-ethyltryptamine was first marketed in 1961 as an antidepressant under the brand name Monase®. It is classified as a reversible MAO-A inhibitor (Fredriksson et al., 2000), but it also causes neuronal serotonin release (Dulawa et al., 1998). Clinically unconfirmed laboratory studies have shown that α-ethyltryptamine can produce MDMA-like effects, in spite of the very substantial differences in molecular structure (Glennon, 1993).

Though apparently an effective antidepressant, α-ethyltryptamine was withdrawn from the market when evidence of neurotoxicity was detected. Illicit use, or at least toxicity resulting from illicit use, is extraordinarily rare. The literature contains one case report describing a 19-year-old woman who took two tablets of what she thought was MDMA. Within a few hours, the woman became disoriented, vomited, and collapsed. The principal autopsy findings were pulmonary edema and terminal aspiration. Epicardial petechiae were noted but almost certainly were the result of attempted resuscitation. The only drug detected was α-ethyltryptamine. The concentration in heart blood was 5.6 mg/L, with 2.4 mg/L in the vitreous, 18.3 mg/L in the liver, 24 mg/L in the kidneys, and 22 mg/L in bile (Morano et al., 1993). A second report describes a patient with a suicidal overdose. The quantity ingested was believed to be approximately 700 mg. The cause of death was malignant hyperthermia, and the postmortem blood concentration was 1.1 mg/L (Daldrup et al., 1986).

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4.5.4 Ergolines

4.5.4.1 Lysergic acid diethylamide

4.5.4.1.1 Introduction. Lysergic acid diethylamide 25 (LSD-25) belongs to the family of alkaloids. The term *ergot* refers to a fungal disease that affects both wild and cultivated grasses. Infection with one of the *Claviceps* species leads to the formation of hard, seed-like nodules instead of the normal seeds produced by the plants. In the Middle Ages, these nodules were referred to as "ergots," but they are properly referred to as sclerotia. Contained within the sclerotia is a group of indole alkaloids, collectively known as ergot alkaloids. Ergotism is a disease, now rarely encountered, that results from ingestion of the sclerotia or the chronic use of ergotamine-containing medications. The main symptom is intense vasospasm (Zavaleta et al., 2001). The most important of the alkaloids is *d*-lysergic acid. LSD is just one of many *d*-lysergic acid derivatives. The hallucinogenic agent lysergic acid amide, found in the morning glory (*Ipomea violcea*), is another. All of the ergot alkaloids act, with varying degrees of specificity, at α-adrenergic, dopamenergic, and serotonergic receptor sites (Dewick, 1998).

4.5.4.1.2 Chemical constants. Lysergide, or LSD-25, is 9,10-didehydro-*N,N*-diethyl-6-methyl ergoline-8β-carboxamide (Figure 4.5.4.1.2.1). The chemical formula is $C_{20}H_{25}N_3O$, and it has a molecular weight of 323.44. When crystallized from benzene, LSD forms pointed, prism-shaped crystals with a melting point of 80 to 85°C (Budavari et al., 1996).

4.5.4.1.3 History. Albert Hoffman synthesized LSD in 1938. At the time, he was a research chemist in the laboratory of Sandoz Pharmaceuticals in Basel, Switzerland, working on the chemistry of the ergot alkaloids. He had isolated lysergic acid from ergot and was in the process of combining it with various amides via peptide linkages. Hoffman's goal was to synthesize new compounds that lacked the toxic side effects of ergot but which still might have positive effects on the circulation. He succeeded in that goal when he synthesized Methergine® (methylergonovine), which is still used today to control postpartum hemorrhage. During the course of his experiments, Hoffman had synthesized a series of compounds related to lysergic acid. The 25th compound that he produced was lysergic acid diethylamide, now known as LSD-25.

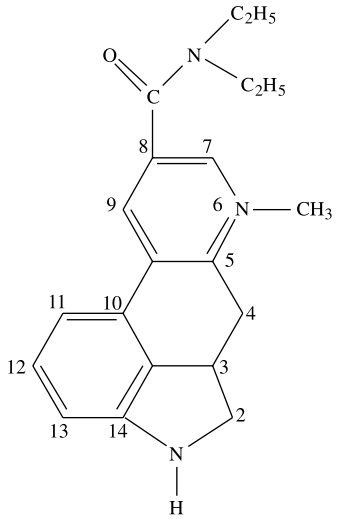

Figure 4.5.4.1.2.1 **LSD-25.** LSD-25 was produced by Albert Hoffman at Sandoz Laboratories. He had isolated lysergic acid from ergot, and was trying to make a chemical agent that would act as a circulatory stimulant. LSD-25 was the 25th compound that he produced.

When Hoffman first tested LSD-25 on animals, the results were disappointing, and he did no further research with LSD-25 for five years. However, in April of 1943, he began working with it again. He accidentally ingested some, and that accident led to the dawn of the modern "psychedelic" age (Hoffman, 1984; Ulrich and Patten, 1991). Sandoz eventually marketed LSD as a product called Delysid®. Psychiatrists were told to try it themselves, and they found out first-hand what the subjective experiences of a schizophrenic were like!

LSD was never a commercial success, but its availability fostered research into the chemical origins of mental illness. None of the theories proposed during the 1950s and 1960s proved to be correct, but they did lead to more modern research into the neurochemistry of schizophrenia. The theories also led to some rather bizarre experiments by the Central Intelligence Agency (CIA), which had became interested in the field of mind control. In pursuit of this end, the CIA mounted a special operation called MK-ULTRA. Prostitutes were used to lure businessmen to brothels, where they were surreptitiously dosed with LSD and their behavior observed. Although all the data about this episode are yet to be disclosed, it appears that no useful new information was generated, and the experiments were abandoned.

The psychedelic age began in the early 1960s when the late Timothy Leary, then a professor at Harvard, undertook his research with psilocybin. He eventually began to experiment with LSD, and was so transformed by his experiences that he stopped experimenting with psilocybin in order to concentrate on the effects of LSD. He gave LSD to some of his students, which resulted in his being forced to leave Harvard in 1962. However, even before he was fired from Harvard, Leary's anthem — "Tune in, turn on, drop out"— had been adopted by the media, and the psychedelic age was launched.

LSD became a scheduled drug in 1965, and at nearly the same time some dubious, unconfirmed studies were published purporting to show that LSD led to chromosomal damage. Decreased availability and fears about toxicity led to a rapid decline in use (Ulrich and Patten, 1991). In the late 1990s, interest in LSD seemed to renew, although reports of

toxicity remain rare. The emergency room component of the DAWN report contains 2096 LSD mentions during the first half of the year 2000, compared to nearly 50,000 mentions for marijuana (Garfield and Kissin, 2000). It is, however, very difficult to estimate the true frequency of use. Even when large doses of LSD are taken, the drug is difficult to detect. The standard dose of LSD today is much lower than during the psychedelic era, and only very small amounts of LSD appear in the urine (concentrations rarely exceed 2 to 3 ng/mL). Because LSD is not included on standard immunoassay screening panels, use estimates must rely on self-reporting, a notoriously unreliable methodology.

4.5.4.1.4 Incidence and epidemiology. No LSD-related deaths were listed in the Medical Examiner component of the most recent DAWN report (Kissin and Garfield, 2000). According to the government's Treatment Episode Data Set (TEDS), which combines data on all hallucinogens (LSD, DMT, STP, mescaline, psilocybin, etc.) into one category, hallucinogens as a group only accounted for 0.1% of admissions to drug treatment facilities in 1998. Those admitted were primarily males of high school and college age, and they were predominantly white (81%). Of the admissions, 51% were between 15 and 19 years of age, and 23% were between 20 and 24 years. Of the hallucinogen users, 86% reported abuse of drugs other than hallucinogens. Marijuana/hashish and alcohol were the drugs most commonly used (59 and 44%, respectively) (Anon., 2000).

4.5.4.1.5 Illicit production. Production of LSD demands considerably more skill than that required for methamphetamine, but it can be made in small, clandestine laboratories. Synthesis is possible from any one of a number of lysergic acid derivatives, including morning glory seeds or synthetic lysergic acid. Detailed instructions on how to harvest and grow ergot (*Claviceps purpurea)* can be downloaded from the Internet. The synthetic process involves potentially explosive solvents, and the investigation of possible clandestine LSD laboratories is a practice best left to individuals with specific training.

Only the *d*-isomer is psychoactive, but it undergoes isomerization at the C8 position. At equilibrium, 90% will be in the *d*- form and 10% will be present as *iso*-LSD (Salamone et al., 1997); *iso*-LSD is usually found as a contaminant in clandestinely produced LSD. And, because *d*-LSD is almost completely metabolized, urine may contain more *iso*-LSD than *d*-LSD.

Once synthesized, the standard practice is to add the LSD to absorbent blotter paper and then divide the paper into small squares, with each square constituting an individual dose. The average LSD content per square, in the year 2000, averaged between 20 and 80 μg (Nelson and Foltz, 1992). A recurring urban myth has it that children may be exposed to the drug when they apply water-soluble tattoos that are handed out at Halloween. In fact, such episodes of poisoning have never been documented.

4.5.4.1.6 Metabolism. Absorption is rapid and complete (Aghajanian and Bing, 1964). LSD is quickly and extensively metabolized in the liver (Lim et al., 1988), with only very small amounts ever appearing in the urine. At least five different metabolites are produced by humans. These include *N*-demethyl LSD (which is sometimes referred to as nor-LSD), 2-oxo-LSD, 2-oxo-3-hydroxy-LSD, 13-hydroxy-LSD, and 14-hydroxy-LSD (Reuschel et al., 1999). There is some dispute over which metabolite predominates. The results of the most recent studies suggest that 2-oxo-LSD is actually just an intermediate in the formation of 2-oxo-3-hydroxy-LSD, the latter being the metabolite found in the highest concentration in the urine (Reuschel et al., 1999).

4.5.4.1.7 Blood and tissue concentration. In the only recent study where substantial doses of LSD were given to volunteers (4 μg/kg), plasma concentrations of LSD peaked at just under .8 ng/mL approximately 1 hour after administration, then fell to zero after 24 hours (Reuschel et al., 1999). The findings of earlier studies suggested that LSD was detectable in plasma for a much longer period of time. In a 1991 study, when a 50-μg dose was given to a volunteer, LSD was still detectable in plasma, by immunoassay, 3 days after administration (Vu-Duc et al., 1991). In 14 emergency room patients with suspected LSD intoxication, LSD concentrations in plasma collected between 2 and 11 hours after ingestion ranged from 0.2 to 7.7 ng/mL (McCarron et al., 1990).

4.5.4.1.8 Testing. After a 50-μg dose, urinary LSD concentrations drop below the 200-μg cutoff in less than 24 hours. Thus, the window for detection is very short. That may explain why LSD testing is not carried out in federally regulated workplace programs, although it is a part of military testing, where urine specimens are not considered to be positive for LSD unless a minimum concentration of 200 pg/mL is present.

When LSD testing is carried out, specimens are screened first with an immunoassay. Assay kits capable of accurately detecting LSD concentrations as low as 0.5 ng/mL are available, but the detection of LSD is complicated both by its nonvolatile nature and by its very low concentrations (Maurer, 1998). For that reason, hair may prove to be a better analyte. LSD accumulates in the hair of chronic users, with concentrations in the range of 8 to 17 pg/mg being reported (Sachs and Kintz, 1998), but concentrations as low as 1 pg/mg can reliably be detected (Rohrich et al., 2000).

Another reason hair may be preferable for testing is the relative instability of LSD in stored urine specimens. Photo degradation occurs if the samples are exposed to sunlight; only 10% can be recovered after 13 hours' exposure. Samples stored in fluorescent light decay more slowly, but values still fall to less than 50% of the initial concentration after two weeks. Urine stored in opaque containers is stable at 25°C for a month, but the loss is much greater at higher temperatures (Reuschel et al., 1999).

4.5.4.1.9 Clinical syndromes. Both LSD and mescaline (a different class of hallucinogen) share a common mechanism of action in that their ability to cause hallucinations correlates directly with their ability to bind to 5HT2 receptors (Aghajanian and Marek, 2000). Changes in pulse rate, respiration, and blood pressure occur, but these may just be secondary to anxiety induced by perceptual changes (Klepfisz and Racy, 1973). Reports in the literature suggest that panic attacks are relatively common, but that frank psychotic episodes are not (Blaho et al., 1997). "Acid flashbacks," though widely publicized, also appear to be uncommon. When formal neuropsychological testing is performed, few, if any, sequalae can be attributed to LSD use (or to the use of any other hallucinogen, for that matter) (Halpern and Pope, 1999).

Because LSD is usually sold impregnated in blotter paper, the likelihood of massive overdose is small, though a cluster of eight cases was reported more than a quarter century ago (Klock et al., 1975). Eight patients "snorted" LSD-tartrate powder that they thought was cocaine. Emesis and collapse occurred, along with signs of sympathetic overactivity, hyperthermia, coma, and respiratory arrest. Half of the patients became hyperthermic. Mild generalized bleeding occurred in several patients, and all eight had evidence of platelet dysfunction (like brain, platelets are rich in 5HT2 receptors). Serum and gastric concentrations of LSD tartrate ranged from 2.1 to 26 ng/mL and 1000 to 7000 μg/100 mL, respectively. Even though five of the eight victims required intubation and ventilatory support, all recovered within 12 hours.

Hyperthermia has been reported in other LSD users who have not taken massive overdoses (Bakheit et al., 1990; Behan et al., 1991, 2000; O'Halloran and Lewman, 1993). Histologic examination of skeletal muscle from some of these individuals showed gross swelling with pale, enlarged individual fibers. Some of the cells showed abnormal vacuolation, but the most striking histologic feature was the presence of intense contraction bands separating segments of swollen myofibrils (Behan et al., 2000). The mechanism for these changes is unclear, but in animal studies the administration of 5HT2 blocking agents completely prevents the hyperthermia associated with serotonin toxicity (Nisijima et al., 2001), suggesting that the entire process is centrally mediated.

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chapter five

Opiates

5.1 Incidence

Medical examiners participating in the federally sponsored Drug Abuse Warning Network (DAWN) program reported 8295 narcotic analgesic-related deaths in 1999, a 49% increase from the 3403 narcotic-related deaths reported in 1990 (Kissin et al., 2000). Heroin toxicity still accounts for nearly half of all narcotic-related deaths (42%), compared to one-third in 1990, and for 41.3% (4820/11,651) of all reported drug-related deaths. Toxicity from the other opiates occurred much less frequently than from heroin, although there have been some important changes since publication of the last edition of this book. Hydrocodone mentions have increased tenfold, and fentanyl, which did not rate a mention previously, was responsible for 53 of the deaths reported to the federal government. Table 5.1.1 lists the other agents that were included in the 1999 DAWN report.

Table 5.1.1 Deaths from Narcotic Analgesics in 1999 DAWN Report

Drug	Number of Mentions	Percentage of Mentions
Heroin/morphine	4820	41.4
Codeine	1395	12.0
Methadone	643	5.5
D-propoxyphene	466	4.0
Hydrocodone	447	3.8
Meperidine	103	0.9
Fentanyl	53	0.5
Hydromorphone	46	0.4
Oxymorphones	15	0.3

Note: A total of 17,898 drug-related deaths were reported in the DAWN survey for 1993. Of these, 3556 (19.8%) were due to cocaine and 3470 (19.3%) were due to heroin. No significant change was seen in the number of deaths attributed to other narcotic agents (511).

5.2 Epidemiology

In the first half of 2000, 292,098 drug-related emergency room visits were reported. Heroin/morphine was the third most frequently mentioned illicit drug, accounting for 47,008

mentions, or 16% of all drug-related emergency room visits. In 1988, the number of heroin-related visits for the entire year was only 38,063; the incidence of heroin-related illness has more than doubled in the last 10 years.

According to the 1998 National Household Survey on Drug Abuse, the prevalence of heroin use remains quite low, with less than 1% of respondents reporting that they had ever used the drug. Still, that amounts to approximately 2.4 million people who have taken heroin at least once within their lifetime. Only one-tenth of that number (253,000) reported active heroin use in the previous year, and 130,000 admitted to current use. By comparison, 11% of the population surveyed reported using cocaine at least once, with 2% having used cocaine in the last year and 1% admitting to using cocaine regularly. Heroin users are more likely to be men than women, and blacks are more likely than Caucasians and Hispanics to report having experimented with the drug at least once. Those aged between 12 and 25 were more likely to report use of heroin within the past year (Greene et al., 2000). These prevalence rates must be interpreted with a great deal of caution, as there is wide variation from region to region.

5.3 *Classification of narcotic agents*

Toxicity may be due to (1) direct effects of the drug or its metabolites, (2) direct effects of adulterants or expients injected along with the drug, or (3) infectious, mechanical, or lifestyle complications associated with the practices of drug abusers. Earlier schemes classified opiates on the basis of their source, as naturally occurring (morphine or codeine); semisynthetic, morphine-based (heroin or hydromorphone); semisynthetic thebaine-based (oxymorphone or oxycodone); or purely synthetic (meperidine or pentazocine) (Inturrisi, 1982).

This classification, while possibly of some interest to forensic chemists, does little to explain the mechanisms of toxicity. Others classify members of these groups as being opiates or opioids; the term *opiates* being reserved for peptides derived from the morphine molecule that stereospecifically bind to opioid receptors. The term *opioids* is used to describe nonpeptide agents that bind at the same receptor sites. These include morphinans typified by butorphanol, the benzomorphans such as pentazocine, the 3,5-diphenylamines including methadone, and phenylpiperidines, especially meperidine. The most useful way to classify these drugs is by their pattern of receptors binding.

5.3.1 *Opiate receptors*

The body produces endogenous pain-relieving substances with molecular structures similar to that of morphine. These substances, endorphins or enkephalins, along with exogenous opiates, such as morphine, bind to opioid receptors located in the brain and throughout the body. Depending on which receptor is activated, the result may be, among other things, analgesia, dysphoria, or respiratory depression. Since earlier editions of this text, most of the human opiate receptors have been cloned and can be expressed in tissue cultures, thereby allowing *in vitro* studies to clarify the drug–receptor interaction. More recently, and more importantly, mice lacking opioid peptides or receptors have been generated by homologous recombination (genetic knockout mice). The chemical and immunohistochemical localizations of receptors, as well as their quantitations, are now feasible, even in postmortem material (Gabilondo et al., 1994; Wehner et al., 2000a,b; Schmidt et al., 2001). These advances are likely to bring about radical changes in the way that drug-related deaths are investigated.

Three basic classes of opioid receptors have been discovered, and each of the main receptors has multiple subtypes (Table 5.3.1.1). Three types of μ (mu) receptors are recognized, each with different functions and, perhaps, different modes of action. They have been given Greek names based on the types of drugs that bind to them. The μ receptor is so named because morphine binds to it. Other molecules that bind at this same site are called μ agonists, not only because they bind to the same receptor, but also because they cause the same effects as morphine. The pain relief and euphoria produced by morphine administration are a consequence of μ receptor binding; knockout mice without this receptor get no pain relief even after massive doses of morphine, nor do they experience respiratory depression. Conversely, knockout mice without δ (delta) and κ (kappa) receptors experience normal analgesia, proving that the δ and κ receptors play no role in supraspinal analgesia (Kieffer, 1999).

Delta receptors are responsible for spinal anesthesia. Even in mice lacking the *MOR* gene (it appears that all three μ receptor subtypes are encoded by the same gene), δ agonists such as deltorphin II still produce analgesia, though not quite as much as when μ receptors are present, indicating that there is "crosstalk" between μ and δ receptors (Matthes et al., 1998).

The function of κ receptors is far less clear. Unlike δ receptors, they do not appear to interact with μ receptors, at least not to any significant degree (Rothman, 1993). However, mice lacking the gene for κ receptors (*KOR*) seem to have less severe withdrawal symptoms than normal animals, suggesting that κ receptor activity changes with long-term opiate abuse (Kieffer, 1999).

In experimental animals, chronic treatment with morphine leads to a decrease in the number of neuronal μ receptors (Werling et al., 1989), and it has long been suspected that a similar situation occurs in humans. However, if such a process does occur, it does so very selectively. Controlled immunohistochemical studies of μ receptor expression in the frontal cortex (Broadman's area 10), caudate nucleus, and thalamic nuclei have found no difference between drug-free controls and chronic heroin users dying of drug overdose (Gabilondo et al., 1994; Garcia-Sevilla et al., 1997; Schmidt et al., 2001).

5.3.2 *Opiate and G proteins*

Opioid receptors chiefly mediate their cellular effects by activating members of a very large and diverse family of G proteins. What happens after coupling occurs in a given cell type seems to depend more on the profile (stoichiometry) of the G protein present in that cell than on the type of opioid receptor present on the cell membrane. These observations suggest that earlier ideas about specific opioid receptors coupling preferentially to one type of effector rather than another are outdated (Connor and Christie, 1999). In individuals not chronically exposed to morphine, a single dose of any opioid acts to inhibit adenyl cyclase activity and decrease cellular concentrations of cyclic adenosine monophosphate (cAMP). Similar reductions in cAMP are not seen in heroin addiction; in fact, just the opposite occurs (Escriba et al., 1994; Hashimoto et al., 1994; Shichinohe et al., 1998). The increases in cellular levels of cAMP appear to be the result of increased concentrations of specific G proteins (Escriba et al., 1994), but the degree of changes seems to depend on where in the brain the measurements are made (Buttner et al., 2000).

Other effector mechanisms are possible. The μ_3 receptor has a much greater affinity for the morphine metabolite, morphine-6-glucuronide (M6G), than for morphine; its activation facilitates nitric oxide production and release (Fimiani et al., 1999). Nitric oxide receptors are widely distributed throughout the body, and their presence is not confined

to central nervous system (CNS) neurons. Opiate-facilitated nitric oxide production clearly plays a role in bronchodilation (Fimiani et al., 1999; Zebraski et al., 2000) and immune function (Makman et al., 1998). Additional functions are likely to be identified in the near future.

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5.4 History of opiate abuse

5.4.1 Origins in antiquity

Opium poppies can be seen on coins and in drawings that antedate written mentions in the Greek literature by at least 1000 years (Kritikos and Papadaki, 1967). Homer and Hesiod discussed the medicinal merits of poppies, and writings from the classical period of ancient Greece frequently mentioned the same subject. In Greece, the poppy was called *opion*, a term derived from the word for "juice" (*opos*). Translated into Latin, *opion* becomes *opium*. For the ancients, the poppy symbolized sleep, occasionally everlasting. The cup given to Socrates contained the standard solution used at the time for purposes of euthanasia and suicide: a mixture of hemlock and opium. Opium was known but used sparingly in Europe during the Middle Ages, possibly because medieval surgeons seemed to have been largely indifferent to the suffering of their patients (Kramer, 1979).

5.4.2 Introduction to Europe and Asia

During the Renaissance, the popularity of opium increased. This was partially due to the efforts of Philippus Aureolus Theophrastus Bombast von Hohenheim, a.k.a. Paracelsus (1490–1540). Paracelsus recognized that, no matter what the cause of a disease, sleep and pain relief were part of the cure; thus, Paracelsus medicated his patients with formulas that contained opium. He prescribed opium in a host of different formulations, calling one of the formulations *laudanum* (from the Latin for "something to be praised"). Laudanum was comprised of one-fourth opium, to which was added henbane juice, crushed pearls and coral, "bone of the heart of a stag, bozar stone, amber, musk, and essential oils." As an alternative preparation, Paracelsus used opium in combination with orange and lemon juice, frog sperm, cinnamon, cloves, ambergris, and saffron (Macht, 1915). Somewhat more streamlined versions of laudanum were used well into the 19th century (Lewin, 1931). In much the same way that Freud later enthusiastically recommended the use of cocaine as a panacea (Freud, 1884), Sydenham (1624–1689) argued that opium was the drug of choice for a range of conditions, not all of them painful (Sydenham, 1848). Thomas Dover, a ship's doctor and one of Sydenham's students, earned his place in history for two contributions: he rescued the real Robinson Crusoe, and he created a powdered opium formulation that became an immensely popular home remedy. Dover's Powder was still used in the early 1900s.

Medical writers began to discuss opiate toxicity as early as 1700. Terry quotes an English physician who claimed to have successfully separated opium's "noxious Quality" from its "palliative" and "curative" actions, thereby avoiding the complications associated with excessive opium use. That physicians over relied on opium should not be surprising: opium worked. It improved the conditions for which it was prescribed. It relieved pain, calmed stomachs, and suppressed coughs. Until the 20th century, such efficacy could be claimed for few other drugs. Because opium was widely available and widely used, it was inevitable that many people would become addicted (Haller, 1989).

In 1803, Sertürner began his experiments with opium, trying to separate its components. In 1805, he published a report announcing that he had isolated an alkaline base in opium called *morphium*. He continued his research on morphium for many years, frequently using himself as a subject; at one point, he nearly died of an overdose. His discovery of morphine was certainly important clinically, but his discovery also marked a sea change in the way chemists thought about the chemicals contained in plants. Prior to the discovery of morphine, it was universally held that plants could only produce

products that were acid or, at most, neutral. It was believed that only metallic compounds could be alkaline. Sertürner's discovery changed all of that. In relatively rapid succession, hundreds of other potent plant alkaloids, including quinine and cocaine, were isolated (Macht, 1915). Commercial morphine production began not long after the isolation of morphine. The founder of England's Royal Pharmaceutical Society, Thomas Morson, started refining and selling morphine in 1821. Merck of Darmstad began wholesale production at about the same time (Berridge, 1987).

Addiction and abuse were major problems by the dawn of the nineteenth century, although there is some evidence to suggest that morphine addiction (as opposed to opium eating) may not have been all that widespread (Kramer, 1979). Patent medications such as Dover's Powder and other "cordials," "carminatives," or "soothing syrups" were nothing more than tincture of opium combined with flavorings and ample amounts of alcohol. Case reports describing "morphia" toxicity were being published with some regularity by the late 1830s.

Perhaps because he was an active proselytizer for opium consumption, the best-known addict of that period was De Quincy. He had first used opium to treat a toothache, but he rapidly developed a formidable habit. At one point, he was consuming more than 20 grams (not grains) per day (De Quincy, 1821). While he was only one of many addicts to be found within London's artistic community, he was the most vocal advocate of opium, having written, among other things, that "happiness might now be bought for a penny, and carried in the waistcoat pocket." De Quincy's *Confessions of an English Opium Eater* was first published in 1821, and a revised, considerably enlarged second edition was published 1856. That same year, Elizabeth Barrett Browning published her acclaimed narrative poem, *Aurora Leigh*. Although Browning was also addicted, and the poem was highly autobiographical, she never argued that much good came from the habit (Bishop, 1994). This probably explains why De Quincy's name is synonymous with drug use and Browning's is not.

Opium was introduced into China by Arab traders during the Tang Dynasty (618–907 A.D). At first, the Chinese used opium only for medicinal purposes. The Pen Tsao Kang Mu, a *materia medica* published in 1590, nearly 1000 years after opium was first introduced into China, makes absolutely no mention of addiction or abuse (Way, 1982). Opium was only taken orally, and then only for treatment of pain and diarrhea. Opium smoking, which probably originated in Java, began nearly a millennium later. The first mentions of opium smoking in China are from the 16th century, occurring at just about the same time that the Portuguese were introducing tobacco to the Chinese. Over the next two centuries, the popularity of opium smoking steadily increased. In 1880, for reasons having more to do with an increasing balance of trade deficit than concerns with abuse, Emperor Chin Ching banned opium importation. The East India Company ignored the ban and continued to smuggle large amounts of opium into China. In 1839, the Chinese government finally decided to take active measures against opium importation. The measures prompted England to declare a war that China quickly lost. Customs figures from 1881 show that opium imports into China were in excess of 6 million kg per year, enough to supply 1 million smokers. In spite of numerous conventions and treaties, addiction remained a major problem in China until the habit was suppressed by Mao Tse-tung in the early 1960s.

Striking historical parallels in the evolution of opium and cocaine abuse can be seen. Thousands of years of coca leaf chewing in South America caused few social, and no detectable, medical problems for the Incas. However, as soon as purified cocaine became widely available in Europe, the amount of cocaine used increased greatly. As the amount

used increased, so did toxicity (Karch, 1989). Taking small amounts of opium orally was medically effective and, at worst, a benign indulgence. Much of orally administered opium is inactivated on its first pass through the liver, so this route of ingestion has some built-in safeguards. Smoking opium is another matter entirely. When smoked, much more morphine gets into the body, blood levels rise more quickly, and no "first-pass" effect occurs. The net result is that when opium is smoked the dosage is effectively multiplied. Not surprisingly, serious toxicity and addiction resulted.

Chinese laborers are said to have introduced opium smoking into the U.S., but opium was already popular in America long before the Chinese immigration. In 1844, the New York City coroner held six inquests regarding opium-related deaths, and 23 inquests on deaths related to laudanum (Woodman and Tidy, 1877). According to U.S. Government figures, over 5 million tons of opium were imported into the U.S. from 1850 to 1877. This figure does not take into account opium smuggled in to avoid taxation, or opium cultivated domestically. Opium was produced in California, Arizona, and the New England states (Brecher, 1972). Like their European counterparts, American physicians could not have practiced without opium. A survey done in Boston in 1888 disclosed that of 10,000 prescriptions dispensed by 35 pharmacies, 15% contained opium and 78% contained opiates (Way, 1982). Whatever the problems associated with opium abuse, they very likely would have been manageable had the hypodermic syringe not become available in the 1870s, and had heroin not been introduced at the turn of the century.

5.4.3 Invention of the hypodermic syringe

In 1855 a Scottish physician, Alexander Wood, published an account of his experiments injecting people with opium (Wood, 1855). He injected tincture of opium, and although his original intent was to achieve something akin to a nerve block, he quickly realized that injected morphine was being carried throughout the body. In the course of his experiments, Wood managed to addict his wife to intramuscular morphine. She probably was the first woman to die of an injected narcotic overdose (Terry and Pellens, 1928).

Wood may have received most of the credit, but the idea of injecting people with narcotics had been around for hundreds of years before he was born. Christopher Wren, the famous architect and professor of astronomy at Gresham College, Oxford, was also a physician. According to the history of the Royal Society, Wren injected dogs with intravenous opium in 1656. Using a quill attached to a small bladder, he injected lean animals with easily visible veins. No fatalities resulted. Wren was so encouraged by his preliminary studies that the following year he tried the same experiment on a man. An ambassador to the Court of St. James volunteered the services of a "delinquent servant." The volunteer was injected with an emetic, which made him faint. Other experiments were even less successful, and this area of research was ignored for nearly 100 years (Terry and Pellens, 1928).

Wood's publication prompted others to experiment with the parenteral injection of many different drugs, but narcotics attracted the most interest, and injection of narcotics soon became standard practice. Hypodermic syringes were said to have been in great demand and short supply during the U.S. Civil War (Figure 5.4.3.1) (Billings, 1905), although the shortage could not have been all that severe, as many of the veterans became addicts. Addiction was slower to evolve as a problem in America than in Europe, but by the 1870s "morphinism" was rampant in both the Old and New Worlds. The lag time may have been partially due to the fact that hypodermic injection did not catch on as quickly in the U.S. as in Europe.

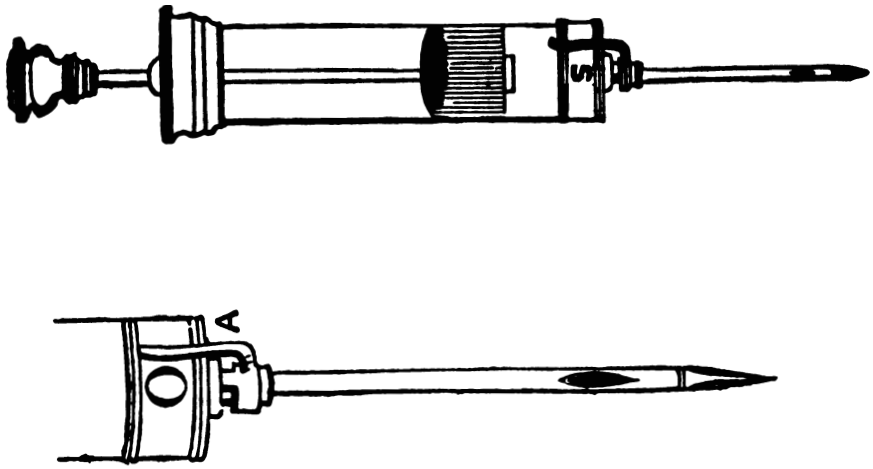

Figure 5.4.3.1 **Hypodermic syringes.** Commercial production of syringes began just before the Civil War. Initially, opiates were injected only subcutaneously. The intravenous injection of morphine and heroin did not become common practice until the 1920s. (Courtesy of the National Library of Medicine.)

Even though addiction was common, neither the mechanism of opiate action nor the process of addiction was even remotely understood. It was widely thought, for instance, that using morphine injections, as opposed to "eating opium," minimized the probability of addiction (Anstie, 1868; Howard-Jones, 1972). Accordingly, treatment modalities for addiction were simplistic to the extreme. Freud's paper *Über Coca*, published in 1884 (Freud, 1884), reflects the thinking of many during that period. Because the effects of cocaine seemed to be so opposite to those of morphine, Freud concluded that cocaine would be a logical treatment for "morphinism." Some prominent physicians, including Erlenmeyer (1885), disagreed, but Freud's notions were widely accepted, and a large group of patients became addicted simultaneously to cocaine and morphine. It is only quite recently, since the discovery of opiate receptors and neurotransmitters, that rational approaches to narcotics addiction have been formulated.

5.4.4 Synthesis of heroin

The other key development in the history of narcotic addiction was the synthesis of heroin. In 1874, C.R. Wright, a researcher at St. Mary's Hospital in London, boiled anhydrous morphine with acetic anhydride and produced a series of acetylated morphine derivatives (Eddy, 1953). One of the derivatives was diacetyl morphine (although the nomenclature was different at the time). He sent samples to an associate at Owens College, London, who assayed the substance for biological activity. The ability of the drug to decrease respiratory rate and blood pressure was quickly noted. For reasons that are not clear, the discovery created very little interest. In 1898, Strube published a paper outlining his favorable results when he had used heroin to treat patients with tuberculosis. He found that the drug effectively relieved severe coughs and allowed patients to sleep. Perhaps more important, he claimed to have observed no ill effects (Strube, 1898). The Bayer Company in Eberfeld, Germany, began commercial production of heroin in 1898 (Figure 5.4.4.1).

Figure 5.4.4.1 **Heroin.** First marketed as a cough suppressant and recommended for the treatment of tuberculosis. Bayer began selling heroin in 1898. The name *heroin* derives from the German for "great" or "heroic." (Courtesy of the National Library of Medicine.)

Bayer had been producing pharmaceuticals since 1889, but the really profitable market for alkaloids (morphine, quinine, cocaine) was largely dominated by other companies such as Merck, Knoll, and Boehringer. Bayer's lead chemist, Felix Hoffman, synthesized heroin on August 21, 1897, just two weeks after he produced aspirin! Bayer pharmacologists began experimenting with both codeine and heroin, carrying out a number of tests on themselves, animals, and their employees. The Bayer chemists concluded, quite mistakenly, that heroin produced less respiratory depression than codeine. Based on those findings, Bayer began production, marketing heroin as a safer, more potent, cough suppressant (Figure 5.4.4.2) (deRidder, 1994).

Whatever the medical profession believed about it, heroin was warmly received by the underground. By 1920, heroin addiction was such a problem that the American Medical Association (AMA) House of Delegates voted to prohibit its importation, manufacture, and sale. Legitimate heroin production in the U.S. ceased after 1924, although low levels of illegal imports persisted. Interestingly, it seems that no one thought to inject heroin intravenously until the early 1920s. The dating is suggested by the fact that the first report describing typical track marks was not published until 1929 (Biggam, 1929). The outlawing of production, along with international treaties and conventions, but most especially the advent of World War II, led to sharp reductions in clandestine imports. In 1950, fewer than 40 heroin seizures were reported within the U.S.

Interest in heroin resurfaced with the advent of the Vietnam War but was temporarily eclipsed by a general disinterest in sedative hypnotics and a superimposed cocaine pandemic. Heroin use, at least when judged by the amount of illicit heroin now being confiscated, is again increasing. In 1990, narcotic analgesics accounted for 57% of all reported

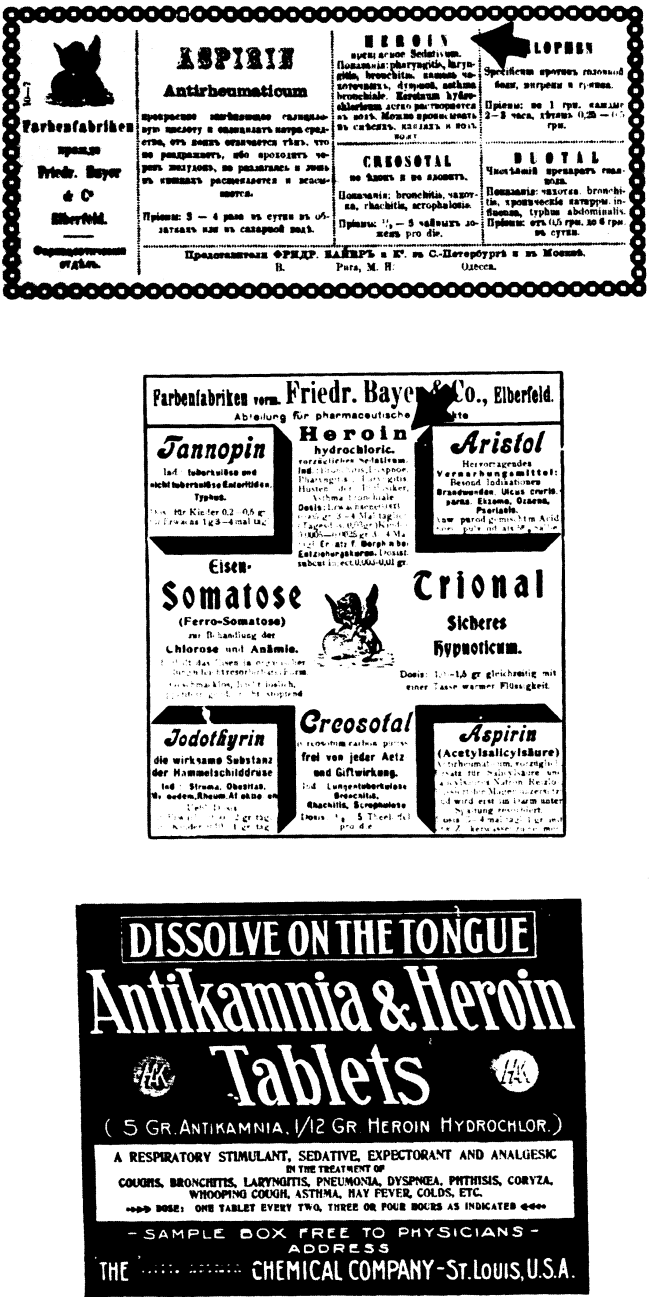

Figure 5.4.4.2 **Heroin.** Because of their effectiveness, heroin and heroin-containing products were not difficult to market. Many different formulations were sold in Europe and in the U.S. (From Kritikos, P. and Papadaki, S., *Bull. Narc.*, 19(4), 5–10, 1967.)

drug-related deaths, with 1976 of the deaths directly attributable to heroin abuse. By 1998, the total number of deaths attributable to analgesic abuse had risen to 7259, with 4330 attributable to heroin alone (Kissin, 2000).

5.4.5 *The first pathology studies*

The first autopsy describing both cerebral and pulmonary congestion was that of a New Yorker who died of laudanum overdose. It was reported by a Dr. Lee in 1852 (Woodman and Tidy, 1877). Autopsy findings in a second narcotic overdose were published in 1862. A young woman drank "gin mixed with a shilling's worth of laudanum." She quickly became comatose and intense meiosis was noted. Autopsy disclosed cerebral congestion; however, the lungs were unremarkable (Slayter, 1862). A forensics text from 1877 mentions that "congestion of the lungs and of the vessels of the brain" are typically seen in opiate-related deaths but cautioned that the findings at autopsy were "neither certain nor characteristic" (Woodman and Tidy, 1877). Understanding of the problem advanced very little until Halpern and Rho (1966b) published their paper, "Deaths from Narcotism: Incidence, Circumstances, and Postmortem Findings." In addition to carefully describing the epidemiology of the disease, the authors systematically described all of the signs that have come to be classically associated with narcotism, including pulmonary edema, portal adenopathy, and track marks. Since then, opiate receptors have been discovered, and other disorders such as heroin-associated nephropathy (Rao et al., 1974) and leukoencephalopathy (Wolters et al., 1982) have been described. Nonetheless, our basic understanding of the pathologic changes produced by narcotic abuse have advanced very little. During the time that has elapsed since the first edition of this book, fewer than a dozen histologic or anatomic studies of narcotic abuse have been published!

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5.5 Cultivation and manufacture

5.5.1 Botany

The Drug Enforcement Agency (DEA) estimated that in 1999 worldwide, opium production totalled 3080 tons, enough opium to produce more than 300 tons of refined heroin (DEA, 2000). From the end of World War II until the late 1980s, opium production was confined to two primary areas: Southeast and Southwest Asia. Government experts now recognize four distinct opium-producing areas: Southeast and Southwest Asia, South America, and Mexico. Sometime during the early 1990s, South American cocaine cartels began cultivating poppies in remote, mountainous regions of northwestern Mexico, Colombia, Venezuela, and Guatemala. Mexican opium production began at about the same time. Mexican heroin is almost always of the distinctive "black tar variety." Table 5.5.1.1 lists opium production by country.

Mexican output reached substantial levels by the early 1990s, and "black tar" Mexican heroin now accounts for most of the market in California and the Western U.S. By the beginning of 1998, most of the heroin seized by U.S. authorities had its origin in Colombia

Table 5.5.1.1 Worldwide Opium/Heroin Production

Area	Tonnage
Southeast Asia	
Burma	1090
Laos	140
Thailand	6
Southwest Asia	
Afghanistan	1670
Pakistan	37
Latin America	
Colombia	75
Mexico	43

Note: Table is based on figures provided by the Drug Enforcement Agency (DEA, 2000). Approximately 10 tons of morphine are required to produce one ton of heroin.

and Mexico; 65% came from South America and 17% from Mexico (Tichacek and Napolitano, 1999), with Southeast and Southwest Asian heroin largely disappearing, even from the east coast, where it traditionally accounted for most of the heroin supply.

Opium production has also begun in the Central Asian republics of the former Soviet Union. The old Silk Road running from Europe to China has been resurrected, except now opium, not silk, is bartered. Opium produced in Afghanistan is smuggled into Tajikistan and Uzbekistan, where it is either refined locally into heroin or sent on to Russia for further refining. Most of the Silk Road production appears destined for Europe, with European heroin seizures having increased from 8 tons in 1993 to over 16 tons in 1994 (Specter, 1995). Growing conditions in all four areas share common characteristics, though very little specific information is available about Central Asian production.

The Papaveraceae family is comprised of 42 genera and approximately 650 distinct species. Just how they should be divided is a matter of some dispute, and at least six different classification schemes have been proposed. *Papaver somniferum* is the most commonly cultivated "opium" poppy, but the wild growing *Papaver setigerum* also contains significant amounts of morphine. Over the years, many hybrids have been developed, but describing a generic "poppy" is difficult, if not impossible. Flowers may be single or double, with variation in both shape and color. Blossoms may be white, red, pink, purple, crimson, or many shades in between. The capsules, from which the juice is extracted, also vary in shape and alkaloid content. A plant can have two, three, or more capsules. Height is also variable and may range from 30 to 150 cm or more (Kapoor, 1995).

The poppy is an annual plant, with a three- to five-month life cycle. This means that, even though the poppy can be cultivated almost anywhere, only one crop per year can be grown in areas with distinct hot and cold, or wet and dry seasons. Poppies cannot be grown in areas subject to frost. The more moderate climate to be found in many parts of Latin America permits year-round cultivation, an advantage that has not gone unnoticed by heroin producers.

When grown in humid regions, the poppy is vulnerable to infection by fungal and plant parasites. Poppies grow well in average soil, but the soil requires treatment with manure or chemical fertilizers. Plants take two to three weeks to germinate and two

months to fully develop. After a field has been weeded and thinned out, as many as 15 plants can be grown in a square meter. After the plant flowers and the petals have fallen off, the capsule continues to ripen for another two weeks, at which time the latex can be harvested. The entire cycle takes less than three months.

Traditional harvesting is a two-step process. First the capsule is incised, allowing the sap to run out and then solidify. Twelve hours after the capsule has been incised the latex is harvested. Incising the capsule is a delicate operation: if the incision is too deep, the latex will run down the inside of the plant and be lost to harvest. Farmers prefer to do the incising at sunrise or sunset. That allows the latex to exude and solidify for 8 to 14 hours. The caked latex can then be scraped off the capsule using a dull blade; however, by the mid-1970s, traditional harvesting techniques had largely been replaced by the use of opium "straw." Instead of collecting resin from the sides of the capsule, the entire plant is dried and processed. Today, most morphine is produced by processing "straw," and very little is manufactured from resin (NCB, 1998).

The yield per acre depends on many variables. Historically, the yield in Turkey and the Mediterranean is said to be 10 kg of opium per hectare. Yields in India are said to be higher, on the order of 30 kg per acre (Kapoor, 1995). Yields in the newer fields being established in South America and in the Central Asian republics have yet to be determined, but it seems likely that they are intermediate, between the high yields reported from India and the much lower yields reported from the Mediterranean countries.

Over 20 different alkaloids have been identified in opium, but only three are of any significance: morphine, codeine, and thebaine. Thebaine has almost no morphine-like activity of its own, but it can be used to manufacture other narcotic agents. Hundreds of semisynthetic derivatives, referred to as Bentley compounds, have been synthesized from thebaine, and many of these do have narcotic effects. A few of the derivatives, such as etorphine, have 1000 times the activity of morphine. Morphine is the principal alkaloid found in opium. It constitutes between 8 and 19% of air-dried opium. Reported ranges for codeine content are from 1.25 to 3.4% (Anon., 1963). Poppy straw, depending on the country or origin, may have a morphine content of anywhere from 0.34 to 1.3%, mainly in the mature capsules of the plant and in the upper part of the stem (NCB, 1998). The amount of poppy straw used each year for alkaloid extraction is on the order of 30,000 tons.

Poppy seeds sold for cooking and baking purposes may contain very substantial amounts of morphine and codeine. In one study, the morphine content was found to be anywhere from 7.3 to 60.1 μg/g of seed, while the codeine content ranged from 6.1 to 29.8 μg/g (Pelders and Ros, 1996). Even commercial poppyseed fillings, used to make pastries, have high alkaloid contents. Concentrations in the range of 17.4–18.6 μg/g (morphine) and 2.3–2.5 μg/g (codeine) have been reported in different lots of the filling. Morphine concentrations as high as 4.5 mg/L have been reported after eating these fillings, and large amounts of morphine may persist in the urine for several days after ingestion (Cassella et al., 1997).

5.5.2 Manufacture

Heroin can be manufactured directly from opium, from semipurified morphine, or from poppy straw. The route utilized depends mostly on the availability of the precursors. Morphine and opium are both sold on the illicit market, and the availability of one or the other depends largely on local conditions, although over the last few decades opium straw has been increasingly used as the starting material for opiate production. Extract derived from poppy straw has a morphine content that ranges from 40 to 80%.

The clandestine separation of morphine from crude opium involves three separate steps. A kilogram of opium is dissolved in 2 L of water along with 200 g of lime, and the resultant solution is poured through a coarse filter. Then, 250 g of ammonium chloride are added to the filtrate, causing the morphine base to slowly precipitate out. The morphine is collected on a fine cloth filter and then washed with water. The crude morphine is mixed with charcoal, and with either hydrochloric or sulfuric acid. The mixture is filtered, and ammonium hydroxide is added to the filtrate, causing purified morphine to precipitate out. The precipitate is collected by filtration and allowed to dry in room air.

In the second phase of production, the dried morphine is added to acetic anhydride, and the mixture is refluxed at a constant temperature for 5 hours. After the mixture has been allowed to cool, it is neutralized with sodium carbonate. The crude heroin that precipitates out is filtered and washed with water. Illicit heroin production can be, to some extent, gauged by demand for acetic anhydride, the key agent in conversion from morphine to heroin. Multi-ton seizures of this compound are not uncommon. In one case, reported to the International Narcotics Control Board, 46 tons of acetic anhydride were smuggled across the border from China into Pakistan. Because the uses of acetic anhydride are so well known, and because sales are tracked by governmental authorities, alternative agents have been used. In the past, ethylidene diacetate was used by Southeast Asian producers. More recently, it has been reported that acetyl chloride was being substituted for anhydride at clandestine laboratories in India (INCB, 1999).

In the final stage of production, heroin is purified by redissolving the crude heroin in boiling water that contains citric acid and charcoal. The mixture is filtered and purified, and heroin is precipitated by the addition of sodium carbonate. If the lab wants to produce the hydrochloride form instead of heroin base, the heroin is redissolved in acetone, and hydrochloric acid is added to the solution.

Depending on market demand, clandestine chemists sometimes synthesize morphine instead of opium. Production begins by dissolving 1 kg of opium in 2 L of water and adding 200 g of slaked lime, 500 mL of alcohol, and 500 mL of ether. The resultant solution is then filtered through a cloth, leaving crude morphine on the cloth. This material is further purified and decolorized by refluxing it with 2 L of dilute sulfuric acid and 250 g of charcoal for about half an hour. This solution is then filtered, and ammonium hydroxide is added to the filtrate. The off-white, semipurified morphine that precipitates out is then air dried, and the hardened dried morphine granules are rubbed against a hard surface to produce a powder (Narayanaswami, 1985).

Clandestine laboratories synthesizing methadone have been reported in the past, but at present fentanyl and its analogs are the only narcotics synthesized clandestinely, and then not very often. The infrequency of this occurrence probably has to do with the fact that the synthesis of fentanyl is more difficult than that of other illicit chemicals such as methamphetamine and phencyclidine. At least three different synthetic routes are possible. The most popular route involves the use of norfentanyl or 3-methyl-norfentanyl intermediates. These are produced from 1-benzyl-4-poperidone by reductive amination with aniline then acetylation and hydrogenation to form norfentanyl. Fentanyl and its analogs are then manufactured by alkylating the piperidine nitrogen (WHO, 1990).

In 1999, because of bad weather, opium cultivation in the Golden Triangle region of Southeast Asia dropped to the lowest level since 1988. Even so, Burma, produced approximately 50% of the world's illegal opium, still managing to produce an estimated 1090 metric tons of opium, convertible to 109 metric tons of heroin. Production in Laos amounted to 140 metric tons of opium, or 14 metric tons of heroin. At the same time, production in Southwest Asia rose, with a total of 53,570 hectares devoted to poppy cultivation, enough

to yield an estimated 1670 metric tons of opium, or 167 metric tons of heroin. Almost all of the increase occurred in Afghanistan, which thanks to very high yields per hectare is now the world's leading source of illicit opium gum.

Even though the Colombian poppy crop amounts to less than 4% of the world's opium production, Colombia is nonetheless the largest poppy grower in the Western Hemisphere, and high-purity Colombian heroin now accounts for much of the heroin in the Eastern U.S. Colombian opium poppy cultivation in 1999 is thought to have increased by nearly 25% to 7500 hectares, capable of yielding 750 metric tons of opium gum or nearly 8 metric tons of heroin. After Colombia, Mexico is the second largest opium producer in the Western Hemisphere. It currently supplies the bulk of the heroin flowing to states west of the Mississippi River. In 1999, an estimated 3600 hectares were under cultivation, yielding a crop that could potentially provide 43 metric tons of opium gum or slightly over 4 metric tons of heroin (USDS, 2000).

5.5.3 Sample analysis

There are, of course, ways to make pure morphine containing no other alkaloids, but these methods are not routinely used by clandestine labs. Thus, the ratio of heroin to acetylcodeine in illicit heroin is nearly the same as the ratio of morphine to acetylcodeine in the illicit morphine that was used to produce the heroin in the first place. Studies have shown that the ratio of heroin to acetylcodeine in an illicit heroin sample may be used to identify the country of origin of that sample. The ratio is fairly high for samples emanating from Afghanistan (20.9:1), and quite low for specimens coming from China (6.38:1) (Narayanaswami, 1985). However, in the final analysis, the ratio of heroin to 6-acetylmorphine and morphine is more an indicator of clandestine lab proficiency than country of origin (O'Neil and Pitts, 1992).

Substances carried over from the original plant or from opium are referred to as adulterants. Substances added with the intent of altering the character of the heroin in some way are also called adulterants. Included in this group are compounds such as quinine, caffeine, and diphenhydramine. The term *diluent* is reserved for those substances devoid of physiologic effects that are added to increase the bulk of the final product. As illustrated in Tables 5.5.3.1 and 5.5.3.2, heroin produced in different regions can be

Table 5.5.3.1 Adulterants Found in Heroin from Mexico, South America, Southeast Asia, and Southwest Asia

Adulterant[a]	Southeast Asia[b]	Southwest Asia[b]	Mexico[b]	South America[b]
Quinine	36	30	27	18
Diphenhydramine	17	3	20	—
Caffeine	22	8	—	8
Acetaminophen	21	8	1	6
Procaine	4	14	—	23
Cocaine	2	3	3	6
Lidocaine	1	3	4	6

[a] Other compounds are occasionally seen, but they are encountered so infrequently that no pattern is discernable.

[b] Numbers indicate the percentage of samples found to contain each adulterant.

Note: Based on data supplied by the Drug Enforcement Administration.

Table 5.5.3.2 Diluents Found in Heroin from Mexico, South America, Southeast Asia, and Southwest Asia

Diluent[a]	Southeast Asia[b]	Southwest Asia[b]	Mexico[b]	South America[b]
Lactose	46	43	39	33
Mannitol	65	73	6	67
Starch	21	19	6	27
Dextrose	5	3	—	6

[a] Other compounds are occasionally seen, but they are encountered so infrequently that no pattern is discernable.

[b] Numbers indicate the percentage of samples found to contain each adulterant.

Note: Based on data supplied by the Drug Enforcement Administration.

characterized by the adulterants and diluents that have been added. In the past, three types of product could be identified: illicit heroin samples from Southeast Asia, Southwest Asia, and Mexico all had distinctive profiles.

One of the adulterants that was often used to help identify samples was noscapine, sometimes called narcotine. It has no opiate activity, but it is the second most abundant alkaloid found in opium. The ratio of noscapine to whole morphine, acetylcodeine, and papaverine can be used to identify the source of an opium sample (Bjornsdottir and Hansen, 1995), because the ratios of other active opiate constituent compounds remain constant no matter how the sample is diluted or adulterated. However, that appears to no longer be the case. In 1999, police in Slovenia intercepted an 11-kg shipment of heroin, and samples from each individual package were analyzed (Klemenc, 2000). Some packages contained no heroin at all, but others contained mainly noscapine (88%) and papaverine (6%). There are two ways to account for the composition of the samples: (1) noscapine had been added as an adulterant, or (2) the heroin had been made by inept clandestine chemists who had trouble isolating the noscapine from the morphine (opium from Southwest Asia usually contains at least as much noscapine as morphine). Whatever the explanation, using noscapine as an indicator of country of origin would seem to be an unwise decision.

During the mid-1990s, the average purity of heroin sold on the streets increased dramatically from 24.5% in 1990, to 35.8% in 1993, to 41.1% in 1998 (Tichacek and Napolitano, 1999). The DEA operates a surveillance system known as the Domestic Monitor Program (DMP), which tracks the purity of street-level heroin. Data generated by that program show that, during 1998, the nationwide average purity for retail heroin from all sources was 41.2%, the highest value ever recorded in that program. The significant rise in purity corresponds to the increased availability of very high-purity South American heroin, sold mainly in the northeastern portions of the U.S. During that same time period, the average purity of South American heroin was 53.4%, followed by Southeast Asian heroin at 36.8%, Southwest Asia heroin at 33.1%, and Mexican heroin at 32.4% (DEA, 1999).

The type of material added as diluents varies from region to region and from time to time, depending on local conditions and on the preferences of the illicit manufacturer. French chemists have noted rather drastic shifts in the composition of seized specimens. They report that during the late 1980s, caffeine and mannitol were the most frequently used diluents, but by 1991 caffeine and mannitol had been almost entirely replaced by paracetamol (Chaudron-Thozet et al., 1992). Specimens from Southeast Asia are usually

diluted with mannitol or lactose. Most of the diluents and adulterants are relatively nontoxic.

Reports during the mid-1990s suggested that the veterinary anesthetic xylazine was being used as a heroin adulterant, and producing toxicity in unsuspecting users. If present in sufficient concentrations, xylazine causes increased pulmonary capillary permeability and sudden-onset pulmonary edema (Amouzadeh et al., 1991). Human data are sparse, but one case report describes a 36-year-old veterinarian who died within a few hours of injecting himself with xylazine. Levels in blood, brain, kidney, liver, and lung were 0.2, 0.4, 0.6, 0.9, and 1.1 mg/kg (or mg/L), respectively (Poklis et al., 1985). No additional reports have appeared since the original index cases.

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5.6 Opiate classification

Based on their molecular structure, the most common narcotic drugs can be divided into five distinct groups: (1) opiates such as morphine; (2) morphinans, such as butorphanol; (3) benzomorphans, such as pentazocine; (4) 3,5-diphenylamines, such as methadone; and (5) the phenylpiperidines, the best known of which is meperidine. Each of the different groups has distinct properties and will be considered separately.

5.6.1 Morphine

Morphine was isolated from opium by Setürner in 1805 (Sertürner, 1806). More than 120 years passed before Sir Robert Richardson characterized morphine's chemical structure in 1927 (Schöpf, 1927), and total synthesis was only accomplished in 1952 (Gates and Tschudi, 1952). The time lag between the discovery of morphine and its chemical characterization is paralleled by the slow evolution in understanding its metabolism and mechanism of action. The principal site of metabolism is the liver, but because the total body clearance of morphine is higher than hepatic flow, questions still remain about extrahepatic metabolism (Säwe et al., 1985b). Questions also remain about the utility of measuring blood and tissue levels. Tolerance occurs, and, as is the case with cocaine, morphine concentrations in individuals for whom morphine was the cause of death overlap concentrations found in cases where the presence of morphine is merely an incidental finding (Karch and Stephens, 2001). Complete overlap also exists between the living and dead; plasma morphine concentrations in patients being treated with heroin-replacement therapy are indistinguishable from those in decedents who have died of heroin overdose (Darke et al., 1997). Worse still, pharmacodynamic studies, no matter whether in normal volunteers or cancer or trauma patients, have failed to disclose any predictable relationship between morphine plasma concentrations and analgesic effects (Glare and Walsh, 1991; Hoffman et al., 1997).

5.6.1.1 Morphine physical constants

Morphine sulfate is essentially the only salt in clinical use. It is supplied as a white, fine, odorless powder. The formula is $C_{34}H_{40}N_2O_{10}S$; it is composed of 61.06% carbon, 6.03% hydrogen, 4.19% nitrogen, 23.92% oxygen, and 4.79% sulfur; and the molecular weight is 668.77. One gram dissolves in 15.5 mL of water at 25°C, but it is insoluble in chloroform or ether. The pH of aqueous solution is approximately 4.8. Even when stored in glass ampules, aqueous solutions of morphine sulfate turn brown when exposed to sunlight, but the discoloration seems to have no effect on the ability to produce analgesia (Budavari et al., 1996).

5.6.1.2 Morphine pharmacokinetic constants

Measured pharmacokinetic constants for morphine vary, depending on the circumstances under which the drug was administered and the underlying health of the individual. Furthermore, major pharmacokinetic differences exist between the parent compound and the metabolites, and these differences can have important clinical and toxicologic consequences. Reported values for morphine clearance have ranged from 9.2 to 28.1 mL/kg/min, with an estimated mean elimination half-life of 1.4 to 3.4 hours. Report values for the volume of distribution have ranged from a low of 2.1 to a high of 4.0 L/kg (Säwe et al., 1981, 1985a; Osborne et al., 1990).

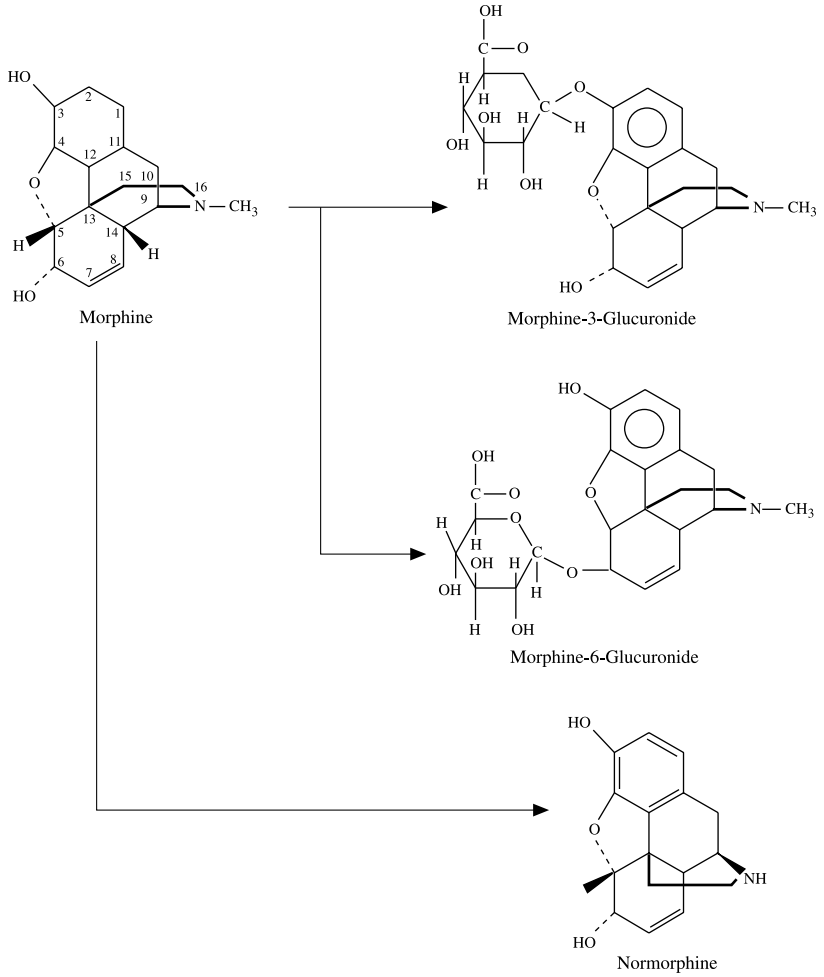

Figure 5.6.1.3.1 Basic elements of morphine metabolism.

5.6.1.3 Morphine metabolism

Morphine undergoes biphasic elimination. During an initial phase lasting only a few minutes, it is rapidly distributed throughout the tissues that receive the highest blood flow — namely, lung, kidney, liver, spleen, and muscle (Brunk and Delle, 1974; Stanski et al., 1978). During a secondary phase, morphine is quickly converted to its principal metabolite, morphine-3-glucuronide (M3G), and somewhat more slowly to smaller amounts of morphine-6-glucuronide (M6G) (Figure 5.6.1.3.1). The transformation occurs mainly in the liver, takes several hours, and involves the production of minor amounts of several other morphine metabolites. Less than 10% of a given dose is excreted in the urine as unchanged morphine.

Most of the morphine, approximately 70%, is converted to glucuronides (57% M3G, 10% M6G) (Hasselstrom and Säwe, 1993) and then excreted via the kidneys. Other morphine metabolites (such as morphine-3,6-diglucuronide, normorphine-3-glucuronide) are produced in very small amounts and appear to be devoid of physiologic effects (Yeh et al., 1979). Elimination of morphine is not affected by renal failure, but excretion of the

glucuronides is. Morphine is not, as once thought, converted to codeine; the presence of codeine in urine after morphine or heroin administration is explained by the presence of codeine impurities that can be detected even in pharmaceutical-grade morphine (Cone et al., 1991).

Because it contains two hydrophilic hydroxyl groups, morphine is water soluble but relatively insoluble in lipids. The amino group pKa is 7.9 and the phenolic group pKa is 9.9, which means that, within physiologic pH ranges, the phenolic portion of the molecule is essentially unionized (Christrup, 1997). During life, approximately half the morphine circulating in the plasma is protein bound (Osborne et al., 1990). Abnormalities of protein binding, such as would be seen in hepatic failure or malignancies, can alter the degree of protein binding and, indirectly, lead to higher circulating levels of free morphine (Säwe, 1986). P-glycoprotein (P-gp)-mediated transport appears to be the central mechanism responsible for the movement of morphine across the blood–brain barrier. Brain uptake and tissue disposition can be disrupted by P-gp inhibitors, including drugs such as verapamil and cyclosporin (Letrent et al., 1999).

Further complicating interpretive issues is the observation that morphine undergoes enterohepatic circulation. When seven healthy volunteers were given 5-mg doses of morphine intravenously, 57.3% was converted to M3G, 10.4% to M6G, and 10.9% appeared unchanged in the urine, leaving 20.8% of the original morphine unaccounted for (Hasselstrom and Säwe, 1993). These observations are in general agreement with animal studies. When rats are injected with M3G, up to 20% of the dose is recovered in bile, with the remainder (80%) being recovered unchanged in the urine (Ouellet and Pollack, 1995). In chronic users, fecal excretion may account for between 7 and 10% of a given dose (Hanks et al., 1988).

5.6.1.4 Morphine metabolites

5.6.1.4.1 Morphine-3-glucuronide. Both M3G and M6G are highly ionized and highly lipophilic (Carrupt et al., 1991), but their ability to cross the blood–brain barrier is significantly less than that of the parent compound (Mignat et al., 1995; Bickel et al., 1996; Wu et al., 1997). The major morphine metabolite, M3G, has almost no affinity for μ receptors and no analgesic properties. Human studies are lacking, but the results of animal experiments suggest that M3G may partly antagonize some of the effects of morphine and possibly play a role in the development of morphine tolerance. The terminal half-life of M3G is 3.9 ± 1.5 hours, significantly longer than that of M6G, which is only 2.6 ± 0.69 hours (Osborne et al., 1990). The apparent volume of distribution for M3G in children under the age of 11 is more than twice that observed in children over that age, and more than seven times the value observed in adults (0.76 vs. 0.33 vs.14 L/kg) (Hunt et al., 1999). The clearance rate for M3G is also higher in young children than in adults (4.9 vs. 0.8 mL/min/kg) and is higher than that of M6G regardless of age. This observation suggests that bioavailability estimates derived from adults are not applicable to children, and that preferential metabolism to M6G or increased clearance of M3G occurs (Hunt et al., 1999).

5.6.1.4.2 Morphine-6-glucuronide. The 3-carbon position in the morphine moiety must remain accessible in order for a molecule to have opiate activity. Because the 3-carbon position is open in the M6G molecule, it is not surprising that this metabolite has analgesic effects in its own right (Osborne et al., 1988). M6G selectively binds both μ_1 and μ_2 receptors (Paul et al., 1989), an action that is thought to explain both the known analgesic properties of this compound, as well as its ability to depress respiration; μ receptor binding also

explains why M6G depresses respiration. Two important differences between morphine and M6G are apparent: M6G produces somewhat less respiratory depression and somewhat greater analgesia (Christrup, 1997), and it does not cross the blood–brain barrier as easily as the parent compound. The liposolubility of M6G is 187-fold lower than that of morphine (Wu et al., 1997). In spite of that difference, M6G injected into peripheral veins does produce analgesia, probably because penetration of the blood–brain barrier by M6G is facilitated by P-gp binding which, in turn, is the result of the expression of the product of the multidrug-resistance (MDR) gene in brain capillary endothelial cells. (Huwyler et al., 1996).

Because the volume of distribution for M6G is so low (0.42 L/kg in children under the age of 11, 0.19 L/kg in older children, and 0.15 L/kg in adults) (Hunt et al., 1999), very little M6G is found in tissues. Measurements made in fat and subcutaneous tissue, for example, disclose only the presence of free morphine, no glucuronides (Levisky et al., 2000). Except for M6G that has been transported into the brain, almost all of the M6G in the body is to be found in the circulation.

While the elimination of morphine itself is unaffected by renal failure, the elimination of psychoactive M6G is, and patients with renal failure may become toxic due to the presence of accumulated metabolite (Ball et al., 1985; Davies et al., 1996; Johnson, 1997; Milne et al., 1997; Dubs et al., 1999; Angst et al., 2000).

Morphine glucuronides excreted in the bile can be deconjugated by bacteria in the gut, and then reabsorbed through the intestinal mucosa (Parker et al., 1980). In some animals, and very likely in humans as well, M3G is synthesized by the gut (Sloan et al., 1991; Milne et al., 1993). As a consequence, morphine glucuronides will continue to appear in the urine for days after the drug was last used, even in healthy individuals who do not have liver or kidney disease, and the process will continue for as long as there is morphine in the bile to be excreted. Concentrations of unchanged morphine in bile may reach extremely high levels. In one study of narcotic-related deaths, the average concentration of morphine in the bile was 312 mg/L (Chan et al., 1986). In Gottschalk and Cravey's (1980) series of 119 cases, the median level of morphine in the bile was 33.7 mg/L.

This combination of enterohepatic circulation and bacterial deconjugation can pose some formidable interpretative difficulties. It is not known with any certainty just how long it takes to clear morphine from the enterohepatic circuit, but it is reasonable to suppose that patients treated with large doses of morphine, such as trauma victims maintained on respirators and former heroin abusers who have entered detoxification programs, may continue to excrete measurable quantities of morphine in the urine for weeks after morphine was last taken. This possibility must be taken into account when interpreting drug-abuse screening tests. After death, free and conjugated morphine are stable in refrigerated blood and urine, at least for 10 days, but in the liver, conjugated morphine is rapidly converted back to morphine (Moriya and Hashimoto, 1997). If the postmortem interval is long, or if the tissue samples have not been frozen, inferences about the time of ingestion based on the ratio of morphine to its metabolites are likely to be misleading.

5.6.1.5 Absorption and routes of administration

Morphine is well absorbed, no matter the route of administration, and bioequivalence exists between subcutaneous and intravenous routes of morphine administration (Stuart-Harris et al., 2000). Unfortunately, very few studies have been done where realistic doses of morphine or heroin have been given to addicts and tolerant subjects. It is not known whether pharmacokinetic parameters derived from healthy volunteers and from cancer patients apply to the massive amounts of drug injected by tolerant addicts.

5.6.1.5.1 Intravenous. A 10-mg bolus, given to healthy volunteers undergoing elective surgery, results in a peak blood level of 200 to 400 ng/mL five minutes after injection (Berkowitz et al., 1975). In a more recent study comparing the pharmacokinetics of smoked and intravenous heroin, measurements were made in two subjects; in one subject peak concentrations ranged from 72 ng/mL after a 10-mg dose to 401 ng/mL after a 20-mg dose. In the second subject, a 3-mg dose produced a peak level of 64 ng/mL, while a 6-mg dose gave a peak of 315 ng/mL. Levels rapidly declined thereafter and reached limits of detection within 30 minutes of injection (Jenkins et al., 1994).

Even after intravenous injection, morphine clearance rates (2.5 to 10 mL/kg/min, with mean ± SD of 6 ± 2.6) and volume of distribution (0.28 to 3.30 L/kg, with mean ± SD of 1.4 ± 1.0) are lower in trauma victims than in healthy volunteer test subjects or cancer patients. These reductions are seen in trauma victims even when hepatic blood flow, as assessed by the rate of lidocaine clearance, is almost normal, suggesting that some other mechanism besides diminished hepatic blood flow is involved (Berkenstadt et al., 1999).

5.6.1.5.2 Subcutaneous injection. Absorption via the subcutaneous route and after intramuscular injection is almost as rapid as the intravenous route. After either route, morphine blood levels peak at 10 to 20 minutes, somewhat longer than after intravenous injection, but not so much longer as to have much clinical significance. The pharmacokinetics for both routes are nearly the same as after intravenous injection, and plasma levels comparable to those seen after intravenous use can be achieved after subcutaneous injection. In one recent study with healthy human volunteers, a dose of 10 mg/70 given intravenously produced a free morphine concentration of 80 ng/mL at 5 minutes, compared to a peak concentration of 74 ng/mL at 15 minutes after the same dose was given as an intravenous bolus (Stuart-Harris et al., 2000).

These similarities may explain why, in the past, subcutaneous injection (known as "skin popping") enjoyed considerable popularity among some groups of abusers. This practice, and the skin lesions commonly associated with it, seem to be less common today than in the past. It may be that "skin popping" has, to some extent, been replaced by smoking. However, given the outbreak of clostridia infections reported from the U.K. in the year 2000 and continued reports of wound botulism (Bergstein et al., 1995; Anderson et al., 1997; Maselli et al., 1997; Passaro et al., 1998; Hiersemenzel et al., 2000) from both Europe and the U.S., it would appear that the practice is far from being abandoned altogether.

5.6.1.5.3 Subcutaneous infusion. The continuous administration of either heroin or morphine is a relatively common practice in Europe, and several types of infusion pumps are available for this purpose. They offer an advantage over other forms of treatment, because continuous parenteral administration avoids the cycles of peak-level sedation and trough-level breakthrough pain and nausea is lessened (Mikkelsen-Lynch et al., 2000). In one study, an infusion of 165 mg/day at the rate of 3.45 mg/hr resulted in a stable serum concentration of 30 to 40 ng/mL, although bioavailability is considerably less after subcutaneous than intravenous dosing (Mikkelsen-Lynch et al., 2000).

5.6.1.5.4 Oral. Routes of administration that avoid first-pass metabolism (intravenous, transdermal, rectal, intramuscular, epidural, and intrathecal) result in lower metabolite production than oral, buccal, or sublingual administration. Approximately 80% of a given dose of morphine is absorbed from the gastrointestinal tract, with nearly half that amount being metabolized during the first pass through the liver. For that reason, oral bioavailability is relatively low, at just over 33% (Lotsch et al., 1999). The amount absorbed

is somewhat unpredictable because the degree to which morphine is subject to extraction and metabolism by the gastrointestinal tract are affected by age, liver function, gender, the presence of food, disease states, and genetic polymorphism (Tam, 1993).

The oral route was popular among the "opium eaters" of the 17th and 18th centuries, when distribution was unregulated and prices were low. Today, it is an impractical route for abusers because it costs too much. Urine measurements have been described in only one case report, from an addict ingesting approximately 1 g of opium per day. Morphine, codeine, normorphine, norcodeine, and noscapine were all found to be present in the urine, but thebaine and papaverine (normal constituents of opium) were not. The concentration of unconjugated morphine (640 ng/mL) was more than twice the concentration of codeine (Cone et al., 1982).

For cancer patients with access to legally supplied morphine, oral administration is a mainstay in the management (Gourlay et al., 1986; Hoskin et al., 1989; Osborne et al., 1990). In stable cancer patients receiving sufficient oral morphine to produce acceptable levels of analgesia, the mean trough serum morphine concentration is on the order of 18 ng/mL. The corresponding mean concentration of M6G is approximately the same as that of free morphine, but concentrations of the inactive metabolite are six to eight times higher than free morphine concentrations. Serum trough concentrations show a 33-fold variation, making it almost impossible to predict either the effectiveness of a given dose or the likelihood of side effects (Klepstad et al., 2000).

Oral overdose, intentional or accidental, can occur (Fisher et al., 1987; Got et al., 1994). In one case involving an intentional overdose with an unspecified number of time-release morphine capsules (MS Contin®), the patient subsequently developed rhabdomyolysis and renal failure in addition to respiratory depression. Concentrations of morphine, M6G, and M3G roughly 36 hours after ingestion were 57, 154 , and 798 ng/mL, respectively. In another case report involving heroin rather than morphine, concentrations of heroin, 6-monoacetylmorphine, and morphine were 109, 168, and 1140 ng/mL, respectively, in blood and 17, 12, and 425 ng/g, respectively, in gastrointestinal contents. Only morphine was detected in the urine, at a concentration of at 3650 ng/mL (Rop et al., 1997).

As heroin supplies have become increasingly pure, more cases of oral heroin overdose have been reported. In one small series from Australia, the median blood morphine concentration of non-injectors dying of heroin overdose was 0.31 mg/L (range, 0.06–0.99 mg/L) (Darke and Ross, 2000). Case reports of infants and children with methadone overdose are also increasingly common, but reports of accidental morphine overdose are not. The discrepancy may be explained by the observation that, while hundreds of thousands of methadone-replacement patients are young enough to have children, most oral morphine preparations are likely to be found in the homes of older individuals with cancer. Nonetheless, accidental overdosage with morphine can occur. One report describes a case of fatal intoxication in an 8-year-old who underwent tonsillectomy. A pharmacist filling the child's prescription mistakenly dispensed a solution containing 20 mg/mL morphine sulfate. The child was given 1 or 2 tsp of the prescription prior to bed and was found dead the next morning. The morphine concentrations were 0.128 mg/L in the blood, 135 mg/L in the bile, and 16 mg/L in the stomach contents (Poklis et al., 1995).

5.6.1.5.5 Rectal. Plasma levels after rectal administration are somewhat higher than after oral morphine but are much less than after parenteral administration (Ellison and Lewis, 1984). This route does not seem to be particularly popular among abusers, at least when compared to the rectal use of cocaine, which is a fairly common practice. One reason may be that rectal administration of morphine significantly reduces first-pass

exposure in the liver, resulting in decreased hepatic transformation of morphine to its pharmacologically active metabolite, M6G (Babul and Darke, 1993).

When 0.6 mg/kg of morphine was given to women undergoing cancer treatment, considerable variation between individuals was observed, but peak concentrations of 31 to 75 ng/mL were reached at between 45 and 120 minutes (Westerling et al., 1982). Fatalities have been reported at levels that were not much higher, and seizures, particularly in neonates, have been reported at levels that were much lower. Morphine-induced seizures have occurred at blood concentrations as low as 9 ng/mL (Koren and Klein, 1992). One report described a postoperative death from cerebral hypoxia. A child had been given several 4-mg morphine suppositories over the course of 4 hours. Blood levels measured 1.5 hours after death were 94 ng/mL (Gourlay and Boas, 1992). Different studies have shown rectal bioavailability to be anywhere from 12 to 61% (Lindahl et al., 1981; Westerling et al., 1982). Pharmacologic manipulation of the morphine medium can improve absorption and result in levels comparable to oral administration. If the carrier medium is acidified, then the percentage of drug not ionized increases, as does absorption.

5.6.1.5.6 Intranasal. Heroin and morphine can both be used intranasally, but the transnasal absorption of morphine is poor, at least when compared to other agents such as cocaine. At the turn of the century, probably up to the mid-1920s, as many people took heroin by nasal insufflation as by injection. Today's abusers seem to have rediscovered this route. Government surveys report that the practice of heroin snorting has become increasingly popular on the "club" circuit, and as heroin prices continue to fall this route can be expected to become increasingly popular. The pharmacokinetics of intranasal and intramuscular heroin have been compared in one study.

Peak heroin concentrations, after either intranasal or intramuscular (i.m.) administration, occur within 5 minutes. Resultant blood levels after 6-mg doses of heroin by either route are on the order of 30 to 40 ng/mL. The mean elimination half-life after intranasal administration was 5.4 ± 4.5 minutes vs. 4.2 ± 0.12 minutes after i.m. administration. Concentrations of 6-acetylmorphine peak at 5 to 10 minutes after administration by either route, with peak levels of 22.6 ng/mL after a 6-mg dose. The elimination half-life was longer for 6-acetylmorphine than for heroin: 10.8 ± 8.4 minutes after intranasal compared to 11.4 ± 5.4 minutes after i.m. dosing with 6 mg. Once the heroin had been converted to morphine, the half-life for morphine following intranasal administration ranged from 90 ± 96 minutes (6-mg dose intranasally) to 168 ± 216 (12-mg dose intranasally) (Cone et al., 1993).

5.6.1.5.7 Inhalation. Opium smoking has never been studied using modern methodologies, but the practice persists in many parts of the world. Daily amounts of opium used vary widely, from less than a gram to 30 g (equivalent to 75 to 3000 mg of morphine) (Kalant, 1997). The resultant plasma concentrations are not known, and the pharmacokinetics of the process has not been characterized. The pharmacokinetics of heroin smoking has been well studied (Jenkins et al., 1994, 1995), and the bioavailability of smoked heroin is unpredictable. Jenkins et al. found that heroin could be detected in the blood within one minute of smoking. Peak levels after smoking 10.6 mg/L were 299 ng/mL in one subject, and 108 ng/mL in another. Blood levels then rapidly declined to limits of detection (under 1 ng/mL) within 30 minutes of smoking. Levels of 6-acetylmorphine peak 1 to 2 minutes after peak heroin levels. Morphine levels rise and fall more slowly. Estimated half-lives of heroin, 6-monoactylmorphine, and morphine were 3.3, 5.4, and 18.8 minutes, respectively. In general, these results are comparable to those observed after intravenous administration.

Anecdotal reports from Europe suggest that the practice of smoking heroin "free base" is increasing. The melting point of heroin is much higher than that of cocaine, so preparing freebase heroin is more complicated than making "crack" cocaine, which probably explains why the practice is not more common. Although the practice of smoking heroin (or "chasing the dragon") has become much more widespread, this route of administration seems to account for relatively few deaths. A review of heroin deaths in Sydney, Australia, from 1992 to 1996 found that fewer than 1% of the deaths were associated with smoking heroin. In the cases where smoking was responsible, the median blood morphine concentration was 0.31 mg/L (range, 0.06 to 0.99 mg/L), and drugs other than morphine were commonly present (Darke and Ross, 2000). In a study of incarcerated Danish heroin users, heroin smokers accounted for nearly a quarter of the cases, with intravenous users having had a longer duration of use, earlier onset of abuse, and more serious somatic complications (Andersen et al., 1996).

5.6.1.5.8 Skin. Morphine is not sufficiently fat soluble to be absorbed through intact skin, at least not in quantities sufficient to produce psychological effects, unless the epidermis has been disrupted. In the mid-1990s, attempts were made at developing a morphine patch. It worked by causing a small epidermal bleb to be formed, allowing drug access to deeper layers of the skin. The results of initial experiments suggested that clinically relevant quantities of morphine could be delivered in this manner; however, the device has not yet come to market (Svedman et al., 1996; Grond et al., 2000). Other opioids, particularly fentanyl and sufentanil, and also meperidine, are well absorbed via this route. Because these other agents are also much more potent than morphine or heroin, transdermal application is quite practical. Time-release patches containing fentanyl are even beginning to appear on the black market (Calis et al., 1992).

5.6.1.5.9 Maternal/fetal considerations. It has been recognized for more than a century that mothers can transfer morphine to their children in breast milk (Anon., 1861). Depending on the degree of lipid solubility, narcotic agents passively diffuse across the placenta. Fetal uptake after maternal dosing with heroin has been studied in the Rhesus monkey, using ^{11}C-heroin and positron tomography. Peak levels in the placenta are reached within a few minutes of administration. Peak maternal levels are twice the fetal level, but by 1 hour fetal blood levels were higher than maternal levels. Concentrations of labeled morphine in the liver quickly rise and quickly fall (Hartvig et al., 1989).

Once the narcotic agents are taken up by the fetus they are metabolized and excreted, but neonates produce morphine glucuronides at a lower rate than older children or adults (Faura et al., 1998). Morphine and its metabolites can be detected in the amniotic fluid (Rurak et al., 1991) or in specimens of hair or meconium (Koren and Maurice, 1989; Little et al., 1990; El Sohly et al., 1999). The results of experimental studies, not yet confirmed in humans, suggest that the concentration of a drug in the meconium is related to amount, timing, or duration of the drug exposure of the fetus *in utero* and that the quantitative analysis of drugs in the meconium might provide information about patterns of maternal use (Silvestre et al., 1997).

The results of animal studies also suggest that morphine metabolites (chiefly M3G) also enter the amniotic fluid, but much more slowly than morphine itself. After 12 hours of continuous infusion of M3G, fetal concentrations amount to less than half those observed in the mother (Gerdin et al., 1990). It is generally accepted that breastfeeding mothers being treated with morphine and codeine do not place their children at risk, at least not in the short term (Spigset and Hagg, 2000).

5.6.1.6 *Tissue disposition*

A very wide range of values have been reported for the volume of distribution of morphine, with some groups reporting values of less than 1 L/kg (Chauvin et al., 1987; Furman et al., 1990; Lotsch et al., 1998; Berkenstadt et al., 1999), while others have calculated values approaching 7 L/kg (Lotsch et al., 1996). The reason for the variation has never been demonstrated with any certainty but could be related to the health of the volunteers studied. In patients with edema and a higher body fluid content, higher values would be expected for the volume of distribution, while in patients with renal failure, where intravascular volume is often decreased, smaller values would be anticipated. Alterations should also be expected in cancer patients, because decreased protein production with secondary decreases in oncotic protein pressure are common, and patients are often cachectic with depleted fat stores. In spite of these difficulties, a value of 2 to 4 L/kg can be assumed for the young and reasonably fit who die of narcotic overdose.

One consequence of the relatively large volume of distribution of morphine is that less than 2% of a given dose is to be found circulating in the blood. After initial intravenous administration, morphine is rapidly distributed throughout the body, with resultant tissue concentrations reflecting the relative blood flow. The time it takes morphine to redistribute, and the final tissue concentrations observed when redistribution is complete, are altered by a number of factors, most especially age (Chan et al., 1975). Postmortem redistribution from tissue to blood can easily double measured blood morphine concentration (Skopp et al., 1996, 1997; Bogusz, 1997), which is why the postmortem ratio of morphine to its metabolites has little, if any, forensic value. The magnitude of the problem was confirmed by a recent meta-analysis of 57 studies with information on 1232 patients. The analysis examined the effects of age, renal impairment, route of administration, and method of analysis on the ratios of M3G to morphine (M3G:M) and M6G to morphine (M6G:M), and the relative concentrations of M3G and M6G. The ratios of metabolites to morphine were so wide (0.001–504 for M3G:M and 0–97 for M6G:M) as to render their calculation worthless for forensic purposes (Faura et al., 1998).

Muscle is an important storage site for opiates just because of its sheer bulk. Several studies have shown that postmortem muscle morphine concentrations are similar to concentrations measured in blood (Worm et al., 1983; Garriott, 1991; Moriya and Hashimoto, 1997). Morphine is not as highly lipophilic as some agents, such as fentanyl, but it does tend to accumulate in fat, where it can be measured after death (Levisky et al., 2000). Morphine crosses the blood–brain barrier, but not so freely as compounds such as heroin and codeine that possess an aromatic hydroxyl group at the C3 position. The passage of morphine across the blood–brain barrier is mediated by P-gp located in brain capillary endothelium. Drugs that interfere with P-gp (such as doxyrubrin) can alter brain morphine uptake and disposition. Morphine tissue disposition does not appear to be altered by the concomitant use of sympathomimetic agents such as ephedrine and phenylpropanolamine (Dambisya et al., 1991), but whether this is also true for methamphetamine and cocaine is not known.

Morphine and its glucuronides are not degraded by formalin, and tissues that have been preserved in formalin can still be analyzed for morphine, with the caveat that morphine will diffuse from tissue into the fixative solution (actually, formalin is a very efficient agent for extracting morphine). In controlled studies, when liver samples were stored in formalin, poststorage concentrations were found to have decreased by approximately 25% and the missing morphine was accounted for by formalin extraction (Cingolani et al., 2000).

Table 5.6.1.6.1.1 Postmortem Blood Morphine Concentrations (n = 40)

	Median Total Morphine	Median Free Morphine
Subclavian	.58	.16
Heart[a]	.76	.19
Femoral	.64	.25

[a] The original paper does not specify from which side of the heart the samples were obtained (samples from the left would be expected to contain higher concentrations than those from the right).

Source: Adapted from Gerostamoulos and Drummer (2000).

5.6.1.6.1 Blood. No matter the degree of postmortem redistribution, in actual practice measurements of morphine and its metabolites in blood samples taken simultaneously from the "heart" (side not specified) and subclavian and femoral vessels yield very similar results. Gerostamoulos and Drummer (2000) made such measurements in a group of 40 patients with an average postmortem interval of 59 hours. The results are shown in Table 5.6.1.6.1.1. In the same study, concentrations of morphine and its metabolites were also determined. The median total morphine concentration was 1.07 mg/L, with corresponding values of 0.32 ± 0.23, 0.03 ± 0.07, 0.16 ± 0.13, and 0.66 ± 0.56 for free morphine, normorphine, M6G, and M3G, respectively.

The values for total morphine reported in the above study are substantially higher than values observed in a second, much larger series of 168 heroin-related deaths reported from San Francisco. In that study, the median concentration of total morphine in right-heart blood was 0.230 mg/L with a mean of 0.433 mg/L (Karch and Stephens, 2001). These values are also higher than those reported by Logan and Smirnow (1996) in another moderate-size series of 48 decedents, where the median morphine concentration in femoral blood was 0.082 (range, 0.006 to 1.20), with a mean of 0.143 mg/L. In "ventricular blood" (side not stated), the median was 0.141 mg/L (range, 0.008 to 836) with a mean of 0.230 mg/L. Though the postmortem interval was shorter than in the study by Gerostamoulos and Drummer, the authors again were unable to detect any evidence for changes in morphine concentrations, though blood taken from the heart had consistently higher concentrations than blood taken from the periphery.

Body packers dying from ruptured drug packets may have heroin and morphine levels that exceed 100,000 ng/mL (Joynt and Mikhael, 1985). Using solid-phase extraction coupled with gas chromatography/mass spectrometry (GC/MS), blood samples in 21 heroin-related deaths had heroin levels of 0 in every case. Mean 6-acetylmorphine levels were 9.9 ng/mL (range, 0 to 82.9), while mean free morphine levels were 222 ng/mL (range, 11.2 to 1277 ng/mL).

Generalizing from these results is extremely difficult for several reasons; the most important is the fact that while heroin-related decedents generally have higher median concentrations of morphine than living patients being treated with maintenance-therapy heroin (0.35 vs. 0.09 mg/L) the blood morphine concentrations of the two groups overlap substantially, ranging from 0.08 to 1.45 mg/L. Living heroin users often have morphine concentrations higher than the median concentration recorded for fatal cases (Darke et al., 1997).

The other critical analytic issue is the origin of the blood sample. After death, basic drugs such as morphine rapidly penetrate the thin-walled pulmonary arteries and re-enter the left ventricular cavity. If the body is supine, and more than a few hours have elapsed, very different concentration measurements may be recorded in blood obtained from the right and left ventricles (Moriya and Hashimoto, 1999). If the origin of the blood samples is not recorded in the autopsy protocol, there is no way to know whether the value measured bears any relationship to concentration values that existed just prior to death. Finally, it is now recognized that the M6G is a potent opiate in its own right, and that it tends to accumulate in the body under certain conditions, especially in cases of renal failure (Peterson et al., 1990; Tighe et al., 1999). Concentrations of M6G are difficult to measure and cannot be deduced by simply subtracting free from total morphine (as most of the conjugated morphine is harmless M3G). It is also recognized that, in the living, morphine blood concentrations cannot be related to levels of pain relief (Hoffman et al., 1997), and pathologists have increasingly begun to conclude that the value of postmortem morphine blood concentration measurement is mainly limited to an assessment of whether a lot or a little of the drug was taken. Attention is shifting to the brain as a more reliable indicator and forensic tool.

5.6.1.6.2 Brain. In the rat model of morphine-related death, free morphine concentrations in the forebrain are initially stable but then begin to rise several days after death. Concentrations in the hindbrain, however, appear to be stable (Sawyer and Forney, 1988; Xu, 1997). Immunohistochemical studies in cases of human overdose show that morphine localizes in the neuronal cytoplasm of the cerebral cortex, hippocampus, basal ganglia thalamus, brainstem, and cerebellum. Binding also occurs, but to a lesser degree, in the endothelium of some brain capillaries (Liu et al., 1996). The human hippocampus is particularly rich in μ receptors (Figure 5.6.1.6.2.1), and immunohistochemical studies show that the ganglion cells located in the hippocampus, as well as their axons and dendrites, concentrate morphine to a very significant degree, particularly in cases of heroin/morphine overdose (Wehner et al., 2000).

Morphine in the hippocampus exhibits a rather narrow range of concentrations. In one human postmortem study, values ranged from 134 to 298 ng/g, with good correlation between morphine concentrations in peripheral blood and hippocampus, although the concentration ranges observed in blood where much wider. For example, one victim of a lethal overdose had a total blood morphine concentration of 1.5 mg/L, but only 298 ng/mL in the hippocampus (Wehner et al., 2000). The limited concentration ranges observed in the hippocampus are presumably explained by receptor saturation. Once all of the μ receptors have bound to morphine, drug still remaining in the blood would be deposited in other tissues.

Overflow from the hippocampus is very likely the explanation for the wide range of blood/brain concentration ratios that have been reported in the literature. In the three heroin users described by Kintz et al. (1989), the blood/brain ratios were 13, 0.24, and 1.5, with tissue concentrations ranging from 0.005 to 0.089 mg/kg of wet brain. In a second small study, cerebrospinal fluid (CSF) and brain levels of 6-acetylmorphine were found to be much higher than levels in blood, liver, lung, and kidney. One individual had a blood 6-acetylmorphine level of 11.3 ng/mL, compared to levels of 58 ng/mL in the CSF and 158 ng/mL in brain. In a second case, blood levels were 16.2 ng/mL, while levels in the cerebrospinal fluid and brain were 38.5 and 53.6, respectively (Goldberger et al., 1994). With the exception of cerebrospinal fluid, the concentration ratio of blood

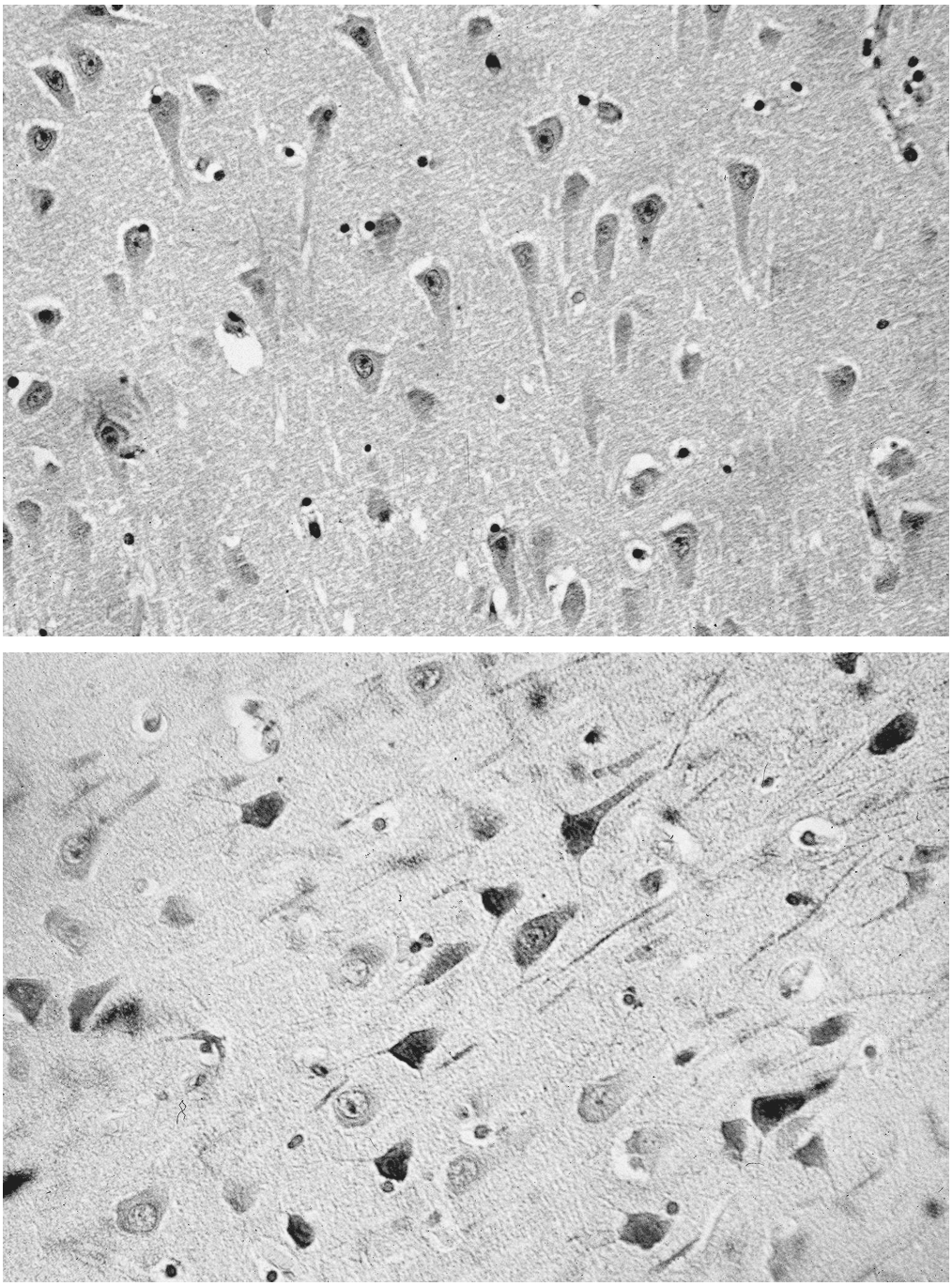

Figure 5.6.1.6.2.1 **Histochemical demonstration of opiate receptors.** The human hippocampus is particularly rich in μ receptors, and immunohistochemical studies show that the ganglion cells located in the hippocampus, as well as their axons and dendrites, concentrate morphine to a very signifi cant degree. The micrograph on the top is from a drug-free control brain and has been stained with antimorphine antibodies. The bottom micrograph shows intense uptake of antimorphine antibodies in brain tissue from a heroin overdose. (Courtesy of Professor Frank Wehner, University of Tubingen.)

morphine to the morphine concentrations in other tissues varies so widely as to make such determinations useless.

Blood/CSF ratios, however, appear to have more predictive value (2.74 ± 1.69). In 89% of reported cases, morphine levels were lower in the CSF than in the blood (Wahba et al., 1993; Moriya and Hashimoto, 1997). Some information about the process has been derived from studies of pain management. Plasma and cerebrospinal fluid steady-state concentrations of morphine, as well as M3G and M6G, were studied in 21 cancer patients being treated with chronic subcutaneous morphine infusions. A moderate but still statistically significant correlation was found between the daily dose of morphine administered and the concentrations of morphine and its metabolites in the CSF. The mean CSF/plasma morphine concentration ratio was 0.36 ± 0.07. As is true for brain/plasma ratios, the correlation between CSF and plasma values was poor (Wolff et al., 1996). The mean M3G and M6G concentrations in CSF were less than 10% of the concentrations found in plasma.

Comparison of the morphine concentrations in the medulla oblongata and the cerebellum provide information on the interval between morphine administration and death. If the postmortem interval is relatively short, the ratio of morphine in the brain stem to the concentration in the cerebellum will be less than 1. Higher ratios suggest that a much longer time has elapsed. (Vycudilik, 1988). The ratio rises above 1 if at least several hours have passed.

5.6.1.6.3 Liver. Morphine concentrations have been measured in several series. In the ten cases analyzed by Felby et al. (1974), the mean concentration was 3.0 mg/kg, and the range was from 0.4 to 18 mg/kg. The two cases reported by Chan et al. (1986) had levels of 7.0 and 2.9 mg/kg in the liver. In another series of 20 narcotic-related deaths, liver concentrations of free morphine ranged from 0.039 to 0.55 mg/kg, with an average value of 0.21 mg/kg. The average blood levels in those same individuals was 0.099 mg/L (Goldberger et al., 1994). Biliary concentrations of 312 mg/L and 248 mg/L in the two cases reported by Chan et al. (1986) were nearly 30 times higher than the blood levels. In other series the differential between liver and bile has not been quite so striking. Kintz found bile levels of 0.087–0.363 mg/L, while concentrations were 0.067–1.424 mg/kg in the liver. The differences have to do partly with the amount taken before death and partly with the chronicity of use (Kintz et al., 1989).

Concentrations of free morphine in the liver may be very high, but that is not the case for heroin. In cases where heroin and its metabolites were all measured, no heroin or 6-acetylmorphine was detected in samples from the liver, even though brain concentrations were 158 ng/mL in one case and 54 ng/mL in another (Goldberger et al., 1994). Quantitation of hepatic morphine levels is a particularly useful approach in the case of exhumations. Blood and urine are unlikely to be available; however, at exhumation soft tissue will be, and formalin embalming does not interfere with the extraction and measurement of free morphine (Levine et al., 1994). Concentrations of morphine glucuronides remain stable in liver for several days after death, but if the cadaver is not refrigerated, or if the postmortem interval is long (>3 days), free morphine will be liberated, and the ratio of free to conjugated morphine will not be a valid indicator of concentrations prior to death (Skopp et al., 1996; Bogusz et al., 1997; Moriya and Hashimoto, 1997).

5.6.1.6.4 Lymph nodes. Enlargement of abdominal lymph nodes occurs more often in active drug users than in normal controls. In one series, birefringent material was detect in portal lymph nodes in 42% of addicts studied, and signs of antigen stimulation, as

evidenced by the number of germinal centers and plasma cells, were twice as common in heroin addicts as in controls (60% for heroin addicts vs. 30 to 40% in normals) (Kringsholm and Christoffersen, 1987). Enlarged hepatic lymph nodes are a common finding in heroin addicts. Whether or not the enlargement is the result of some toxic effect exerted by morphine itself or the contaminants injected with it is not known, but some evidence for morphine immunotoxicity does exist. In rats chronically treated with either morphine or methadone, both the relative weight of the mesenteric lymph nodes and cell density in the medullary cords increase (van der Laan et al., 1995). Whether this change also occurs in humans is not known. It is known, however, that human lymph nodes concentrate morphine, and in some cases nodes taken at autopsy may have higher concentrations of morphine than blood and bile. In the only systematic study published, levels ranged from 0.03 to 0.87 mg per 100 g of tissue (Nakamura and Choi, 1983).

5.6.1.6.5 Other biofluids. Most of the opiates can be detected in saliva, but results must be interpreted with some caution. The oral or intranasal use of these drugs may result in very high saliva levels due to high concentrations of drug in the oral cavity (Wang et al., 1994). As might be expected, for the first hour after intranasal heroin administration saliva morphine concentrations far exceed those in plasma (Cone et al., 1993; Goldberger et al., 1993). Simultaneous measurement of morphine in saliva, plasma, and urine have shown that urine concentrations of morphine may be as much as 100 times greater than concentrations measured in saliva, and 16 times higher than levels in the plasma (Cone, 1990). Because of its increased lipid solubility, heroin appears in saliva much more quickly than morphine (Wang et al., 1994), but neither compound is likely to be detectable in saliva for much more than 12 hours. Low doses of heroin (less than 5 mg) are unlikely to be detected in saliva at all (Gorodetzky and Kullberg, 1974).

Cerebrospinal fluid levels peak three hours after a dose of morphine is given intramuscularly, and at equilibrium the ratio of CSF to plasma is very nearly 1:1. The elimination half-life of morphine from CSF is the same as the elimination half-life of morphine from the blood (Nordberg, 1984). Measurements made in patients undergoing lumbar myelography 1.5 hours after they had been given 10 mg intramuscular doses of morphine revealed CSF levels of morphine, M6G, and M3G of 8.8 ng/mL, 35 ng/mL, and 55 ng/mL, respectively (Laizure et al., 1993). CSF morphine levels higher than 20 ng/mL are thought to be consistent with narcotic-induced fatal respiratory depression (Logan and Luthi, 1994).

The kinetics of heroin and morphine in vitreous humor have not been studied in detail, but the results of the few studies that have been published suggest that the blood/vitreous ratio for morphine is approximately 6, with vitreous concentrations being lower than blood concentrations 95% of the time (Wahba et al., 1993; Scott and Oliver, 1999). The codeine/morphine concentration ratio in vitreous humor is generally similar to that reported for blood and urine, suggesting that vitreous measurement can be used as the basis for differentiating among fatalities induced by codeine or morphine (heroin) (Lin et al., 1997).

Even though no apparent correlation exists between 6-monacetylmorphine concentrations in blood, vitreous, and urine, if blood is positive for 6-monacetylmorphine (6MAM), then vitreous is likely to be positive as well (Scott and Oliver, 1999). In one series of 29 heroin-related deaths, 6MAM was present in concentrations above a quantitation limit of 1 ng/mL in the urine of 89% of the cases (mean, 170 ng/mL), in the cerebrospinal fluid of 68% of the cases (mean, 10 ng/mL), and in the vitreous humor of 75% of the cases (mean, 107 ng/mL) (Pragst et al., 1999).

5.6.1.6.6 Urine. After it has been converted to the glucuronide, urinary excretion is the main route for morphine elimination. In previous autopsy studies, urine concentrations of conjugated morphine have ranged from 100 to 120,000 ng/mL (Säwe, 1986). Measured concentration depends largely on the volume of urine that is allowed to collect between measurements (Cone, 1990). In 29 victims of heroin overdose, the blood/urine ratio for morphine was 2.53 ± 5.45, but the range was so wide (0.006 to 25.2) that drawing any sort of inference is impossible (Wahba et al., 1993). For 168 heroin-related deaths investigated by the San Francisco Medical Examiner's office in 1999, total morphine concentrations in the urine ranged from less than 10 to 85,000 ng/mL, a result strikingly similar to Säwe's original study more than 15 years ago (Karch, 2000). No study measuring urine morphine concentration after dosing with specific amounts of heroin has ever been published.

Racial and inter-ethnic differences must also be considered. Chinese subjects have a higher clearance rate for morphine than Caucasians primarily because they form more glucuronide than Caucasians do, and they do so more quickly. Whether or not these differences will have a bearing on drug detection is not clear, but the differences certainly can have clinical significance; in nontolerant subjects, equal doses of morphine produce more respiratory depression and a greater drop in blood pressure in Caucasians than in Chinese (Zhou et al., 1999).

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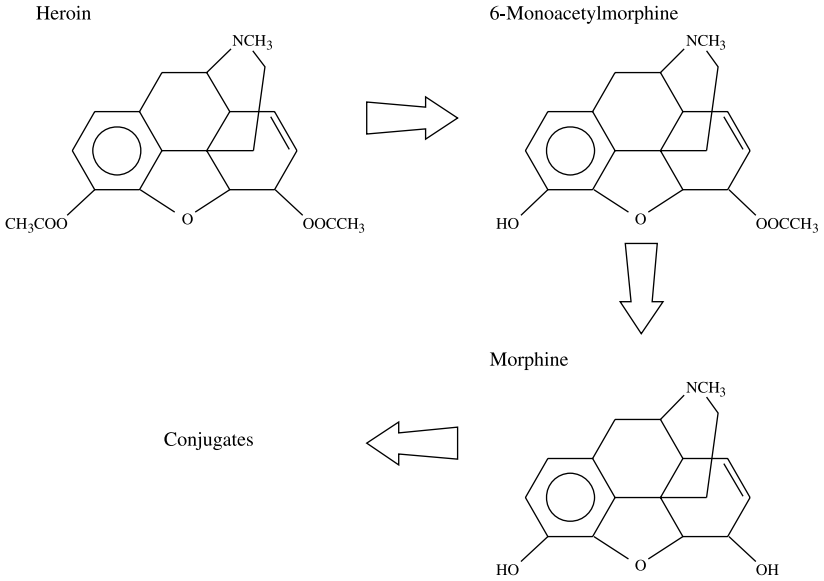


Figure 5.6.2.1 **Heroin metabolism.** Heroin is rapidly deacylated to 6-monoacetylmorphine and then to morphine.

5.6.2 Heroin

Heroin is a synthetic morphine derivative that was first sold by Bayer in 1898. It is produced by the acetylation of the two hydroxyl groups of morphine. Once in the body, heroin is very rapidly converted by deacetylation to 6-acetylmorphine and then to morphine (Figure 5.6.2.1). Conversion to 6-acetylmorphine is completed within 10 to 15 minutes. The total conversion of heroin to morphine is completed within a few hours. Heroin does not cross the nasal mucosa as readily as cocaine, and bioavailability via this route is poor, at least when compared to cocaine. The poor bioavailability of heroin probably explains why, in both the U.S. and Europe, intravenous injection is still the preferred route of administration. Now that the purity of street heroin has increased so drastically (from approximately 4% in the 1970s to nearly 50% today) (Tichacek and Napolitano, 1999), bioavailability is no longer a limiting factor, and the practice of nasal insufflation appears to have become increasingly popular. A total of 4820 heroin-related deaths were reported in the 1999 DAWN survey.

Heroin can also be volatilized, usually by heating it on a piece of folded tinfoil, and the fumes then inhaled. In Hong Kong, heroin used for this purpose was often dyed red, and as the fumes rose from the foil they could be imagined to have the undulating shape of a dragon's tail, explaining why the practice is called "chasing the dragon." Alternatively, the lighted end of a cigarette can be dipped in powdered heroin and then smoked. To keep the heroin from falling off the end of the cigarette, the smoker has to hold his head tilted backwards. Heroin can also be mixed into the contents of a cigarette. None of these routes is particularly effective. Studies have been done in addicts comparing urinary excretion after heroin was administered by injection, volatilization, and smoking in the form of a cigarette. The mean percentage of morphine recovered after injection was 68%, after volatilization it was 26%, and after cigarette smoking it was only 14% (Kramer, 1990; Strang et al., 1997). The pharmacokinetics of heroin smoking and "snorting" is reviewed in Table 5.6.2.1.

Table 5.6.2.1 Tissue Levels from Five Cases of Acutely Fatal Heroin Overdose

Tissue	Range
Blood	0.06–0.90
Urine	0.21–6.60
Bile	0.09–1.25
Stomach contents	0.01–0.03
Lung	0.09–0.18
Liver	0.07–0.29
Kidney	0.01–1.18
Heart	0.09–0.10
Spleen	0.11–0.95
Brain	0.01–0.10
Vitreous humor	0.03–0.35
Testicle	0.03–0.09
Muscle	0.01–0.04

Note: Values are in mg/L or mg/kg. Urine and bile specimens were hydrolyzed to free morphine from its conjugate.

Source: Adapted from Kintz et al. (1989).

5.6.2.1 Tissue distribution

The half-life of 6-acetylmorphine is so short that it usually is not quantitated. In six volunteers given single doses of heroin (3.0 and 6.0 mg), the urine half-life averaged 0.6 hours, with a total detection time of 2 to 8 hours. In contrast, free morphine and total morphine were detectable in the urine for up to 24 hours after heroin administration (Cone et al., 1991).

Simultaneous measurements of morphine and its metabolites in cases of heroin overdose have been reported. In a German study, morphine, M3G, M6G, and 6MAM were quantitated simultaneously in 21 heroin-overdose victims. Blood concentrations of morphine ranged from 8–1539 ng/mL, M3G from 111–941 ng/mL, M6G from 32–332 ng/mL, and 6MAM from 0–73 ng/mL. The levels of morphine were correlated with glucuronide values and with 6MAM (Bogusz et al., 1997). Very similar results, for the glucuronides at least, have been reported from Australia (Gerostamoulos and Drummer, 2000) and from the U.S. (Logan and Smirnow, 1996).

Concentrations of morphine, M3G, and M6G are generally lower in blood and in vitreous humor than in CSF, but the concentrations of morphine and molar ratios of M6G to morphine in blood and CSF correlate very well. Thus, the presence of much more morphine than glucuronide is thought to be consistent with ingestion immediately prior to death. However, the ratio of morphine to its metabolites is highly dependent on the time elapsed from death until tissue sampling (postmortem interval) and on which tissue is being sampled. Gerostamoulos and Drummer (2000) did not find significant differences between morphine and metabolite concentrations in samples taken from subclavian, heart, and femoral regions, nor did they observe any significant differences between concentrations measured on arrival at the morgue and concentrations measured, on average, 59 hours later. The finding suggests that significant postmortem redistribution of morphine and its metabolites seems unlikely.

Nonetheless, over-reliance on morphine-to-metabolite ratios could lead to erroneous conclusions (Skopp et al., 1996). Morphine has a very large volume of distribution (V_d of 2–5 liters), but the volume of distribution of the metabolites is small (V_d <1). At equilibrium, virtually all the free morphine is found in tissue, while all the glucuronides are found in the blood. The movement of less than 1% of free morphine from tissue back into postmortem blood would double the observed concentration and lead to the erroneous conclusion that morphine concentrations at the time of death are much higher than they actually were. For the present, the issue remains unresolved.

Tissue levels in heroin body packers carrying balloons full of heroin in their intestines may reach astronomic levels. A woman who had swallowed a number of packets containing 25% heroin was found to have a 6-acetylmorphine level of 184,000 ng/mL. Morphine and codeine levels were equally impressive (120,000 and 1700 ng/mL, respectively) (Joynt and Mikhael, 1985).

5.6.2.2 Excretion and detectability

The conversion of heroin to morphine is so rapid that the probability of detecting heroin in either blood or urine is small. However, once the conversion to morphine is complete, the limits of detection are the same as for morphine itself. Testing for opiates in urine is a problem. Poppy seeds are widely eaten and they contain both morphine and codeine, but not heroin. Poppy seeds from different origins contain widely variable amounts of morphine (2 to 251 μg/g) and codeine (0.4 to 57.1 μg/g) (Pettitt et al., 1987; Pelders and Ros, 1996), but under no circumstances will innocent poppyseed eaters have detectable levels of 6-acetylmorphine. Small amounts of 6MAM may also be ingested directly as contaminants produced along with heroin in the manufacturing process (O'Neil and Pitts, 1992).

Because 6MAM is only detectable for a few hours, the presence or absence of 6MAM cannot be used to reliably separate innocent poppyseed ingestion from heroin abuse. If 6MAM is not detected, that may only mean that heroin use occurred more than three or six hours earlier. When 6MAM is not detected, distinguishing innocent poppy ingestion from heroin abuse can be problematic. In the past, the distinction was made by relying on the presence of confirmatory evidence such as track marks. That approach was never very effective, and now that some heroin users insufflate the drug, it cannot be relied upon. Workplace drug-testing regulations have been altered to reflect that reality. When workplace drug-testing regulations were first put in place, the urinary concentration cutoff for morphine was 300 ng/mL. That number has now been raised to 2000. In addition, any specimen with concentrations exceeding the 2000 ng/mL cut off must now also be tested for the presence of 6MAM. If no 6MAM is detected, the test is considered to be negative.

Although not yet officially recognized, there are several other ways available to distinguish narcotic abuse from poppyseed ingestion or the innocent use of narcotic-containing cough medications. One way is to test urine for thebaine, a naturally occurring compound found in poppy seeds. It is not present in refined heroin, but does appear in the urine of poppyseed consumers. Volunteers given an 11-g dose of poppy seeds were found to have urine thebaine concentrations ranging from 2 to 81 ng/mL (Cassella et al., 1997), but thebaine is not detected in the urine of heroin users. Another alternative is to test hair. Both 6MAM and M6G are deposited within the hair matrix and remain stable there for many months (Rothe and Pragst, 1995; Cassella et al., 1997). The only problem with this approach, and it is largely theoretical, is that heroin samples can also contain 6MAM. That means that the presence of 6MAM, like the presence of heroin itself, might be the result of external contamination (as in the case of a customs officer who confiscates a large quantity of heroin).

5.6.3 Codeine

5.6.3.1 General considerations

Codeine is one of the naturally occurring alkaloids found in opium. Depending on where the poppies are grown, samples of opium have a codeine content of 0.7 to 2.5%. Codeine was first isolated from opium by Robiquet in 1832, 27 years after Sertürner isolated morphine. Most of the codeine consumed in antitussive and analgesic mixtures is of semisynthetic origin, produced by the methylation of morphine. The DAWN report for 1990 listed only 501 codeine-related deaths. That number nearly tripled, rising to 1395 by 1999. Codeine now accounts for 12% of all reported drug-related deaths (Kissin et al., 2000).

Tons of codeine compound are consumed annually, but very important questions about codeine metabolism and toxicity remain unanswered. For example, it has been suspected for half a century that the pain-relieving properties of codeine, which are about one-fifth those of morphine, arise from its conversion to morphine (Sanfilippo, 1948); however, the actual mechanism still remains unknown. More important, at least as far as investigations of toxicity are concerned, is the fact that variation exists in inter- and even intra-individual ability to metabolize codeine (Chen et al., 1991b; Yue et al., 1991a,b; Lee et al., 1997; Caraco et al., 1999).

The major metabolic pathways for codeine are glucuronidation and demethylation, but most of codeine is converted to codeine-6-glucuronide, an inactive metabolite. Much smaller amounts may be converted to norcodeine, which is believed to be psychoactive (Fraser et al., 1960). During the last decade it has become apparent that, depending on an individual's genetic makeup, significant amounts of codeine may be shunted to pathways yielding pharmacologically active products. *O*-demethylation of codeine leads to the production of morphine, which exerts substantially greater narcotic effects than codeine (Figure 5.6.3.1.1). Codeine that has been converted to morphine is, in turn, converted to M3G or M6G. All of these compounds are excreted in the urine, where somewhat less than 90% of a single dose can be recovered within 48 hours, mostly as codeine-6-glucuronide (Chen et al., 1991b; Hedenmalm et al., 1997). The important consideration here is that codeine metabolism yields three different compounds with known psychoactivity: morphine, normorphine, and morphine-6-glucuronide.

5.6.3.2 Codeine physical constants

Codeine is (5α,6α)-7,8-didehydro-4-5-epoxy-3-methoxy-17-methylmorphinan-6-ol. The formula is $C_{18}H_{21}NO_3$, and the molecular weight is 299.37. The melting point is 154 to 156°C. One gram dissolves in 120 mL of water or 2 mL of room-temperature alcohol. It is also sometimes called methylmorphine or morphine monomethyl ether (Budavari et al., 1996).

5.6.3.3 Routes of administration

The radioimmunoassay used in early studies of codeine metabolism, because they measured both codeine and its metabolites, almost certainly yielded spuriously high concentrations of codeine in the plasma and urine (Chen et al., 1991b). That is no longer the case, and specific antisera can be used to quantitate morphine, codeine, and each of their main metabolites simultaneously (Beike et al., 1999). Measurements in healthy volunteers given a 50-mg oral dose of codeine indicate that peak concentrations are reached within 1 to 2 hours after oral administration, and that the plasma half-life is on the order of 2.4 to 3.2 hours (Chen et al., 1991b; Yue et al., 1991a,b; Lafolie et al., 1996). Peak blood concentrations after an oral dose of 50 mg in healthy, normal metabolizers averaged 140 ng/mL (Yue et al., 1991b). The peak concentration of codeine in the saliva is nearly three times that

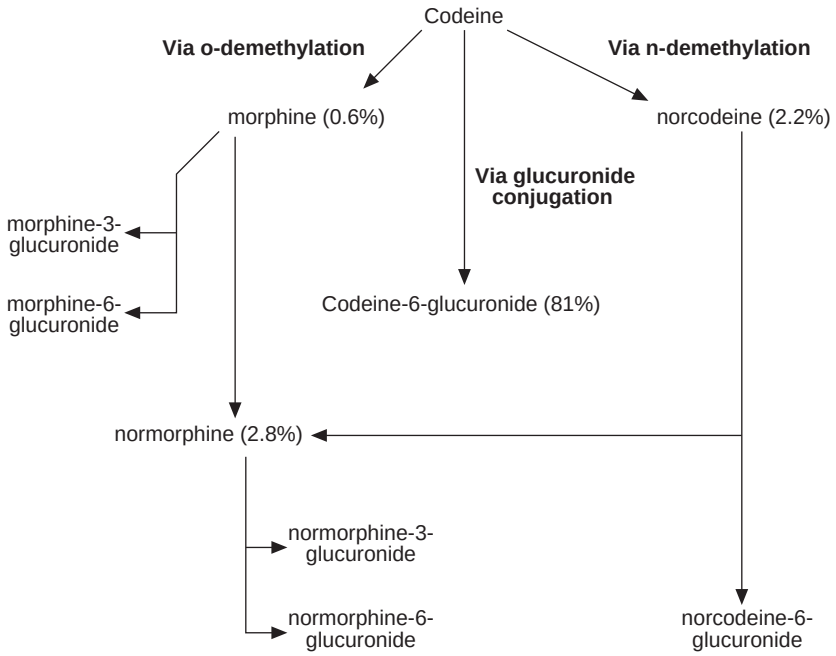


Figure 5.6.3.1.1 Human metabolism of codeine.

measured in the blood, even though the half-life in both fluids is approximately 3.2 hours (Chen et al., 1991b). Resultant blood concentrations after alternative routes of administration have not been reported.

5.6.3.4 Role of genetic polymorphism

After oral dosing, plasma levels of codeine glucuronide reach concentrations 5 to 10 times higher than those of codeine (Chen et al., 1991b; Lafolie et al., 1996). Chronic administration of codeine does not appear to alter its kinetics, but the genetic makeup of an individual affects analgesia, toxicity, and drug detection. Codeine metabolism is under monogenic control. The ability to form M6G, morphine, and norcodeine from codeine can be predicted by an individual's ability to hydroxylase debrisoquine. Approximately 10% of Caucasians, and a much larger percentage of Chinese, are poor hydroxylators. The formation of morphine from codeine is mainly mediated by the polymorphic enzyme CYP2D6. On average, an extensive hydroxylator converts approximately 6% of a given dose of codeine (demethylation followed by conjugation) to morphine. The morphine so formed is then metabolized to the usual metabolites, including M6G and normorphine. At equilibrium, peak morphine peak concentrations reach values approximately one-tenth the peak codeine concentration (see Table 5.6.3.4.1) (Chen et al., 1991b; Tseng et al., 1996).

Poor hydroxylators, with a polymorphic form of the CYP2D6 enzyme, still produce morphine from codeine, but much less than the extensive metabolizers (less than 1% conversion), and concentrations of morphine and its metabolites in their plasma may be so low that they are not measurable. Nonetheless, these metabolites are formed, and they do appear in the urine. Urine screening tests for opiates will be positive in both poor and extensive metabolizers, but they will remain positive significantly longer in extensive metabolizers (mean, 33 hours for extensive metabolizers vs. 17 hours for poor metabolizers)

Table 5.6.3.4.1 Effects of Genetic Polymorphism on Codeine Metabolism

Drug	Hydroxylators	Non-hydroxylators
Codeine	411 ± 219	239 ± 60
Codeine-6-glucuronide (C6G)	4090 ± 3380	3890 ± 949
Norcodeine (NC)	48 ± 26	48 ± 13
NCG	108 ± 44	146 ± 8
Morphine-3-glucuronide (M3G)	186 ± 121	9.1 ± 8.2
Morphine-6-glucuronide (M6G)	41 ± 23	Not detectable
Normorphine (NM)	41 ± 33	Not detectable
Morphine (M)	27 ± 23	Not detectable

Note: Values are in nmol/dL. All measurements are from healthy volunteers who had been previously screened for the ability to hydroxylate debrisoquine.

Source: Data derived from Yue et al., 1991b.

(Hedenmalm et al., 1997). The forensic significance of these observations requires further elaboration, but it should be apparent that some individuals will have more psychoactive material in their bloodstreams than simple measurements of morphine or codeine levels would indicate. The opposite is also true. Individuals likely to be slow hydroxylators should have little or no morphine detectable in their blood if the only drug taken was codeine. Morphine will be detectable in their urine, even if only for a short time.

It had been thought that small amounts of morphine were metabolically converted to codeine (Boerner and Abbott, 1973), but, in fact, that is not the case (Yeh, 1974; Yeh et al., 1975). The codeine detected in urine gets there because it is present in morphine in trace amounts, even in pharmaceutical-grade morphine preparations (Vaughan and Dennis, 1979). Thus, the presence of codeine should not be presumed to be evidence for anything but the ingestion of codeine. The presence of trace amounts of morphine, on the other hand, can be accounted for by the metabolic conversion of codeine to morphine.

Difficulties can also be caused by the less well-known conversion of codeine to hydrocodone. Allegations of illicit hydrocodone use have been made against individuals taking physician-prescribed oral codeine who strenuously deny ever taking hydrocodone, but who nonetheless have positive urine opiate immunoassay tests subsequently confirmed by GC/MS. Generally, the hydrocodone concentrations in these cases are quite low, on the order of 100 ng/mL. These low concentrations are the result of a minor metabolic pathway leading to the conversion of small amounts of codeine to hydrocodone. Hydrocodone may remain detectable in the urine for several days, even after the administration of only one dose of codeine (Oyler et al., 2000).

5.6.3.5 Codeine tissue disposition

Data on the tissue distribution of codeine are sparse and, given the known conversion of codeine to morphine, and to its active metabolite M6G, are impossible to interpret. The results of the few studies that have been done suggest that total and free codeine concentrations, in cases where codeine is clearly the cause of death, completely overlap concentrations in cases where codeine is an incidental finding. And, while hair morphine concentration measurements can be used to assess morphine tolerance after death (Tagliaro et al., 1998), it is not clear whether hair codeine measurements can be used in the same fashion.

Simultaneous measurements of blood and bile concentrations in codeine-related deaths disclosed a mean blood morphine concentration of 0.29 mg/L (range, 0.10–0.89 mg/L) with 38 mg/L in bile (range, 3.3–112 mg/L). Codeine concentrations measured at

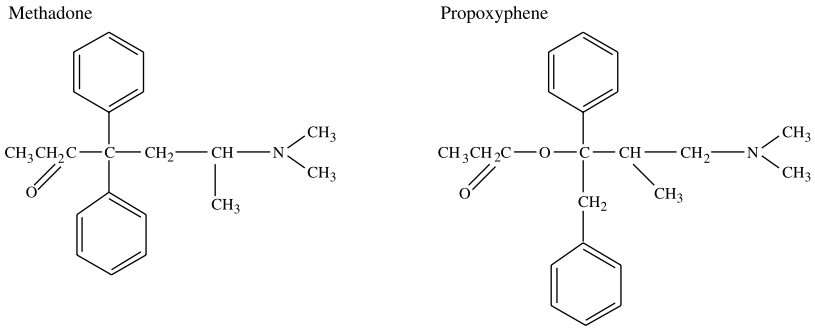


Figure 5.6.4.1 **Methadone and propoxyphene.** Even though it is not obvious, the methadone molecule contains the same basic structures as all the other morphine-related analgesics. Propoxyphene is a derivative of morphine.

the same time were 0.06–6.4 mg/L (mean, 1.5 mg/L) in blood, and 0.22–89 mg/L (mean, 24 mg/L) in bile (Table 5.6.3.5.1) (Crump et al., 1994). Results were not very different in a second study of 107 codeine-related deaths. In only six of the cases (8.8%) was codeine considered to be the actual cause of death. The mean concentration of total codeine in femoral blood was 4.0 ± 2.3 mg/L (range, 2.1–8.0 mg/L), while the mean concentration of free codeine was 1.3 ± 0.9 mg/L (range, 0.4–2.8 mg/L). Free and total codeine concentrations were not significantly different in cases where other drugs were present and where codeine was not deemed to be the cause of death (Gerostamoulos et al., 1996).

5.6.4 Methadone

Methadone belongs to a class of compounds referred to as diphenylpropylamine derivatives. Drugs in this class have a general formula that at first glance bears little relationship to the basic morphine molecule, but which in fact contains the same basic structures common to all morphine analgesics (Figure 5.6.4.1). Methadone is supplied as a racemic mixture, but almost all of the opiate activity is due to the *l-* form. In the 1999 DAWN survey, 643 methadone-related deaths were reported, amounting to 5.5% of all reported narcotic deaths for that year (Kissin et al., 2000). Even though the absolute number of methadone-related deaths has increased, the percentage of deaths due to methadone has actually been gradually declining since 1990 (7.5% in 1990). The decline is unexplained, but it may have to do with the relatively slow increase in the total number of methadone maintenance programs and the limited availability of methadone on the black market. This trend may reverse once methadone-prescribing rules are liberalized.

Until 1965 when it was introduced as a maintenance drug for heroin addicts, methadone was seldom prescribed, probably because in some individuals its half-life can exceed 50 hours. Today, in spite of the introduction of new agents such as L-LAAM and buprenorphine, methadone continues to be the drug of choice for the treatment of heroin addiction. It is also prescribed with increasing frequency for cancer patients and for those with intractable pain (Berland, 2000). It has been suggested that methadone treatment normalizes the depressed immune function normally observed in heroin addicts (Novick et al., 1989), although that idea is still debated (Mazzone et al., 1994; De Waal et al., 1998). If methadone does reverse long-term heroin-related immunosuppression, it may have more to do with improved lifestyle and decreased number of intravenous injections than with any direct effect of methadone (McLachlan et al., 1993; Radkowski et al., 1996).

5.6.4.1 Methadone physical constants

Methadone is 6-dimethylamino-4,4-diphenyl-3-heptanone. The chemical formula is $C_{21}H_{28}ClNO$. It has a molecular weight of 345.91 and is composed of 72.92% carbon, 8.16% hydrogen., 10.25% chloride, 4.05% nitrogen, and 4.63% oxygen. Twelve grams dissolve in 100 mL of water, but methadone is essentially insoluble in ether. The pH of an aqueous 1% solution varies from 4.5 to 5.6. Aqueous solutions may be autoclaved for up to one hour without disruption of the molecule (Budavari et al., 1996). In the U.S., brand names include Dolophene® and Methadose®. The S- form of methadone exerts little narcotic effect, but pure R- isomer is expensive to make; a racemic mixture of methadone is used in both the U.S. and Europe.

5.6.4.2 General considerations

Blood methadone concentrations cannot be interpreted in isolation; additional historical and clinical information will always be necessary. Tolerant individuals may take doses of methadone that would induce fatal respiratory depression in naïve users. In one study, heroin addicts treated with methadone doses ranging from 180 to 260 mg/day experienced no adverse effects (Walton et al., 1978). On the other hand, deaths have been reported in addicts who were just beginning methadone maintenance, receiving a mean dose of only 57 mg/day (Drummer et al., 1992). Inter-individual response varies considerably and is dependent on sex, weight, use of concomitant medications, duration of methadone treatment, previous exposure to other opioids, and on plasma concentrations of α-1-acid glycoprotein (Garrido and Troconiz, 1999).

Most methadone-related deaths occur during the first few weeks of maintenance therapy, a result of advancing the dosage so quickly that fatal respiratory depression occurs (Coleridge et al., 1992; Caplehorn and Drummer, 1999). The relative risk of such an occurrence is nearly seven times higher than in untreated heroin addicts and 97.8 times higher than for methadone maintenance patients who have been in maintenance for more than two weeks (Wu and Henry, 1990; Caplehorn and Drummer, 1999).

In the U.S., the amount of methadone diverted to the black market is limited by the relatively small number of heroin users enrolled in methadone programs. Of the estimated 810,000 heroin addicts in the U.S. in 1999, only 115,000 were participating in methadone maintenance programs (Henry, 1999). Nonetheless, methadone is sold on the black market, and opiate-naïve individuals who experiment with methadone are at considerable risk.

Clinical trials have shown that for effective prevention of human immunodeficiency virus (HIV) seroconversion and prevention of heroin use, methadone doses of at least 90 mg/day (Loimer and Schmid, 1992) and plasma concentrations in excess of 100 ng/mL (Holmstrand et al., 1978; Tennant, 1987) are required. Heroin addicts treated with higher doses of methadone are less likely to test positive for opiates than those treated with lower doses or with placebo (Strain et al., 1993). Patients receiving 40 mg of methadone per day were found to be more than twice as likely to use heroin than those receiving 80 mg/day (Caplehorn et al., 1993). Ultimately, however, methadone dosages must be individualized to account for variations in tolerance and dependency (Wolff and Hay, 1994).

5.6.4.3 Metabolism and pharmacokinetics

Information about the clinical toxicology of methadone is largely derived from studies of healthy volunteers given single doses of methadone or cancer patients injected with methadone intravenously (Inturrisi et al., 1987). Studies of drug addicts suggest that measurements made in the chronically ill falsely underestimate methadone's terminal half-life and volume of distribution (Kristensen et al., 1996; Wolff et al., 1997; Rostami-

Hodjegan et al., 1999). In practice, plasma methadone concentrations in maintenance patients, even compliant ones, have been found to vary considerably. In one study, values ranged from 20 to 1308 ng/mL with a mean concentration of 451.4 ± 306 ng/mL (Loimer and Schmid, 1992).

Methadone undergoes *N*-demethylation in the liver. Its principle metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, commonly referred to as EDDP, is produced by liver microsomes, mainly CYP3A4. Methadone induces hepatic production of microsomal enzymes, and methadone metabolism is accelerated in chronic users. Naïve users take much longer to clear methadone from their circulation, which is one reason they are at greater risk for overdose. However, even long-term patients are at risk if they take another drug, illicit or prescription, that competes for CYP3A4 (Foster et al., 1999, 2000). Because of the large inter-individual variations, and because of the possibility of drug interactions, clinicians have begun to rely on measurement of the plasma methadone-to-EDDP ratio as an indicator of safe and effective dosing.

Various reports have placed the normal value for the methadone-to-EDDP ratio at between 18 and 22 (de Vos et al., 1998), depending on whether pure *l*-methadone, or *d,l*-methadone has been administered. For unexplained reasons, the ratio seems to be much lower in postmortem blood samples (means value of 13.6:1 in 38 methadone-related fatalities) (Karch and Stephens, 2000). Methadone-to-EDDP ratios can also be measured in urine, but the results must be interpreted with caution, because methadone may be produced by thermal degradation when urine samples are placed in the injection ports of the gas chromatographs (Galloway and Bellet, 1999).

One way to prevent the diversion of methadone to the black market is to check the urine of clients to make sure that they have, in fact, taken their methadone. The only problem with this approach is that some individuals are rapid methadone metabolizers. They convert methadone into a metabolite called EMDP (2-ethyl-5-methyl-3,3-diphenylpyrroline), and the conversion can occur so quickly that no methadone is detected by conventional urine screening immunoassays.

Another confounding issue in the interpretation of blood methadone concentrations is α-1-acid glycoprotein. Like the P-450 system, production of this protein is genetically heterogeneous. At least three main phenotypes of α-glycoprotein are recognized, and each of these has a different affinity for methadone (Callaghan and Riordan, 1993). In studies with human volunteers, measured free fractions of racemic, *d*-methadone, and *l*-methadone ranged from 10 to 14% (Eap et al., 1990), with the remainder bound to various proteins. The main reason for the inter-individual variation was α-glycoprotein binding. In hospitalized heroin addicts, the severity of abstinence symptoms correlates with α-glycoprotein concentrations; the higher they are, the worse the symptoms (Garrido et al., 2000).

The variation in half-life among individuals is wide, with reported values ranging from 13 to 58 hours (Inturrisi and Verebely, 1972a,b; Goldstein and Herrera, 1995). In opioid addicts, methadone kinetics are best described by a single-compartment model. The volume of distribution is large (6.7 L/kg), and the clearance rate is low (3.1 mL/min/kg). The observed elimination half-life of 26.8 hours in addicts is substantially lower than earlier estimates had suggested (Wolff et al., 1993).

Methadone clearance is altered when it is taken with other drugs. When alcohol and methadone are taken at the same time, which is a fairly frequent occurrence, the metabolism of each is enhanced, and withdrawal symptoms can ensue (Kreek, 1981). When methadone and cocaine are taken together, methadone plasma levels decrease, apparently because the cocaine accelerates methadone excretion (Tennant and Shannon, 1995). Because methadone increases CYP3A4 activity, and because this cytochrome is involved with the metabolism

of so many drugs, numerous interactions are possible. CYP3A4 is found in both the small bowel and liver. That means it can oxidize a broad spectrum of drugs even before they have entered the systemic circulation (Ereshefsky and Dugan, 2000).

Drugs that inhibit CYP3A4 metabolism can be expected to increase blood methadone concentrations. Unfortunately, the same drugs that inhibit CYP3A4 also inhibit P-glycoprotein production, which leads to even higher free methadone concentrations. Some of the better known CYP3A4 inhibitors include traconazole, ketoconazole, clarithromycin, erythromycin, nefazodone, ritonavir, and grapefruit juice. Conversely, drugs that induce CYP3A4, such as some of the nucleoside analogs used to treat HIV infection, can cause a precipitous drop in methadone blood concentration and bring on withdrawal symptoms (Fromm et al., 1997; Iribarne et al., 1997; Heelon and Meade, 1999).

The amount of methadone required to produce clinical effects is also altered by the body's immune response. Antimethadone antibodies can be detected in more than half of the heroin users chronically treated with methadone. If these same individuals are HIV positive, then antibodies against methadone are present in nearly all, which may explain why blood methadone concentrations are higher in HIV-positive than in HIV-negative patients (398 vs. 265 ng/mL) (Gamaleya et al., 1999).

5.6.4.4 Routes of administration

Oral absorption of methadone is excellent, and when compliance is good a high degree of correlation exists between the dose administered and the plasma level that results. Over the range of 3 to 100 mg, plasma methadone concentrations increase by 263 ng/mL for every milligram of methadone per kilogram of body weight. A similar, nearly linear, concentration increase is also observed in saliva, although the peak levels are somewhat higher, and the half-life somewhat longer (Wolff and Hay, 1992). In cancer patients, a 10-mg intravenous injection produced a peak plasma level slightly above 500 ng/mL, falling to below 100 ng/mL at one hour (Inturrisi et al., 1987). Blood and plasma concentrations after the less common routes of administration have not been measured.

5.6.4.5 Autopsy findings

Methadone maintenance clients are likely to have some cutaneous stigmata of past intravenous heroin abuse, and are very likely to be infected with hepatitis C virus, even if histologic changes are not evident. Table 5.6.4.5.1 lists the most frequent abnormalities detected at autopsy in a series of 38 methadone-related deaths (Karch and Stephens, 2000). While most of the autopsy findings such as terminal aspiration and pneumonia (15.6%) are recognized complications of intravenous opiate abuse, necrotizing fasciitis is much less common, and the apparent connection is unexplained.

5.6.4.6 Postmortem blood concentrations

Methadone blood concentrations in fatal cases overlap completely with those found in methadone maintenance program participants and in decedents where death is due to trauma and the presence of methadone simply an incidental finding. In a study of 38 decedents where methadone was detected, the mean blood methadone concentration was 975 ± 681 ng/mL, the mean blood EDDP was 253 ± 529 ng/mL, and the mean blood methadone-to-EDDP ratio was 13.6. Urine concentrations of methadone ranged from 5 to 6 mg/L, and were the same in individuals where methadone was an incidental finding and in those where it was the cause of death. The mean blood methadone-to-EDDP ratio for the entire group of 38 was 13.5 ± 17.4, but the range was so wide, from 0.572 to 60,

Table 5.6.4.5.1 Autopsy Findings in Methadone Users

Diagnosis	Number	Percent (%)
Track marks	13	34.2
Coronary artery disease	9	21.0
Cirrhosis	7	18.4
Pneumonia	6	15.7
Hepatic fibrosis	5	13.1
Fatty liver	4	10.5
Necrotizing fasciitis	4	10.5
Birefringent crystals	4	10.5
HIV	3	7.8

Source: Based on an analysis of 38 cases investigated by the Office of the San Francisco, CA, Medical Examiner (Karch, S. B. and Stephens, B. G., *West. J. Med.,* 172(1), 11–14, 2000. With permission.)

that determination of the ratio was of no diagnostic value. An incidental finding was the presence of cocaine in nearly half the decedents, and morphine in nearly a third (Karch and Stephens, 2000). A study from England analyzed findings in 55 cases where methadone poisoning was given as the sole cause of death. The mean methadone concentration in adult cases was 584 ng/mL (median, 435; range, 84 to 2700). The value was not significantly lower when other drugs were present (Milroy and Forrest, 2000). Given the degree of overlap of findings in cases where methadone is, and is not, related to the cause of death, it is simply impossible to distinguish between the two categories on the basis of toxicology testing alone.

5.6.4.7 Maternal–fetal considerations

There is general agreement that infants born to mothers being treated with methadone are significantly less mature and lower in weight than control infants. More than half of all such infants can be expected to develop neonatal abstinence syndrome, and most stay in the hospital longer than infants not exposed to drugs (Kelly et al., 2000). However, it is also agreed that methadone treatment during pregnancy is vastly preferable to either medical detoxification or leaving heroin-addicted women dependent on street drugs; treatment reduces maternal and fetal morbidity and mortality (Kandall et al., 1999).

During the first day of life, maternal plasma methadone levels correlate significantly with neonatal plasma methadone levels. It also has been observed that the severity of central nervous system signs of withdrawal correlate with the rate of decline in the infants' plasma methadone levels (Doberczak et al., 1993). In 21 neonates with symptoms of withdrawal, the mean maternal methadone level 16 hours after delivery was 183 ± 118 ng/mL, while the mean plasma level in samples drawn from the infants at the same time was 26 ± 8 ng/mL. Methadone levels decreased in the infants at the average rate of 0.2 ± 0.3 ng/mL/hr.

Nursing mothers excrete methadone in their milk, but exposure is minimal and insufficient to produce symptoms. The mean milk-to-plasma ratio was 0.44 (0.24–0.64). Assuming an average milk intake of 0.15 L/kg/day and a bioavailability of 100%, the infants received less than 3% of the methadone ingested by the mother. Methadone concentrations in 7 of the infants were below the limit of detection (Wojnar-Horton et al., 1997).

5.6.5 Propoxyphene

5.6.5.1 General considerations

Propoxyphene is a methadone molecule derivative, but unlike methadone, propoxyphene is a relatively weak μ agonist and has only mild analgesic properties. In the past, propoxyphene overdose was much more common than it is now, and it was associated with large numbers of fatalities (Soumerai et al., 1987). Propoxyphene is particularly toxic because, in addition to exerting the usual respiratory depressant effects common to all μ-agonist narcotics, propoxyphene and its principal metabolites also act as local anesthetics, with potent membrane stabilizing activity.

In the U.S., deaths attributable to propoxyphene have been gradually decreasing quite considerably. The 1999 DAWN survey reported 466 propoxyphene-related fatalities, accounting for 4% of all reported drug-related fatalities for that year (Kissin et al., 2000b). The decline in fatalities is partially explained by the way that propoxyphene is now formulated. Early formulations contained a pellet of propoxyphene inserted at the end of a capsule containing aspirin or acetaminophen, and it was a simple matter to remove the pellet and dissolve it in water for injection. That practice was eliminated years ago, and propoxyphene preparations were repackaged in such a way as to make the separation of propoxyphene all but impossible. Virtually all episodes of propoxyphene toxicity are now due to oral ingestion.

Propoxyphene-related deaths are more common in Europe, particularly in Scandinavia. In Sweden, from 1992 to 1996, propoxyphene was detected in 7.5% of nearly 25,000 forensic autopsies, with the rate having increased by 25% from 1992 to 1996 (Jonasson et al., 1998). A preponderance of the propoxyphene deaths reported by the Swedish researchers involved relatively young men, under the age of 45 years (Jonasson et al., 2000). In Denmark, the typical victim of propoxyphene poisoning uses the drug for suicidal, not "recreational," purposes. Most have a history of psychiatric disease and concurrently use alcohol (Leander et al., 1997).

5.6.5.2 Physical constants and names

Propoxyphene is [S-(R,S)]-α-[2-(dimethylamino)-1-methylethyl]-α-phenylbenzenethanol propanoate ester. Its formula is $C_{22}H_{29}NO_2$, and it has a molecular weight of 339.48. In the U.S., propoxyphene is sold as propoxyphene hydrochloride: Darvon® Compound-65 and Darvon® Pulvules (Eli Lilly & Co.), Wygesic® tablets (Wyeth-Ayerst Laboratories), generic propoxyphene hydrochloride (Mylan Pharmaceuticals), and in various generic combinations with acetaminophen alone or with caffeine. Propoxyphene napsylate is sold as a generic and under the brand name Darvocet-N® (Eli Lilly & Co.).

5.6.5.3 Metabolism and pharmacokinetics

Propoxyphene is absorbed rapidly from the gastrointestinal tract (Giacomini et al., 1980; Young, 1983; Flanagan et al., 1984). Peak plasma concentrations occur within one to two hours after a single oral dose and are not very high because propoxyphene undergoes extensive first-pass metabolism in the liver. Peak propoxyphene levels after a single 65-mg dose, in healthy young volunteers, ranged from 260 to 900 ng/mL, with a mean of 590 ng/mL. In this same group, the half-life ranged from 6.4 to 26.4 hours, with a mean of 13 hours. Simultaneous measurements of nordextropropoxyphene showed peak levels ranging from 510 to 2140 ng/mL, with a mean of 1950 ng/mL. The half-life for the metabolites is much longer than that of the parent compound, with a mean value of 22.2 hours.

Propoxyphene is metabolized by the CYP3A4 microsome which oxidizes it to norpropoxyphene, the principle metabolite. If propoxyphene is co-administered with other drugs that compete for CYP3A4, such as carbamazepine, acetazolamide, macrolide antibiotics, isoniazid, metronidazole, verapamil, diltiazem, cimetidine, and some antidepressants, then potentially dangerous plasma elevations of other drugs could result (Spina et al., 1996).

No metabolic differences between the sexes are detectable, but age has definite effects on propoxyphene metabolism. The half-life of dextropropoxyphene in the young is only 13 hours, but it rises to over 35 hours in the elderly. Similarly, the half-life for norpropoxyphene in young adults is approximately 22 hours, rising to over 40 hours in the elderly (Flanagan et al., 1984). Age-related changes in metabolism are not unique to propoxyphene. They can occur with almost any drug that undergoes hepatic oxidation followed by renal excretion. Excretion can be prolonged in individuals with liver impairment, where first-pass oxidation is reduced and concentrations of propoxyphene in the circulation are increased.

Norpropoxyphene has a longer half-life than propoxyphene. It accumulates in cardiac tissue, where it blocks not only the inward sodium current but also the potassium currents. The orderly sequence of depolarization is disrupted, conduction is delayed across the myocardium, and not enough calcium enters the myocytes to allow them to contract normally. Myocardial contractility decreases, causing cardiac output and blood pressure both to drop. Neither treatment with β-adrenergic agents nor pacing has proven very effective (Whitcomb et al., 1989; Wu et al., 1997; Ulens et al., 1999). Propoxyphene-induced respiratory depression is readily reversed by narcotic antagonists but myocardial depression is not, because it is not mediated by μ receptors.

It is believed that when propoxyphene is co-administered with ethanol, first-pass hepatic transformation is decreased, and higher blood concentrations of propoxyphene result (Oguma and Levy, 1981). The importance of an ethanol–propoxyphene interaction is difficult to assess. In the case series reported from Sweden, where propoxyphene was detected in 7.5% of forensic autopsies (n =1782), ethanol was simultaneously detected in less than one-quarter of all cases (Jonasson et al., 1998). Clearly, co-ingestion of ethanol is not required to cause fatalities.

5.6.5.4 Tissue distribution

Propoxyphene is highly lipid soluble, and large amounts are sequestered in fat tissue. Fatalities were frequent during the mid-1970s, and levels at autopsy have been reported for hundreds of cases (Cravey et al., 1974; Baselt and Wright, 1975; McBay, 1976; Hudson et al., 1977; Caplan et al., 1985). In the past, it was generally assumed that serious toxicity was associated with levels greater than 1 mg/L, and fatalities were associated with levels of over 2 mg/L. But, as with all opiates, tremendous overlap exists, and fatalities have occurred at much lower levels, while at the same time, higher values have been observed as incidental findings.

Postmortem measurements are unreliable. Measured concentrations depend entirely on the area in the body from which the blood samples are drawn. This variability was dramatically illustrated by a study completed in the early 1990s (Yonemitsu and Pounder, 1992). Multiple blood and tissue samples were obtained from four decedents who had died of propoxyphene poisoning. A second and third set of samples were obtained 24 and 48 hours later. In every case, the lowest blood concentrations were observed in peripheral blood samples. When the levels in the peripheral blood measured 3.5 mg/L, the concentration in the aorta was 1.9 g/L, nearly 55 times higher! When blood was drawn from the pulmonary artery, the propoxyphene concentration increased twofold at 24 hours and threefold at 48 hours.

Given the wide variations in values that can be measured in the same cadaver's blood, drawing any conclusions from quantitative propoxyphene levels is risky. The same caveat applies to measurements made with muscle and other tissues. Analysis of these tissues is certainly a valid way to demonstrate the presence of propoxyphene, but results cannot be assumed to reflect plasma values at the time of death (Langford et al., 1998). For forensic purposes, it may still be more useful to look at the individual's electrocardiogram. Truly toxic propoxyphene levels will produce distinctive EKG changes (Whitcomb et al., 1989), including QRS prolongation, bundle branch block, and, in extreme cases, asystole. The antemortem demonstration of these abnormalities is likely to be more probative than postmortem blood concentration measurements. The cause of death should never be determined by reference to blood and tissue concentration reported in earlier postmortem studies or by comparison with "therapeutic" concentrations reported in the living.

5.6.5.5 Excretion and detectability

Propoxyphene is not a National Institute on Drug Abuse (NIDA) drug; furthermore, none of the current standard immunologic screening tests for opiates reacts with propoxyphene, at least not to any significant degree. The propoxyphene would not even be detected on a standard NIDA urine-screening test (Cone et al., 1992). Nonetheless, propoxyphene remains detectable in the urine for very long periods of time, and, given a half-life of 22 hours for norpropoxyphene, the drug or its metabolite should still be detectable for at least four days. Changes associated with the process of putrefaction can sometimes cause EMIT® urine tests (which are frequently used to screen postmortem urine specimens) to give false-positive results for propoxyphene (Sloop et al., 1995). The issue is easily resolved with confirmation testing.

5.6.5.6 Maternal–fetal considerations

Propoxyphene is excreted in mothers' milk, but not in quantities likely to produce any effect on their infants, provided that propoxyphene is not used regularly over a long period. Propoxyphene and norpropoxyphene excretion in breast milk was studied in six healthy nursing mothers. Breast milk concentrations generally followed plasma levels, with approximately the same ratio of norpropoxyphene to propoxyphene (2.6) observed both in plasma and milk. The ratio of drug in the milk and plasma was 0.417 for propoxyphene, and 0.382 for norpropoxyphene. Both parent drug and metabolites are cleared from the milk at the rate of 4 mL/hr, with a mean half-life of 3.68 hours for propoxyphene and 5.49 hours for norpropoxyphene (Kunka et al., 1984). Nursing infants are unlikely to ingest amounts that will cause any detrimental effects during short-term treatment. The possibility of norpropoxyphene toxicity occurring after long-term exposure cannot be ruled out (Spigset and Hagg, 2000), although actual examples of such toxicity have never been reported.

5.6.6 Fentanyl

5.6.6.1 General considerations

Fentanyl (Figure 5.6.6.1.1) is a μ agonist, a synthetic phenylpiperidine derivative closely related in structure to meperidine (Demerol®), but with very different effects on the cardiovascular system. Fentanyl is not detected by routine drug-screen tests, so the total number of deaths that occur may be seriously underestimated. The 1999 DAWN survey reported 53 fentanyl-related deaths, amounting to less than half a percent of all drug deaths. Fentanyl was first introduced into clinical practice in the early 1960s. On a weight-

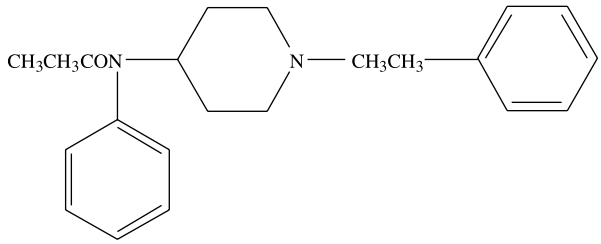


Figure 5.6.6.1.1 **Fentanyl.**

for-weight basis, it is 50 to 100 times more potent than morphine. Other fentanyl-related compounds are even more potent. The *cis*-isomer of 3-methylfentanyl, which has been manufactured by clandestine laboratories in the Russian Federation, is thought to be 5500 times more potent than morphine (Sorkin et al., 1994). According to the United Nations, at least 12 different fentanyl analogs have been sold on the illicit drug market (WHO, 1990).

The first two fentanyl-related deaths in the U.S. were reported in 1979. Both decedents were found with their injection paraphernalia at their sides, and postmortem examination revealed typical findings associated with narcotic overdose: needle tracks and pulmonary edema. Toxicology tests of blood and tissue samples, and even of the injection paraphernalia, were negative for opiates. Six additional deaths occurred before it was finally determined that the individuals had taken α-methylfentanyl (Kram et al., 1981).

In the early 1990s, most fentanyl-related deaths occurred in drug abusers (Henderson, 1991). From 1990 to 1996, the amount of fentanyl prescribed in the U.S. increased by more than 1000%, from 3263 to 41,371 g (Joranson et al., 2000), mainly because the fentanyl patch (Duragesic®) is now so widely prescribed for patients with cancer and chronic pain. With so much fentanyl being prescribed, it is inevitable that some of the patches ultimately find their way onto the black market, where abusers, unacquainted with the potency of the drug, are at great risk. Removal of patches from the bodies of dead cancer patients has even been reported (Flannagan et al., 1996).

The number of patches finding their way to the street is still relatively small and, more often than not, patches found on a decedent's body are there because the decedent was being treated for a medical condition. Pathologists are increasingly being confronted with the task of determining whether the presence of fentanyl is an incidental finding or the cause of death. As with any other opiate, tolerance occurs (Albrecht et al., 1997; Bot et al., 1998), and isolated blood concentrations cannot be used to make the diagnosis of fentanyl overdose.

Clustered outbreaks of fentanyl-related deaths have been reported (Hibbs et al., 1991; Smialek et al., 1994; Kronstrand et al., 1997), but most fentanyl-related deaths are sporadic, involving either drug abusers with illegally acquired patches, or addicted medical professionals injecting themselves with intravenous fentanyl. A well-recognized connection exists between practicing in certain medical or nursing specialties and substance use, particularly among anesthesiologists and other staff working in the operating room (Ward et al., 1983; Storr et al., 2000; Trinkoff et al., 2000).

5.6.6.2 Physical constants and names

Fentanyl is *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]propanamide. Its formula is $C_{22}H_{28}N_2O$, and it has a molecular weight of. 336.48. The melting point is 83 to 84°C (Budavari et al., 1996). Fentanyl is extremely lipophilic, more so than any other currently

available opiate. The mean apparent partition coefficients of oxycodone, morphine, meperidine, and fentanyl in *n*-octanol at pH 7 are 0.7, 0.5, 10.5, and 399, respectively, giving fentanyl a 570-times greater affinity for fat than morphine (Poyhia and Seppala, 1994). Fentanyl is sold in the U.S. as the Duragesic® transdermal system. The patches are sold in four different strengths (2.5, 5, 7.5, and 10 mg per patch). Fentanyl citrate (or injection) is sold under several brand names, including Actiq® (Abbot Laboratories), and in combination with the neuroleptic drug droperidol (Astra USA). Alfentanil hydrochloride is available as Alfenta® (Janssen Pharmaceuticals), and sufentanil is sold as Sufenta® (Janssen Pharmaceuticals).

5.6.6.3 Pharmacology and pharmacokinetics

Like any other opiate, fentanyl acts at the μ receptor. In clinical studies, fentanyl produces the same adverse effects as other opioids, namely sedation, nausea, vomiting, and constipation. In addition to the anticipated side effects, however, fentanyl can cause rigidity of the chest wall muscles, resulting in a condition known as "wooden chest syndrome" (Jackson, 1994). Unexpected increases in muscle tone may make ventilation difficult and pose a significant danger during endoscopic procedures, a situation where fentanyl is often administered. The results of animal studies suggest that increased muscle tone is in some way related to altered serotonergic transmission (Jaros and Kolasiewicz, 1995).

Treatment with fentanyl causes modest increases in intracranial pressure and equally small decreases in mean arterial blood pressure and cerebral perfusion pressure. Much the same thing happens after treatment with intravenous morphine. It had been thought that these actions occurred because fentanyl disrupts cerebral autoregulation (DeLima, 1993). That explanation no longer seems plausible, and perfusion abnormalities, when they do occur, do not seem to be clinically significant (DeLima, 1993).

Loss of consciousness occurs at plasma fentanyl concentrations of 34 ± 7 ng/mL (Lunn et al., 1979), but respiratory depression may be detected at levels as low as 1 to 5 ng/mL (Fung and Eisele, 1980; Andrews et al., 1983). The plasma level required to produce effective analgesia in surgical patients is 1 to 3 ng/mL, with wide interpatient variability (Gourlay et al., 1988), and values in this range can also be associated with severe respiratory depression. Respiratory depression is observed in human volunteers at plasma concentrations between 2 and 3 ng/mL (Cartwright et al., 1983).

5.6.6.4 Routes of administration

After an oral dose of 15 μg/kg, peak plasma concentrations in healthy volunteers averaged 3.0 ng/mL. Peak plasma levels after administration of that same amount intravenously are nearly 10 times higher. The terminal elimination half-life, however, is approximately 7 hours after either intravenous or oral administration (Streisand et al., 1991). The half-life is considerably longer after transdermal administration, on the order of 13 to 25 hours (Grond et al., 2000).

Outside of the operating room, fentanyl is most often given by transdermal application. Fentanyl released from a specially designed patch is adsorbed into the underlying skin, forming a depot in the upper skin layers. Absorption is slow, and plasma fentanyl concentrations remain undetectable for 1 to 2 hours after a patch has been applied. By the time 8 to 12 hours have elapsed, plasma concentrations approximate those seen when fentanyl is given intravenously (Calis et al., 1992).

Very great intra- and inter-individual variation can be seen in the time from patch application to minimal effective plasma fentanyl concentrations (1.2 to 40 hours). The time required to reach maximum serum concentrations also varies considerably, with the

maximum not occurring until 12 to 48 hours after the patch has been placed. By the third day of wear, a steady state is reached, and can be maintained as long as patches are renewed every 72 hours. Plasma fentanyl concentrations gradually decline over the second and third day, but not enough to lose effectiveness. Because a depot has been formed in the skin, fentanyl continues to be absorbed into the systemic circulation even after a patch has been removed (Grond et al., 2000).

The delayed action and absorption of drug after transdermal application has clinical and toxicologic consequences. Postoperative pain usually peaks long before plasma fentanyl concentrations do, making it difficult to determine just how much drug must be given. In the past, this uncertainty led to an unacceptably high incidence of respiratory depression, which is why the postoperative use of fentanyl is now generally thought to be contraindicated (Fiset et al., 1995; Grond et al., 2000).

Abusers who first apply a patch experience neither an immediate "high" nor respiratory depression. If more than one patch is available, they may even apply a second, with lethal consequences. This course of action is not so unlikely as it might sound, because the abuser may be applying a used patch. When immediate results are not observed, it may be wrongly concluded that no more drug is left in the patch. In fact, the opposite is the case. An analysis of fentanyl patches worn by hospice patients disclosed that 0.7 to 1.22 mg still remained in the 2.5-mg patches, and 4.46 to 8.44 mg remained in the 10.0-mg patches (Marquardt et al., 1995; Flannagan et al., 1996; Yerasi and Butts, 1997; Kramer and Tawney, 1998). And, of course, if respiratory depression occurs, just removing the patch will do nothing to stop further fentanyl absorption.

Fentanyl can be smoked or snorted. It has been reported that clandestine labs sometimes manufacture two forms of the drug, one for "shooters" and one for "snorters" (WHO, 1990). In either case, small amounts of fentanyl are mixed with very large amounts of mannitol, lactose, and occasionally heroin. No studies on absorption by nontraditional routes such as rectal, vaginal, or nasal application have been published.

Lozenges containing fentanyl citrate have been used to premedicate children before surgery. When fentanyl is given by this route, plasma concentrations peak in 20 minutes, and may reach levels of 3 to 4 ng/mL (Anon., 1994). As with adults, great variation exists in the plasma concentration finally achieved, and very little relationship between measured drug concentrations and pain relief has been observed (Dsida et al., 1998).

Abusers have been known to heat patches and inhale the fumes. At least one death has been attributed to the practice (Marquardt and Tharratt, 1994). As might be expected, absorption after inhalation is prompt and complete. A 1994 case report describes an individual who collapsed after only one inhalation. The concentration was 2.6 ng/mL in femoral blood , 3.3 ng/mL in the vitreous, and 122 ng/g in the liver. The pharmacokinetics of nasal insufflation has not been studied, but clinical trials with hospice patients have shown that effective relief of breakthrough pain can be achieved via this route (Zeppetella, 2000).

5.6.6.5 Metabolism and excretion

After an initial rapid uptake by lung and fat, fentanyl is slowly released. Metabolism occurs mainly in the liver, but when fentanyl citrate is given orally, it is subject not only to first-pass metabolism in the liver, but also metabolism by the same P-450 3A4 microsomes located in the duodenum. Piperidine *N*-dealkylation with the formation of norfentanyl is the predominant metabolic pathway; however, small amounts of fentanyl undergo amide hydrolysis to despropionylfentanyl and alkyl hydroxylation to hydroxyfentanyl. Secondary metabolites are also formed; small amounts of hydroxynorfentanyl undergo *N*-dealkylation to yield hydroxyfentanyl (Labroo et al., 1997).

Studies in surgical patients have shown that unchanged fentanyl appears in the urine very shortly after administration and persists in most for up to 24 hours. By 72 hours, fentanyl is undetectable. Norfentanyl appears in the urine almost as quickly as fentanyl, but in much higher concentrations. Norfentanyl is detectable in the urine of all surgical patients for 48 hours, and in half of the patients for periods as long as 96 hours. Neither fentanyl nor its metabolites are consistently detectable in saliva (Silverstein et al., 1993).

Radioimmunoassay screening kits for the detection of fentanyl, sufentanil, and alfentanil are commercially available. GC/MS can reliably be used to measure fentanyl and sufentanil with a detection limit approaching 0.5 ng/mL (Schwartz et al., 1994). Procedures have also been described for simple extraction of fentanyl using commercially available extraction tubes and GC/MS. Although the limit of detection is not as low as limits attained using other methodologies, the technique is particularly useful for verifying that medical personnel are actually discarding fentanyl and not saline-filled syringes (Kingsbury et al., 1995).

5.6.6.6 Tissue concentrations

All of the fentanyls are highly lipid soluble and distribute widely throughout the body (Hess et al., 1972). When administered intravenously, 3 to 4% is secreted into the gastric juice, where there is minimal reabsorption (Stoeckle et al., 1979). Thus, the detection of fentanyl in gastric contents does not imply oral administration (Table 5.6.6.6.1).

In a series of 112 fentanyl-related deaths described by Henderson (1991), fentanyl concentrations in blood ranged from 0.2 to >50 ng/mL, and urine concentrations ranged from 0.2 to >800 ng/mL. If the few individuals with extremely high levels are excluded, then the mean fentanyl level at autopsy was 3.0 ± 3.1 ng/mL in the blood and 3.9 ± 4.3 ng/mL in the urine. In the handful of deaths due to fentanyl citrate (the pharmaceutical-grade product used as an intravenous anesthetic), blood concentrations have ranged from 3 to 27 ng/mL (Garriott et al., 1984; Matejezyk, 1988). Blood and tissue concentrations were recently described in a series of 25 decedents wearing transdermal patches (Table 5.6.6.6.2). While the observed blood concentrations ranged from 1.8 to 139 ng/mL, the mean blood concentration in eight decedents being treated for cancer was 3.6 ng/mL (range, 2–7 ng/mL). Concentrations in abusers were generally much higher (Anderson and Muto, 2000).

Table 5.6.6.6.1 Steady-State Tissue/Blood Partition Coefficients for Fentanyl in Rats After a 6-hr Infusion

Organ/Tissue	Relative Level
Plasma	1
Brain	4
Liver	4
Heart	5
Stomach	14
Kidneys	14
Lungs	15
Pancreas	24
Fat	30

Source: Adapted from Björkman et al., 1990.

Table 5.6.6.6.2 Blood and Tissue Fentanyl Concentrations in 25 Decedents Wearing Transdermal Fentanyl Patches

Organ/Tissue	Concentration Range (ng/mL)
Heart blood	1.8–139
Femoral blood	3.1–43
Vitreous	<2.0–20
Liver	5.8–613
Bile	3.5–262
Urine	2.9–895
Gastric content	0–1200
Spleen	7.8–79

Source: Adapted from Anderson and Muto, 2000.

Table 5.6.6.6.3 Comparison of Blood Levels in Fentanyl-Related "Overdose" Deaths and Levels Seen in Anesthetized Patients Dying of Surgical Complications

	Deaths from Fentanyl Overdose	Deaths at Surgery
Blood	11–233 ng/mL	5–45 ng/mL
Brain	20–194 ng/mL	18–85 ng/mL
Liver	28–1000 ng/mg	41–158 ng/mg

Source: Adapted from McGee et al., 1992.

McGee et al. (1992) compared blood and tissue levels in seven overdose deaths with fentanyl levels observed in anesthetized patients dying at surgery (Table 5.6.6.6.3). As is the case with transdermal patches, overdose deaths tend to be associated with concentrations 5 to 10 times higher than those observed in anesthetic and/or surgical death.

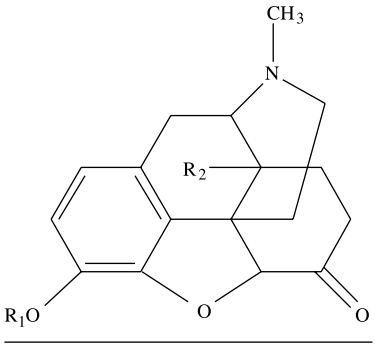
As is true in all opiate-related deaths, other drugs are frequently detected. In nearly 40% of the fentanyl-related deaths alcohol is also present, frequently at high levels. In 20% of the cases, cocaine was also detected (Henderson, 1991). In deaths associated with the use of the transdermal patch, other drugs are almost inevitably present (Anderson and Muto, 2000).

5.6.6.7 Autopsy findings

The autopsy findings in fentanyl-related deaths are the same as in heroin overdose: pulmonary and cerebral edema. If transdermal patches are present, a host of underlying pathologic conditions can be anticipated. Some of these, such as opportunistic pneumonia in HIV patients, may obscure the anticipated drug-related abnormalities.

5.6.7 Other opiates

Other opiates are abused with some frequency, but the incidence of untoward events is low. For example, heroin accounted for 41.3% (4820) of all drug-deaths reported in the 1998 DAWN survey, but during that same period only 46 deaths were attributed to hydromorphone (Dilaudid®) and 262 deaths to oxycodone (Percocet®, Percodan®, and



	R_1	R_2
Hydromorphone	-H	-H
Hydrocodone	$-CH_3$	-H
Oxymorphone	-H	-OH
Oxycodone	$-CH_3$	-OH

Figure 5.6.7.1.1 **Synthetic opiates.** Produced by substitution at position R_1 and R_2.

Tylox®) (Kissin et al., 2000a). Taken together, meperidine, hydrocodone, and oxycodone accounted for less than 2% of all deaths reported in the DAWN survey and less than 2% of the emergency-room visits reported to the survey (Kissin et al., 2000a). Propoxyphene-related deaths are somewhat more common, with 423 reported in 1998, but even then there are still 10 heroin-related deaths for every death attributed to propoxyphene. Most of these less popular opiates are not reliably detected by the immunologic screening tests used to detect morphine and codeine (Cone et al., 1992), and under federal drug-testing rules the presence of these drugs cannot be reported, even if present. Federally regulated workplace programs only test for five drugs: cocaine, phencyclidine, marijuana, methamphetamine, and morphine. Different rules apply to the nuclear and transportation industries, and it appears that workplace testing will eventually be expanded to check for the less common opiates.

5.6.7.1 Hydromorphone (Dilaudid®)

Hydromorphone, 4,5-epoxy-3-hydroxy-17-methylmorphinan-6-one, is a semisynthetic opiate, the hydrogenated ketone derivative of morphine (Figure 5.6.7.1.1). It is also an active metabolite of hydrocodone (Otton et al., 1993). Its formula is $C_{18}H_{21}NO_3$, and it has a molecular weight of 299.37. In the U.S. it is sold under the brand name Dilaudid® (Knoll Pharmaceutical). Generic hydromorphone is sold by Astra USA, Wyeth-Ayerst Laboratories, Elkins-Sinn, Mallinckrodt, and Endo. Various dosage forms are available, including tablets, powders, oral liquids, rectal suppositories, and injectables.

Hydromorphone is a μ agonist that, on a weight-for-weight basis, is 7 to 10 times more potent than morphine (Mahler and Forrest, 1975). It has been available for many years, but during the last 5 years it has come into much wider use, chiefly in the management of chronic pain syndromes. Because it is more potent than morphine, it can be prepared in more concentrated aqueous solutions. In spite of its potency, and in spite of persistent strong underground demand for this drug, hydromorphone use is seldom associated with toxicity. Even though the number of hydrocodone-related deaths reported in the DAWN survey increased from 18 deaths in 1993 to 46 in 1999, hydromorphone still only accounted for 0.39% of all reported drug deaths (Kissin et al., 2000b).

Hydromorphone is well absorbed. After intravenous injection, more than 90% is cleared from the plasma and redistributed into tissue stores within 10 minutes. This is almost exactly the same pattern observed with intravenous morphine and intravenous methadone (Hill et al., 1991). The minimum plasma concentration necessary to relieve severe pain is 4 ng/mL (Reidenberg et al., 1988). The average elimination half-life is 3 hours, but there is very substantial intersubject variation. In one of the few published studies on this subject, a 40-μg/kg bolus given intravenously produced average plasma concentrations of 7 ng/mL at 15 minutes, 5 ng/mL at 30 minutes, and 4 ng/mL at 1 hour. The kinetics are not dose dependent. Humans mainly excrete the 3-glucuronide (Cone et al., 1977), and the results of limited studies suggest that its volume of distribution is significantly higher than that of morphine (Hill et al., 1991).

Less than 6% of hydromorphone is excreted unchanged in the urine. Older measurements of blood and tissue levels are difficult to interpret because the radioimmunoassays cross-reacted with the glucuronide metabolites, resulting in final concentrations that were probably falsely high. New cases are uncommon enough that modern studies of postmortem drug concentrations are simply not available. Depending on the manufacturer, urine screening tests now on the market may or may not detect hydromorphone (Smith et al., 1995).

Hydrocodone, along with oxycodone and even codeine, is metabolized by cytochrome CYP2D6 to metabolites that have even greater μ receptor activity. CYP2D6 is genetically polymorphic, and 4 to 10% of Caucasians lack CYP2D6 activity altogether because they have inherited two nonfunctional alleles (see Section 5.6.3.4). The results of animal studies suggest that CYP2D6 deficient individuals (known as poor metabolizers) are, in fact, less likely to become addicted to oral opiates (Tyndale et al., 1997).

As discussed in Section 5.6.3.4, interpretative problems can arise because of the conversion of codeine to hydrocodone. Allegations of illicit hydrocodone use have been made against individuals taking physician-prescribed oral codeine who strenuously deny ever taking hydrocodone but who nonetheless have positive urine opiate immunoassay tests subsequently confirmed by GC/MS (Oyler et al., 2000). Generally, the hydrocodone concentrations in these cases are quite low, on the order of 100 ng/mL. Of course, once codeine has been converted to hydrocodone, there is nothing to prevent further conversion of hydrocodone to hydromorphone. However, given the small amount of hydrocodone formed, the amount of hydrophone produced would not be clinically significant, although hydromorphone might well be detected in trace amounts (Kaplan et al., 1997).

As a potent μ agonist, hydromorphone overdose can be expected to produce all of the classic symptoms of opiate intoxication. Studies in abusers have not been done. Autopsy data are scarce, and no evidence exists to suggest that hydromorphone abuse causes any unique pathologic alterations. Abusers often inject crushed oral tablets, and angiothrombotic lung disease can result from repeated injections; secondary pulmonary hypertension can also result. Diagnosis can be facilitated by the identification of birefringent crystals in the lung (Section 5.6.7.3).

5.6.7.2 Hydrocodone

Hydrocodone, 4,5-epoxy-3-methoxy-17-methylmorphinan-6-one, has almost the same structure as codeine, the only difference being substitution of an oxygen for a hydroxyl group at position 6. The formula of hydrocodone is $C_{18}H_{21}NO_3$, and it has a molecular weight of 299.37 (Budavari et al., 1996). In the U.S. it is sold under multiple brand names and in liquids, tablets, and syrups, though not as an injectable. Brand names include Anaplex® (ECR Pharmaceuticals); Codiclear® and Codimal® (Central Pharmaceuticals);

Donatussin® (Laser); Duratuss™ (Whitby Pharmaceuticals); Endal® (Forest Pharmaceuticals); Histussin® (Sanofi Winthrop Pharmaceuticals); Hycodan®, Hycomaine®, and hydrocodone (Du Pont Pharmaceuticals); Hydrocet® (Carnrick Laboratories); Lorcet® (UAD Laboratories); Lortab® (Whitby Pharmaceuticals); Pneumotussin® (ECR Pharmaceuticals); Protuss® (Horizon); Tussend® (Monarch); Vicodin® (Knoll Pharmaceuticals); and Zydone® (Du Pont Pharmaceuticals).

Alone or in combination with other drugs, hydrocodone was responsible for 45 deaths in 1990. Since then, the number of hydrocodone-related deaths increased to 447 in 1999, accounting for 3.8% of all drug-related deaths reported in the 1999 DAWN survey (Kissin et al., 2000b). Like morphine, hydrocodone binds to the μ receptors, but not nearly so strongly as hydromorphone. In general, opiates containing a methoxyl group at position 3, as hydrocodone does, had less affinity for μ receptors than their own *O*-demethylated metabolites (e.g., hydromorphone) (Chen et al., 1991a). On the other hand, hydrocodone is an effective cough suppressant because it binds to δ opiate receptors more avidly than opiates that do not share its methoxyl substitution (Kotzer et al., 2000).

Hydrocodone is well absorbed from the gastrointestinal tract. Approximately 25% is excreted unchanged in the urine, while the remainder can be metabolized via a number of routes, including *O*-demethylation, *N*-dealkylation, and 6-keto-reduction to the corresponding 6-α- and 6-β-hydroxy metabolites. Some of these routes lead to the production of active metabolites. Within the first 24 hours, 70% of hydrocodone is excreted unchanged in the urine, and the remainder is excreted by 72 hours (Cone et al., 1978). Urinary metabolic ratios of hydrocodone/hydromorphone are highly correlated with the degree of CYP2D6 activity present; so-called "slow metabolizers" (i.e., individuals missing both alleles for the CYP2D6 gene) cannot convert hydrocodone to hydromorphone (Otton et al., 1993).

Reports of toxicity are extremely rare (Morrison, 1979; Watson et al., 1998), as are reported cases of overdose, and no distinctive features are associated with hydrocodone-related deaths. When hydrocodone overdose is reported, it is almost always co-ingested with other drugs (Morrison, 1979; Meeker et al., 1995; Balikova and Maresova, 1998). Some bacteria possess the ability to synthesize hydrocodone (*Pseudomonas putida*). Whether this ability is shared by the bacteria normally associated with putrefication of human cadavers is not known, but if small amounts of hydrocodone are unexpectedly detected in postmortem specimens, the results should be interpreted with caution.

5.6.7.3 Oxycodone (Tylox®, Percodan®)

Oxycodone, (5α)-4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one, is a semisynthetic derived from codeine. The formula of oxycodone is $C_{18}H_{21}NO_4$, and it has a molecular weight of 315.37 (Budavari et al., 1996). Oxycodone is sold only in oral formulations and, until very recently, only in combination with non-narcotic agents such as acetaminophen. Pure oxycodone is now available as a time-release capsule. Brand names include OxyContin®, OxyFast®, and OxyIR® (Purdue Frederick), Percocet® and Percodan® (Du Pont Pharmaceuticals), Roxicodone™ (Roxane Laboratories), Tylox® (Ortho-McNeil Pharmaceuticals), and various generic combinations of oxycodone with acetaminophen or aspirin (Mallinckrodt, Watson, Roxane). Of all drug-related deaths reported in the 1998 DAWN survey, 262 (2.3%) were oxycodone related (Kissin et al., 2000a).

Oxycodone is an effective opioid analgesic widely used for the treatment of cancer pain and also for pain relief in cases of severe skeletomuscular injuries. In clinical studies of cancer patients, oral oxycodone and oral morphine appear to provide comparable pain

relief. On a weight-for-weight basis, morphine administered intravenously is three times more potent than oral oxycodone (Zhukovsky et al., 1999).

Microsomal CYP2D6 catalyzes the *O*-demethylation of oxycodone to form oxymorphone. This conversion is inhibited by fluoxetine, its nor-metabolite, and by most of the other selective serotonin re-uptake inhibitors (SSRIs), though not some of the newer antidepressants (Brosen, 1998; Fu et al., 2000). It is not uncommon for cancer patients to also be taking antidepressants which means that, deprived of the benefit of active metabolite formation, they may not achieve the same pain relief as those not taking SSRIs. Higher doses of oxycodone (with resultant higher blood concentrations of the parent compound) will be required.

A dose of 4.5 mg given orally results in blood levels of 9 to 37 ng (Renzi and Tam, 1979), with urine concentrations of its *O*-demethylated metabolite peaking in under 8 hours and falling to under 300 ng in 24 to 48 hours (Smith et al., 1995). Therapeutic blood levels are less than 100 ng/mL. Oxycodone has an elimination half life of 2 to 5.5 hours (Poyhia et al., 1991). Detection of oxycodone abuse is problematic because it is cleared from the urine so rapidly; the window for detection using TDx® and EMIT® testing is under 24 hours. In some test systems, because of the antibody used for detection, oxycodone may remain completely undetected (Smith et al., 1995).

Little is known about the postmortem toxicology or pathology of oxycodone-related deaths. No unique pathologic findings are recognized, although, as is the case when any oral agent is pulverized and injected, the possibility for angiothrombotic arteriopathy exists, and birefringent crystals may be detected in the lungs.

The ability to metabolize oxycodone is reduced in patients with liver and/or kidney disease. Oxycodone pharmacokinetics has been studied in volunteers with end-stage liver disease, both before and after transplantation. Prior to transplantation, the median elimination half-life of oxycodone was 13.9 hours (range, 4.6–24.4 hours) (Tallgren et al., 1997). In patients with diminished renal function, the mean elimination half-life is prolonged because the volume of distribution is increased and clearance reduced (Kirvela et al., 1996). Measured postmortem blood oxycodone concentrations in patients with renal comprise are, therefore, likely to be altered by the process of postmortem redistribution (Cook et al., 2000).

In a study of nine oxycodone-related deaths, most of them polydrug abusers, femoral blood concentrations were between 600 and 1400 ng/mL, with a mean of 900 ng/mL. The differences between blood concentrations in cases where oxycodone was the cause of death and cases where it was an incidental finding were sufficiently wide to suggest that, concerns about postmortem redistribution aside, postmortem blood concentrations of less than 600 ng/mL are an unlikely cause of death (Drummer et al., 1994).

5.6.7.4 Oxymorphone (Numorphan®)

Oxymorphone, (5α)-4,5-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one, is a semisynthetic opioid with pure μ agonist properties. The formula of oxymorphone is $C_{17}H_{19}NO_4$, and it has a molecular weight of 301.34 (Budavari et al., 1996). It is sold in the U.S. under the brand name Numorphan®, available as an injectable or as a suppository (Du Pont Pharmaceuticals) (Budavari et al., 1996). Oxymorphone is well absorbed after all routes of administration (Poyhia et al., 1993). Oxymorphone-related deaths are rare, with only 15 cases listed in the 1999 DAWN survey (Kissin et al., 2000). Because it is not detected by the most widely used urine screening tests, the true incidence of oxymorphone abuse is impossible to gauge (Smith et al., 1995).

Oxymorphone is 7 to 10 times more potent than morphine. The results of animals studies suggest that oxymorphone can be administered by nasal inhalation; plasma concentrations rapidly increase, and nasal bioavailability is 43% (compared to >60% when given orally) (Hussain and Aungst, 1997). Oxymorphone is extensively metabolized. The main metabolite appearing in the urine is conjugated oxymorphone (12.7 to 81.7% administered dose), but smaller amounts of 6-β- and 6-α-carbinols are produced by 6-keto reduction of oxymorphone. More than 80% is excreted in the first 24 hours, with great variation from individual to individual (Cone et al., 1983). The hepatic cytochrome P-450 2D6 (CYP2D6) converts oxycodone, via *O*-demethylation, to oxymorphone; however, pharmacodynamic studies indicate that the ability of oxycodone to relieve pain has little to do with oxymorphone formation (Kaiko, 1997).

Oxymorphone does not cause histamine release, and its use is not associated with the occurrence of flushing and puritis normally seen after heroin or morphine administration (Duthie and Nimmo, 1987), which may explain why this agent is occasionally used as an intravenous anesthetic agent. However, oxymorphone is capable of producing profound respiratory depression for up to 5 hours after administration (Patt, 1988). The postmortem toxicology and pathology of this drug have never been systematically studied.

5.6.7.5 Meperidine

Meperidine, a synthetic phenylpiperidine derivative, is 1-methyl-4-phenyl-4-piperidine-carboxylic acid ethyl ester. The formula of meperidine is $C_{15}H_{21}NO_2$, and it has a molecular weight of 247.34 (Budavari et al., 1996). Meperidine is the only member of this class known to cause toxicity or death with any regularity. In 1999, meperidine accounted for 0.9% of narcotic-related deaths (103 deaths vs. 4820 for heroin). Although the absolute number of such deaths has increased, the percentage of drug-related deaths due to meperidine has remained constant, at least within the U.S. (Kissin et al., 2000); in fact, reported episodes of meperidine abuse have actually decreased (Joranson et al., 2000). Like fentanyl, access to meperidine is limited, and when episodes of abuse do occur they usually involve medical personnel.

Meperidine is well absorbed by all conventional routes of administration. In healthy volunteers, the maximum observed concentration of parenteral meperidine, no matter whether the drug is given intravenously or subcutaneously, occurs within 10 minutes. Peak concentrations after intramuscular administration are reached after 20 minutes; 45 minutes after meperidine is taken orally (Schmitt et al., 1994).

Peak plasma concentrations vary greatly from individual to individual and do not correlate closely with analgesic effects. After intramuscular administration, resultant plasma concentrations of approximately 500 ng/mL are to be anticipated (Edwards et al., 1982; Erstad et al., 1997). After oral dosing, maximum plasma levels are seen from 0.5 to 1.5 hours later (Pond et al., 1981). Evidence indicates that chronic heroin users may metabolize meperidine more slowly than non-drug-users and, as a result, they may develop higher blood levels (Houghton et al., 1993). Because substance abuse is a frequent finding among trauma victims (McLeod et al., 1999), the potential for meperidine toxicity should not be ignored.

Meperidine has an apparent volume of distribution significantly greater than that of heroin or morphine (4.4 vs. 3.3 L/kg), and a half-life that is more than a third longer (approximately 3.2 vs. 1.9 hours) (Pond et al., 1981; Edwards et al., 1982). Liver carboxylesterases catalyze meperidine hydrolysis to meperidinic acid and ethanol (Zhang et al., 1999). Meperidine also undergoes hepatic oxidization to normeperidine (Figure 5.6.7.5.1), and in patients with cirrhosis meperidine clearance is reduced and bioavailability

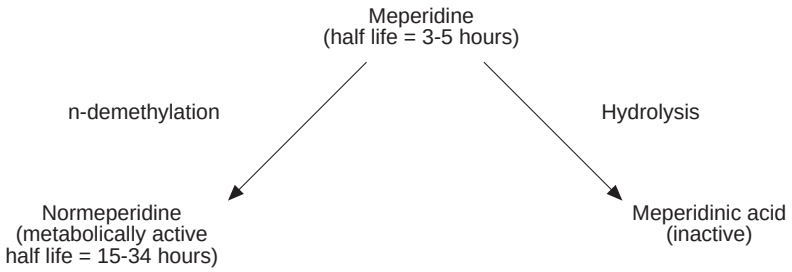


Figure 5.6.7.5.1 **Meperidine metabolism.** The metabolite normeperidine has about half the analgesic potency of meperidine and is also neurotoxic. The half-life of normeperidine is much longer than that of meperidine, and toxic levels may accumulate in individuals with renal impairment.

increased (Tegeder et al., 1999). Normeperidine is metabolically active, with approximately half the analgesic potency of meperidine. It is also neurotoxic (Jiraki, 1992), and it has a much longer half-life than the parent compound (Pond et al., 1981). Even though meperidine is mainly metabolized in the liver, toxic accumulation of its neurotoxic normeperidine, with resultant seizures, may occur in those with diminished renal function (Chan and Matzke, 1987; Hassan et al., 2000). Meperidine-induced neurotoxicity is not reversed by opiate antagonists, but meperidine-induced respiratory depression is. There are reports in the literature of prolonged narcosis, especially in elderly patients receiving high doses (Chan et al., 1975).

Meperidine is a negative ionotrope, and intravenous administration causes a significant but transient decrease in blood pressure. It is rapidly taken up by the myocardium, but just what effect it exerts on the myocardium to cause decreased output is not clear (Upton et al., 1999). Like morphine, meperidine causes histamine release and exerts atropine-like effects on heart rate (Bowdle, 1998).

Serotonin syndrome can occur if meperidine is administered at the same time as a drug such as dextromethorphan, pentazocine, tramadol, monoamine oxidase inhibitors (MAOs), or SSRIs. Symptoms include confusion, fever, shivering, diaphoresis, ataxia, hyperreflexia, myoclonus, and occasionally diarrhea. Serotonin syndrome occurs when excess serotonin is available within the central nervous system and, in particular, when concentrations at the 5-HT1A-receptor sites are elevated. Serotonin syndrome is something of a rarity; symptoms are usually mild and self limited, although the occurrence of hyperthermia signals a poor outcome, and requires aggressive cooling measures (Sporer, 1995; Upton et al., 1999; Weiner, 1999).

If large doses of meperidine are given, normeperidine accumulates in the plasma (Koska et al., 1981). In normal individuals the terminal half-life of normeperidine is anywhere from 15 to 34 hours, but in the presence of renal impairment clearance may require 3 or 4 days, and toxicity, when it occurs, may be prolonged (Szeto et al., 1977). In control studies, only 5% is excreted unchanged in the urine, while more than 25% is excreted as meperidinic acid or normeperidinic acid.

The postmortem toxicology of meperidine has been poorly studied. Meperidine blood concentrations measured in one study of six autopsies ranged from 4300 to 12,000 ng/mL (Siek, 1978). Hepatic drug concentrations were twice the blood concentrations of patients who were intravenous users, but only one-half the blood concentrations if the individuals had taken the meperidine orally. Clinical evidence of normeperidine toxicity has been reported, with concentrations ranging from 425 to 1900 ng/mL and normeperidine-to-

meperidine ratios of 0.79 to 5.4 (Szeto et al., 1977). The importance of pre-existing renal disease in cases of meperidine toxicity is illustrated by one case report describing a heroin addict with end-stage renal failure; he was found to have a meperidine blood concentration of only 60 ng/mL, while at the same time the normeperidine concentration was 3000 ng/mL (Jiraki, 1992).

5.6.7.6 Pentazocine (Talwin®)

Pentazocine differs from the other agents in that it is both a narcotic agonist and antagonist. It is active at κ- and δ-receptor sites but is a μ-receptor antagonist. Pentazocine is (2α,6α,11R)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol. The formula for pentazocine is $C_{19}H_{27}NO$, and it has a molecular weight of 285.43 (Budavari et al., 1996). Deaths from pentazocine are so uncommon that they do not rate a separate mention in the 1998 DAWN report (Kissin et al., 2000a). Oral formulations, either alone or in combination with aspirin or acetaminophen, are sold under the brand names Talacen® caplets and Talwin® compound tablets (Sanofi Winthrop Pharmaceuticals). Oral tablets containing pentazocine combined with naloxone are sold as Talwin® Nx (Sanofi Winthrop Pharmaceuticals) and in the generic form by Watson Laboratories. Perhaps because most of the medical complications attributable to pentazocine result from parenteral injection, that form of the drug has been withdrawn from the U.S. market.

Pentazocine is less than half as potent as morphine. Oral formulations provide pain relief roughly comparable to that expected with dextropropoxyphene/acetaminophen combinations (Henry, 1985). In the past, pentazocine abuse was a fairly common occurrence; however, the practice is now extremely uncommon, at least in the U.S., where parenteral formulations are no longer available and where most of the pentazocine formulations sold are formulated with the narcotic antagonist, naloxone. No pentazocine-related deaths were mentioned in the Medical Examiner component of 1998 DAWN survey, nor were any pentazocine-related emergency-room visits reported (Kissin et al., 2000a).

Peak pentazocine blood concentrations occur 15 minutes to 1 hour after intramuscular administration, but only after several hours if the drug has been given orally. Bioavailability is high, and even though absorption is relatively slow, oral administration results in pentozacine concentrations almost as high as those seen after intramuscular injection. The peak level after a 75-mg oral dose averages 160 ng/mL (Berkowitz and Way, 1969; Berkowitz, 1973).

Nearly two-thirds of pentazocine circulating in the blood is protein bound, but the volume of distribution of pentazocine is nonetheless quite high (7.1 ± 1.4 L/kg). In adults, the half-life is just under 5 hours (Yeh et al., 1986). The concentrations in whole blood and urine samples collected from two volunteers over a 6-hour period after intramuscular injection of 15 mg of pentazocine were 13.5–59.3 ng/mL and 0.39–4.00 μg/mL respectively (Seno et al., 2000). In an earlier study, the peak blood concentrations after 45 mg had been given intramuscular was 140 ng/mL. When a 30-mg dose of pentazocine was administered intravenously, blood concentrations as high as 1000 ng/mL occurred within 5 to 10 minutes (Agurell et al., 1974). As is true of other opioids, the ability to metabolize pentazocine via oxidative pathways is reduced in patients with hepatic cirrhosis. Consequently, clearance is decreased while oral bioavailability is increased (Tegeder et al., 1999).

Toxicology textbooks and occasional journal articles still describe the practice of injecting crushed tablets of the antihistamine tripelennamine and pentazocine ("Ts & Blues") (Halpern and Davis, 1982). The practice, though well publicized, was never widespread and ceased many years ago. Today, if the term is employed by a drug user, it is more

likely being used to describe the practice of injecting crushed tablets of Ritalin® than pentazocine (Carter and Watson, 1994).

Tolerance occurs (Swanson et al., 1973), and without knowledge of the individual's past history, attributing a specific event or outcome to an isolated toxicologic finding is impossible. Patients have survived with blood concentrations of 9 mg/L (Stahl and Kasser, 1983). Very high drug concentrations occur in the brain, often exceeding those found in the blood. Pentazocine also accumulates in the liver, bile, and kidney. Extensive first-pass metabolism occurs in the liver, as do both oxidation and glucuronidation. (Pittman, 1973; Pittman and Davison, 1973).

With the exception of the tendency of pentazocine to produce severe myositis and fibrosis (Schiff and Kern, 1977; Das et al., 1999), long-term parenteral abuse of the drug results in the same set of complications as the abuse of any other opiate (King and Betts, 1978). Although it has never been reported, there is reason to suppose that evidence of catecholamine toxicity, much like that seen in cocaine users, might be apparent. Pentazocine causes increased release of epinephrine from the adrenals (Fukumitsu et al., 1991; Ellmauer et al., 1994). It has been suggested that the resultant increases in pulse and blood pressure might place individuals with pre-existing coronary artery disease at increased risk (Ellmauer et al., 1994). In instances of pentazocine-related death, it should not be surprising if anatomic findings are consistent with catecholamine toxicity, such as contraction band necrosis.

5.6.7.7 Buprenorphine

Buprenorphine, [(5α,7α,S)]-17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6,14-ethenomorphinan, is a semisynthetic opioid derived from thebaine. It is 25 to 50 times more potent than morphine. The formula of buprenorphine is $C_{29}H_{41}NO_4$, and it has a molecular weight of 467.65 (Budavari et al., 1996). Abuse of this agent is not a significant issue in the U.S., and no buprenorphine-related fatalities are listed in the 1999 DAWN report.

Buprenorphine is classified as a partial opioid agonist. As such, it produces pain relief and other effects similar to those of morphine. On a weight-for-weight basis, it is 20 to 25 times more potent than morphine (Wallenstein et al., 1986) and has a slower onset of pain relief and longer duration of action. Plasma concentrations of 0.5 ng/mL are sufficient to produce surgical analgesia (Amani et al., 1997); during daily buprenorphine maintenance, plasma concentrations greater than 0.7 ng/mL of buprenorphine and norbuprenorphine prevent the occurrence of withdrawal symptoms.

Buprenorphine can be given by any route, but very great inter-individual variability in biovailability (51.4 and 27.8% for sublingual and buccal routes, respectively) and peak plasma concentrations (Kuhlman et al., 1996) has been observed. Studies in humans are lacking, but measurements in animals show that after nasal administration bioavailability is very high, and maximal plasma concentrations occur almost as rapidly as after parenteral administration (Lindhardt et al., 2000). This observation raises the possibility that buprenorphine could be abused by "snorting."

Like morphine, but unlike most other opioids, the major metabolic pathway for buprenorphine is glucuronidation, not oxidation. Microsomal oxidation does occur (CYP3A), but only small amounts of norbuprenorphine are produced. Except in the presence of end-stage disease, glucuronidation is generally not impaired by liver disorders, which means that the buprenorphine pharmacokinetics is not effected either (Tegeder et al., 1999). Free buprenorphine is not detected in urine, although both parent compound and norbuprenorphine can be detected in feces after either oral or sublingual

administration for as long as a week after ingestion. Extensive enterohepatic circulation of buprenorphine occurs (Cone et al., 1984). Renal disease has no effect on buprenorphine metabolism or distribution (Hand et al., 1990; Davies et al., 1996).

In the U.S., buprenorphine is used mainly for the treatment of chronic pain, although elsewhere this drug has become an increasingly popular alternative to methadone for treatment of heroin dependence. The shift is based largely on a number of successful clinical trials (Cami et al., 1991; Auriacombe et al., 1994a,b; Fischer et al., 1999), and also upon experimental studies with human volunteers. Positron emission tomography (PET) scans of heroin users demonstrate increased numbers of μ receptors in the inferofrontal cortex and anterior cingulate regions of the brain, and treatment with buprenorphine has been shown to reduce the number of available receptors (Zubieta et al., 2000). Another reason for the increasing interest in buprenorphine is that the results of *in vitro* studies have indicated that buprenorphine, unlike morphine, does not depress immune responses or activate the hypothalamic–pituitary–adrenal axis (Gomez-Flores and Weber, 2000).

French law was changed in 1996 to allow general practitioners to prescribe buprenorphine to heroin addicts. As in the U.S., French law limits methadone prescribing to special government-controlled centers. When the law was first changed, there were concerns that toxicity and lethal outcomes might be more frequent with buprenorphine than methadone. The results of recent studies indicate, however, that death rates with methadone replacement therapy are nearly three times higher than with buprenorphine (Auriacombe et al., 2001).

In animal studies, buprenorphine treatment causes a statistically significant but clinically insignificant change in pulse and blood pressure (Martinez et al., 1997). In patients undergoing open-heart procedures with cold cardioplegia, pretreatment with buprenorphine is cardioprotective; postoperatively there is improved metabolism and higher cardiac output. The protective effect is in some way related to activation of μ opiate receptors (Boachie-Ansah et al., 1989), and there is interest in the use of this drug as an adjunct during heart surgery.

Buprenorphine can usually but not always be detected in hair samples, at concentrations ranging from 6 to 597 ng/g (mean, 137 ng/g) (Tracqui et al., 1998). It is very stable in refrigerated blood samples, with recovery rates of more than 70% after 6 months of storage (Hadidi and Oliver, 1998). Concentrations of buprenorphine and its primary metabolite norbuprenorphine in postmortem blood range from 1.1 to 29.0 ng/mL (mean, 8.4 ng/mL) and 0.2 to 12.6 ng/mL (mean, 2.6 ng/mL), respectively. As is true for morphine and heroin, these concentrations overlap those that have been reported in clinical settings, where there is no evidence of toxicity. Somewhat surprisingly, given the high degree of protein binding by buprenorphine, extensive tissue distribution occurs. Buprenorphine accumulates in bile, where concentrations may reach values of more than 75 mg/L. Norbuprenorphine seems to have the same pattern of distribution as the parent compound, although measured concentrations are generally very much lower than those of the parent compound.

5.7 Interpretation of opiate blood and tissue concentrations

5.7.1 Introduction

Causation cannot be determined from isolated toxicologic measurements. Whether or not a specific blood level causes death, morbidity, or even significant impairment depends not only on the findings at autopsy but also on what is observed at the scene, and on the

individual's past medical and drug history (Harding-Pink and Fryc, 1991). Information may be available from many sources, including the emergency room and the records of physicians who attended the patient in the past. In some cases, historical sources can provide information not obtained at autopsy or toxicologic testing. This is especially true in cases of advanced decomposition, and in cases when the individual is HIV seropositive (Harding-Pink and Fryc, 1991).

5.7.2 Urine testing

The accurate interpretation of urine opiate test results requires quantitation of the amount of codeine and morphine present. Poppyseed ingestion ensures the presence of both codeine and morphine in the urine. A prescription for codeine could explain the presence of some, but not massive amounts of morphine in the urine. After oral dosing with codeine, 5 to 15%, and possibly more, will be excreted in the urine as free or conjugated morphine (Fell et al., 1983; Gjerde et al., 1991). Under current federal workplace testing rules, urine specimens are considered to be presumptively positive if an opiate concentration in excess of 2000 ng/mL is detected. For confirmation, retesting with gas chromatography and mass spectrometry is required; morphine or codeine must be present in a concentration of at least 2000 ng/mL. To specifically prove heroin ingestion, at least 10 ng/mL of 6-monoacetylmorphine must also be demonstrated, but the half-life of this compound is so short that this criterion is often not met. Obviously, these cutoffs and rules do not apply in cases of drug-death investigation.

Heroin use can explain the presence of both morphine and codeine in the urine, because heroin is rapidly converted to morphine, and because heroin is often contaminated with small amounts of codeine (Young and Lik, 1977). Humans, however, do not metabolize morphine to codeine (Mitchell, 1991). Codeine-containing cough syrups (one syrup sold in Japan and Southeast Asia is responsible for a large percentage of positive tests at the U.S. Army testing lab in Hawaii) and poppyseed-containing pastries both cause positive urine tests for opiates. Poppy seeds contain both morphine and codeine, and very high levels can be seen if substantial amounts (several teaspoons) are eaten (El Sohly et al., 1988; Selavka, 1991). It may not be possible to resolve the situation if the individual being tested has a prescription for codeine and also claims to have eaten poppy seeds. In that case, his urine might well have more morphine than codeine in it, even if the person was not abusing drugs!

The commercial opiate assays currently in general use are unlikely to cross-react with synthetic and semisynthetic opiates, partly because the original federal regulations regulating workplace programs are specific for morphine. However, newer assay systems are being introduced and rules modified so that the detection of drugs such as oxymorphine is not only possible, but also allowable.

5.7.3 Blood testing

Opiate abusers become tolerant of the respiratory depressant effect of the drugs, and the existence of tolerance makes interpretation of blood concentrations extremely difficult. In cases of acute overdose, where death is obviously due to respiratory depression or pulmonary edema, blood concentrations have ranged anywhere from 100 to 2800 ng/mL (Felby et al., 1974; Richards et al., 1976; Reed et al., 1977; Moffat et al., 1986; Logan et al., 1987; Sawyer et al., 1988; Steentoft et al., 1988; Kintz et al., 1989; Logan and Smirnow, 1996; Bogusz et al., 1997; Gerostamoulos and Drummer, 2000). Many of these reports were

published before it was appreciated that M6G was as metabolically active as morphine itself. Thus, the range of reported values in these cases is very broad and, as in the case of the older literature where only total morphine was measured, not very accurate. The same absolute concentration values may be associated with death in one individual, yet produce minimal symptoms in another who is tolerant. Morphine blood concentrations in living addicts receiving maintenance heroin may, in fact, be substantially higher than in individuals dying of heroin overdose (Darke et al., 1997). Obviously, blood morphine concentrations cannot be interpreted in isolation.

Special considerations apply to postmortem testing. While morphine and its glucuronides are extremely stable in refrigerated blood and in plasma samples, they are not stable in postmortem blood. Temperature, exposure to light, length of sample storage, and bacterial overgrowth all affect the final measured concentration. Morphine and M6G decompose in stored whole postmortem blood; the longer the sample is stored and the higher the temperature, the more likely decomposition is to occur. Most of the change is a result of bacterial hydrolysis of morphine glucuronides; bacteria can be cultured from postmortem blood within 5 hours of death (Melvin et al., 1984). The longer the period of storage and the higher the storage temperature, the more morphine deconjugates (Skopp et al., 2001).

Inferences about causation may be possible, however, if hair morphine concentrations are measured at the same time as blood. Tagliaro et al. (1998) observed that morphine concentrations in the hair in overdose victims are comparable to hair concentrations in former heroin users enrolled in rehabilitation programs. Hair from individuals in both groups contain substantially less morphine than hair from living, active heroin users. The combination of high postmortem blood morphine concentration and low (or unmeasurable) hair concentrations indicates a lack of opiate tolerance, suggesting the occurrence of heroin/morphine-related death.

5.7.4 Cause of death determination

Toxicology test results must never be considered in isolation. Examination of the death scene may reveal details that can confirm, or cast doubt on, the toxicology results. Halpern (1972) was one of the first to point out that there is a sameness about heroin-related deaths. More often than not, the heroin user is found on the street or in an alley, injecting by himself and dying in isolation. Decedents are much more likely to be male (>70%), mostly in their mid-20s (Louria et al., 1967; Cherubin et al., 1972; Wetli et al., 1972). Drug paraphernalia is likely to be at the victim's side, and in some instances the needle may still be in the arm. Under such circumstances, if the blood morphine level were found to be quite low, then an examiner would be justified in wondering if heroin overdose was really the cause of death. Conversely, if a well-dressed middle-aged woman was found dead in a doorway with no injection apparatus but with high blood morphine concentrations, then the medical examiner would be justified in wondering if opiate overdose was really the cause of death.

When fentanyl is responsible, decedents are usually found at home or at work (often a hospital) (Henderson, 1991). As with heroin, victims are more likely to be men, but the average age tends to be considerably older (32.5 years). The probability of finding drug paraphernalia is about the same (>60%) in both fentanyl- and heroin-related deaths. Regardless of which drug is involved, if other individuals are present at the time of death, it is likely they will make every effort to remove any evidence of illicit drug use.

Historical information is important, because deaths in opiate abusers are more likely to occur when they have been abstinent. It is important to establish whether the individual has just been released from jail or a detoxification program (Harding-Pink and Fryc, 1991). It is also important to establish whether or not alcohol has been consumed. The combination is notoriously lethal, but the mechanism of enhanced toxicity is unexplained. In the study by Ruttenber et al. (1990) of 505 heroin-related deaths, those who had not been drinking had higher morphine levels in their blood and bile (500 and 7500 ng/mL, respectively) than those individuals who had been drinking (300 and 3000 ng/mL, respectively). These findings suggest that opiate abusers who also use alcohol are occasional users with lower levels of tolerance, placing them at greater risk for overdose.

The historical record is equally important when investigating methadone-related deaths. Inter-individual responses to methadone vary considerably and are dependent on sex, weight, use of concomitant medications, duration of methadone treatment, previous exposure to other opioids, and plasma concentrations of α-1-acid glycoprotein (Garrido and Troconiz, 1999). Methadone induces the enzymes required for its own metabolism. As a consequence, naïve users are at much greater risk for overdose than individuals who have been taking methadone for some time (Wu and Henry, 1990; Caplehorn and Drummer, 1999).

Autopsy findings may or may not be helpful in opiate-related deaths. If the lungs are frothy and weigh 2000 grams and the morphine blood level is 1000 ng/mL, then the diagnosis is obvious. However, pulmonary edema is not present in every case of heroin overdose, blood levels much lower than 1000 ng/mL can cause respiratory depression, and cutaneous stigmata may be absent (Kintz et al., 1989). Even if some relationship between morphine blood concentrations and specific effects were known, there is no guarantee that postmortem blood concentrations accurately reflect concentrations in the immediate antemortem period. The results of very convincing animal and human studies suggest that after death all basic drugs, not just morphine, rapidly diffuse from depots in the lung back into the left ventricle. Blood samples obtained from the left side will yield falsely elevated results (Moriya and Hashimoto, 1997, 1999). Femoral blood sampling is much less subject to this sort of artifact. For that reason alone, over-reliance on measurements made in heart blood (autopsy reports rarely specify from which side the sample has been obtained) are to be avoided (Cook et al., 2000).

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5.8 *Medical consequences of opiate abuse*

As patterns and practices of drug abuse change, so does the clinical profile of the drug users. More than a quarter of a century has passed since the last systematic analysis of autopsy findings in narcotic abusers was published (Wetli et al., 1972). For purposes of comparison, unpublished data from the office of the San Francisco Medical Examiner are provided. It seems likely that similar patterns occur elsewhere, but in the absence of a national study it is impossible to be sure.

In San Francisco in 1999, morphine was detected at autopsy in 154 individuals. The mean age of the decedents was 46 years, but the range was very great (16 to 71 years). The concurrent rate of cocaine abuse was extremely high, with 72 of the decedents (47%) testing positive for both drugs, which no doubt explains why many of the individuals showed evidence of the same anatomic changes associated with stimulant abuse. The ten most frequent anatomic diagnoses are listed in Table 5.8.1. Eleven of the decedents (7%) had clinically apparent HIV infections that had been diagnosed prior to their deaths.

Table 5.8.1 Most Common Anatomic Diagnoses in Heroin Abusers (n = 154)

Diagnosis	Percent (%)
1. Pulmonary edema	46
2. Track marks	44
3. Birefringent crystals in lung or liver	27
4. Pneumonia	18
5. Hepatic steatosis	16
6. Severe coronary artery disease	12
7. Hepatitis	12
8. Myocardial fibrosis	11
9. Extensive aortic atherosclerosis	9
10. Cerebral edema	9

Source: Unpublished data, office of the San Francisco Medical Examiner.

Several changes from the 1970s are apparent. In San Francisco, as in many other parts of the U.S., nearly all intravenous heroin abusers are infected with hepatitis C virus (HCV). HCV infection is acquired more rapidly than either hepatitis B or HIV, probably because among intravenous drug users the prevalence of HCV is so much greater than the prevalence of the other two diseases. Whether this accounts for the existence of liver disease in nearly a third of the heroin users autopsied is, again, unknown. The relatively advanced age of the decedents may explain why so many had multivessel coronary artery disease and/or extensive aortic atherosclerosis. On the other hand, the findings might equally well be explained by the concurrent use of cocaine, a practice known to accelerate the occurrence of coronary artery disease.

5.8.1 Dermatologic sequelae

Skin lesions are associated with all types of intravenous drug abuse, but they are more common among opiate abusers than stimulant abusers. The difference is somewhat surprising, because stimulant abusers inject much more frequently than do opiate abusers, a practice that might be expected to produce more damage. The difference has to do with the properties of the drugs themselves. Stimulants do not cause histamine release, so their use is seldom associated with pruritus or excoriations. Most of the cutaneous complications associated with intravenous opiate abuse are produced by the adulterants and expients injected along with the opiates.

5.8.1.1 Fresh needle punctures

Recent injection sites are usually apparent, although in sophisticated users these marks may be difficult to find. The presence of dried blood on the surface of the skin surrounding a puncture is confirmatory evidence that death occurred almost immediately following injection (Hirsch, 1972). The antecubital fossa is the preferred site for self-injection, but punctures may be detected at the wrist, under a watchband, or between the toes. The path of the needle may be confirmed by making a skin incision immediately adjacent to the suspected site. This will reveal the presence of small subcutaneous hemorrhages that occur after venipuncture (Halpern, 1972). Alternatively, a single longitudinal incision can be made on the flexor surface of the arm from mid-biceps to distal forearm, and the subcutaneous tissues exposed by either blunt or sharp dissection.

Subcutaneous hemorrhage may not be evident in every case, but chemical analysis of tissue around the needle track often yields evidence of the drug injected. Demonstration of drug in skin taken from a suspected injection site does not, by itself, prove that the drug was injected at that site. If the decedent survives for even a few minutes, the circulation will have distributed drug throughout the body, including the skin! The only way to prove that drug was introduced into the body at a particular site is to sample skin from both sides of the body; the concentration on the side in question should be significantly higher than on the other.

The bioavailability of heroin is poor when insufflated (at least when compared to cocaine), but the purity of street heroin is now so high that heroin "snorting" has become common practice. The situation may arise where track marks are not evident. If there is even the remotest suspicion that a narcotic was used and was responsible for death, the nasal cavity should be examined and then swabbed with saline for toxicology testing. Of course, the same considerations apply to nasal (or mucosa at any other site) swabs as for skin tests. The detection of drug on the mucosa does not prove that it was applied there, only that the drug was circulating throughout the body.

5.8.1.2 *Atrophic scarring*

Novice abusers, and the occasional experienced abuser who cannot find a vein, may inject subcutaneously, usually on the flexor aspect of the arm. Absorption of heroin is good by this route, but the deposition of expients in the subcutaneous tissue eventually leads to the development of oval or irregularly shaped lesions measuring 1 to 3 cm. Lesions are slightly depressed and often hyperpigmented. Most lesions are found at the sites of healed abscesses, but they may occur without abscess formation. This type of lesion has been recognized for more than half a century, but the dermatopathology remains poorly characterized and the etiology unclear. Early workers suggested that such a lesion is a direct result of the effect of heroin on the skin (Light and Torrance, 1929), but adulterants or infectious agents are just as likely to be the cause. Evidence indicates that the pH of the solution injected rather than the drug itself may be what determines whether tissue injury occurs (Pollard, 1973; Thomas et al., 1995). Microscopic examination of healed atrophic lesions usually reveals subcutaneous fibrosis. Foreign body granulomas may or may not be present, but birefringent material, such as talc or starch crystals, is likely to be seen (Hirsch, 1972).

5.8.1.3 *Abscesses and ulceration*

Abscesses are common in heroin abusers who inject subcutaneously. The practice, which frequently causes infected abscess at the site of injection, is known as "skin popping" (Webb and Thadepalli, 1979; Orangio et al., 1984). Lesions occur primarily on the extensor surfaces and lateral aspects of the arms and hands but may also be seen almost anywhere on the body. Injection into the subclavian area and the femoral triangle may cause life-threatening infections (Pace et al., 1984), as can injection into the intercostal vessels (Gyrtrup, 1989). Ulcers have a punched-out appearance, with indurated borders surrounding a central core of granulation tissue. Nothing distinguishes the appearance of injection site abscesses from any other sort of soft tissue abscess. Reports from the older literature suggested that the responsible organisms are usually *Staphylococcus* and *Streptococcus* (Sapira, 1968), but many different Gram-negative organisms have also been cultured, and polymicrobial infections are not uncommon (Webb and Thadepalli, 1979).

In the year 2000, there was an outbreak of clostridial infection among heroin abusers in the U.K. At least 37 deaths and many more cases of infection were reported (Anon., 2000a,b,c). All types of clostridia are cardiotoxic to some degree (Sugimoto et al., 1991), but it appears that the strain responsible for the U.K outbreak was much more cardiotoxic than most; refractory heart failure was a prominent feature in most of those who were hospitalized. Only heroin users who injected subcutaneously were affected. The responsible organism was *Clostridium novyi* type A, the same organism that was responsible for thousands of deaths from wound infection during World War I. Today, *Clostridium novyi* type A infection most often involves domestic animals (Seifert et al., 1996), and infection in humans is nearly unheard of.

Public health officials suspect that the outbreak in the U.K. occurred because spores of the bacteria were present in the heroin that addicts were injecting. Clostridia spores can lie dormant in soil for months or years and only become active when they are placed in an oxygen-free environment, which probably explains why the outbreak involved only drug users who injected directly into skin and muscle. Similar outbreaks due to different strains of clostridia have occurred in California, but evidence of cardiotoxicity in the California cases was conspicuously lacking (Maselli et al., 1997). Some speculate that the outbreak occurred because heroin dealers added diatomaceous earth to their product as a diluent. This form of powdered earth looks very much like heroin, at least to the naked

eye, and it might prove a tempting substitute for some of the more traditional materials used to dilute heroin. Unfortunately, diatomaceous earth contains spores of bacteria which can germinate if injected under the skin.

5.8.1.4 "Track" marks

This lesion was first described in 1929. It was observed in a heroin addict who had contracted malaria from intravenous injections (Biggam, 1929). The lesions were said to resemble railroad tracks because they were linear, indurated, and hyperpigmented. What tracks look like and how rapidly they will form depends on what is being injected. The expients found in illicit cocaine and methamphetamine are usually water soluble, so "track" marks are an uncommon finding in this group of abusers (Wetli et al., 1972). Paregoric, on the other hand, causes an intense sclerotic reaction, and when paregoric injecting was popular in the 1960s, addicts ran out of peripheral veins so quickly that they resorted to injecting themselves in the neck and groin (Lerner and Oerther, 1966). Heroin, even in its adulterated form, is less sclerotoxic than paregoric, but prolonged use will eventually cause thickening and sclerosis of the subcutaneous veins.

The skin overlying the sclerotic veins becomes hyperpigmented, probably as a result of the underlying chronic inflammatory process (Vollum, 1970), but the degree of hyperpigmentation depends largely on the individual's coloration, not necessarily on how long the addict has been injecting himself. Discoloration of the surrounding skin can also be the result of inadvertent tattooing. Addicts may try to sterilize their needles with a match flame, causing small amounts of soot to be deposited on the outside of the needle. The soot is then carried into the skin at the time of injection. Addicts have traditionally tried to conceal these marks by tattooing or even by burning themselves in the hopes of scarring the entire area (Wetli, 1984; Martinez and Wetli, 1989; Sperry, 1991, 1992).

The histologic appearance of sclerotic veins varies (Schoster and Lewis, 1968). There may be only fibrous thickening of the vein wall, consistent with a low-grade, chronic inflammatory process. In other instances, thrombophlebitis, sterile or septic, may occur. The results are difficult to predict, and Halpern (1972) even commented that on occasion the veins repeatedly used by addicts "show less evidence of closure by thrombosis than the veins of patients subjected to repeated punctures by physicians for medical purposes."

5.8.1.5 Tattoos

Tattoos are sometimes used to conceal the scars and track marks associated with intravenous drug abuse, though that hardly explains the frequency of this finding in addict subpopulations. The practice derives its name from the Tahitian word *tatau* which means "the results of tapping," the way in which Tahitians tattoos were applied. Tattooing dates back to antiquity. Tattoos have been found on Egyptian mummies from the Eleventh Dynasty, making the practice at least 4000 years old (Sperry, 1991).

Tattoos are applied in jail using the "melted-toothbrush" technique. Any pointed object, such as a bedspring or matchbook staple, can be used as a needle. The end of a plastic toothbrush is then melted in a flame and the smoky residue collected. The residue is mixed with soap and water to form an ink (Sperry, 1991). A great deal of significance was once attributed to the design and location of these tattoos. Symbols on the thumb webbing were said to indicate criminal specialties. The results of more recent studies suggest that hand-web tattoos probably have significance only in the prison where they are applied (Martinez and Wetli, 1989). In some specific subpopulations, such as the Marielitos, tattoos may represent religious symbols or themes, but these interpretations are not generalizable to other subgroups.

5.8.1.6 "Puffy hands" syndrome

Lymphedema sometimes occurs in chronic users. The condition was first described in the 1960s. The hands become smooth and slightly edematous with obliteration of the normal anatomic landmarks, but pitting edema is absent. In contrast to the changes seen in the hands of myxedematous patients, the skin in addicts with "puffy" hands is thin and smooth. The skin on the volar aspect of the forearm is also normal, even though evidence of repeated injections can be seen in both antecubital fossae (Abeles, 1965; Ritland and Butterfield, 1973).

5.8.1.7 Necrotizing fasciitis

Necrotizing fasciitis was first described over 120 years ago. As commonly used, the term refers to a severe infection of the superficial fascia and subcutaneous tissue. Initially, the infection does not involve the overlying skin (Wojno and Spitz, 1989). In the absence of drug abuse, necrotizing fasciitis usually occurs in diabetics or in patients with severe atherosclerosis, where the infectious process is initiated by surgery or even by minor trauma.

Several case reports and studies have been published that suggest a link between necrotizing fasciitis and the use of nonsteroidal antiinflamatory drugs (NSAIDs) (Zerr and Rubens, 1999). If such a link does exist, and the issue is still debated, the most likely explanation is that NSAIDs mask the signs and symptoms of an existing infection, leading to a delay in diagnosis, although others have suggested that nonsteroidals may somehow decrease the immune response. Of course, narcotic abuse would have exactly the same effects, masking pain and leading to delayed diagnosis (Holder et al., 1997).

Once established, infection and necrosis rapidly spread through fascia and subcutaneous tissues. The overlying skin looks normal until very late in the course of the disease, and the underlying muscle is usually not involved either (Tehrani and Ledingham, 1977). Hematogenous seeding may occur, involving organs throughout the body. Even purulent myocarditis has been reported as a complication. The fact that the overlying skin looks normal may delay the diagnosis and lead to a fatal outcome (Wojno and Spitz, 1989). At one time it was thought that Gram-positive aerobes were the causative agents, but in more recent studies the etiology has been polymicrobial. In a recently published review of 182 patients with documented necrotizing soft-tissue infections, wound cultures grew an average of 4.4 microbes. Infection was due to a single pathogen in only 28 instances (15%). Nearly half the patients had combined aerobic and anaerobic growth. The most common organisms, listed in declining order, were Bacteroides species, aerobic *Streptococcus*, *Staphylococcus*, *Enterococcus*, *Escherichia coli*, and other Gram-negative rods (Elliott et al., 2000).

5.8.1.8 Histamine-related urticaria

Skin excoriations are common, but it is not clear if the skin excoriations are the result of narcotic-induced pruritus or psychological disorder (Young and Rosenberg, 1971). Histamine release in narcotic abusers is not a true IgE-mediated allergic response (Hermens et al., 1985). Opiates act directly on mast cells to produce histamine release. The process is thought to be G-protein mediated (Barke and Hough, 1993). The amount of histamine released depends on the dose of opiate administered. In one series, more than 20% of the patients receiving postoperative opiates developed urticaria (Withington et al., 1993). In some instances, the amount of histamine liberated can be large enough to cause hypotension, in addition to erythema and tachycardia. Not all narcotics cause histamine release. Elevations in plasma histamine occur after dosing with intravenous morphine, meperidine, and diacetylmorphine (heroin) but not after treatment with fentanyl or sufentanil (Flacke et al., 1987).

5.8.1.9 Fungal lesions

Candida infections of the mouth, esophagus, upper airway, and lungs are recognized as "indicator" diseases for AIDS. The prevalence of oral thrush in AIDS patients is 40 to 90%. The prevalence of esophageal involvement is much lower, only 4 to 14% (Redfield et al., 1986). As a rule, in AIDS patients *C. albicans* infections are limited to the mucosa. Disseminated disease does not occur unless the infected individual is also a heroin user or has some other similar risk factor (steroid therapy, indwelling catheter, severe granulocytopenia) (Dupont and Drouhet, 1985).

Candida-related febrile septicemia with cutaneous involvement is a disorder confined to heroin addicts. The syndrome was first described in 1981 when a cluster of cases occurred in Paris (Drouhet et al., 1981). Subsequently, hundreds of additional cases were reported across Europe and Australia, but only sporadic cases have been reported in the U.S. (Collignon and Sorrell, 1983; Hogeweg and de Jong, 1983; Hogeweg et al., 1983; Saint-Jean et al., 1983; Calandra et al., 1985; Odds et al., 1987; Bisbe et al., 1992; Lafont et al., 1994; Martinez-Vazquez et al., 1998). Epidemiologists eventually linked the outbreak to the use of poorly soluble heroin which had been exported from Iran ("brown" heroin). In order to dissolve the heroin for injection, users added lemon juice or some other acidifying agent (Mellinger et al., 1982). It was found that even bottled lemon juice could become contaminated with the *C. albicans* found on an addict's skin (Berger et al., 1988; Bisbe et al., 1992). A significant majority of the cases have been due to a single strain of *Candida*, serotype A, biotype 153/7 (Shankland and Richardson, 1988). Subcutaneous lesions are seen in 75 to 100% of the cases, ocular involvement in approximately 60%, and ossteoarticular involvement in 20 to 50% (Dupont and Drouhet, 1985).

Typically, symptoms occur within 2 to 24 hours after the last heroin injection. Chills, fever, headache, and profuse diaphoresis quickly follow. Within one to three days, patients develop disseminated folliculitis and scalp nodules. Any hair-bearing area may be involved, but the scalp is the most common site (Dupont and Drouhet, 1985). Painful cutaneous nodules, usually measuring less than 1 cm, erupt quite suddenly. As many as 100 of these nodules may be present, and it is said that the scalp of such an individual feels like "a sack of marbles." Smaller pustules may be seen adjacent to the nodules. The pustules strongly resemble lesions produced by staphylococcal or streptococcal infection, but microscopic examination discloses yeast and filaments of *C. albicans*. Biopsy of the follicular nodules is more likely to be diagnostic than blood cultures. Gomori–methenamine–silver staining will reveal bifurcated filaments of *C. albicans* admixed with an intense, mixed inflammatory infiltrate (Drouhet and Dupont, 1991).

Since the initial reports were first published, others have appeared describing the same syndrome after injection of methadone-containing syrup diluted with orange juice (Scheidegger et al., 1993; Moller et al., 1997), after injection of buprenorphine tablets diluted in lemon juice (Scheidegger and Frei, 1989), and even after intravenous methamphetamine use (Mohri et al., 1991) and cocaine (Le Thien et al., 1998).

5.8.1.10 Miscellaneous cutaneous abnormalities

Other skin disorders are occasionally seen, but none with sufficient frequency to be of any diagnostic value. Sapira described a rosette of cigarette burns around the neck. After self-injecting with opiate, abusers may fall asleep with cigarettes in their mouths, resulting in burns of the anterior chest when the head falls forward (Sapira, 1968). Other lesions reflect usage patterns that were unique to a specific time and place and are mainly of interest as historical curiosities. In the late 1800s, when opium smoking was still popular, the presence of cauliflower ears (swelling of the auricles) was considered almost pathognomonic for

opium use. They were the result of lying for long periods on opium beds with hard wooden pillows (Owens and Humphries, 1988).

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5.8.2 Cardiovascular disorders

5.8.2.1 Introduction

The frequency of heart disease in opiate abusers is not known. Except for endocarditis and the various complications associated with HIV infection, it is not even clear that heart disease is any more frequent among opiate abusers than it is in controls (Kringsholm and Christoffersen, 1987). In Siegel and Halpern's classic paper on the "Diagnosis of death from intravenous narcotism," heart disease is not even mentioned (Siegel et al., 1966), nor were any significant cardiac abnormalities noted in the study by Wetli et al. (1972) of 100 consecutively autopsied narcotic abusers. When Louria et al. (1967) analyzed the discharge diagnosis of addicts admitted to Bellevue Hospital's general medicine service, the incidence of endocarditis was under 10% and no other cardiac disorders were noted. At the other extreme is the comprehensive study by Dressler and Roberts (1989b), in which they analyzed 168 drug-related deaths and found that the incidence of cardiac abnormalities approached 100%.

Interpreting the older studies and some of the newer ones is difficult, if not impossible. The phrase "narcotic addict" has never been used consistently. In the past it was often applied to any sort of intravenous drug abuse, even though the effects of sympathomimetic drugs are manifestly different from those of opiates. In early studies, chemical confirmation of the diagnosis was lacking, with the diagnosis of opiate abuse based solely on clinical findings. Such inferences would be inadmissible in court; the only reason these observations ever made their way into the peer-reviewed medical literature at all was the inability, at the time, to accurately detect drugs in postmortem material.

Even after toxicologic screening became available, the limits of detection were far higher than they are today. Another confounding factor is that almost all of the studies, old and new, have been uncontrolled. The very high frequency of cardiac lesions reported

by Dressler and Roberts (1989b) cannot be generalized. Their study was uncontrolled, and many of the 168 cases they examined had been referred to the National Heart, Lung and Blood Institute, presumably because the original prosecutors suspected that cardiopulmonary abnormalities were present. Findings in this study are utterly at odds with the experience of most medical examiners. Only one controlled study has compared the cardiopulmonary pathology in opiate-related deaths with the findings in a group of age-matched controls. Many changes could be identified in the lungs of opiate users, but the hearts of the addicts differed in no significant way from those of the controls (Kringsholm and Christoffersen, 1987).

The frequency with which a particular cardiac lesion is observed depends on the pattern of drug abuse within the population being studied. When Rajs reviewed the cardiac pathology in a group of 25 intravenous drug users he found contraction band necrosis, fibrosis, and inflammatory infiltrates (Rajs and Falconer, 1979), but amphetamine abuse was common in the population studied, and the changes observed are consistent with that fact. In some areas, especially Europe, the injection of pills meant for oral use is still a fairly common practice. In those localities, granulomatous lung disease and pulmonary hypertension are common, and the spectrum of cardiac lesions seen at autopsy is likely to reflect that fact (Crouch and Churg, 1983).

An increasing number of drug-related deaths are due to violence and not to any direct opiate-mediated effect or medical complications of opiate abuse. The frequency of incidental cardiac lesions in addicts dying of trauma has never been tabulated. Because of the HIV pandemic, heart disease in opiate users has come to be almost synonymous with HIV disease. The most common lesions observed in HIV-infected patients are listed in Table 5.8.2.1. In spite of treatment advances, the pattern of HIV complications at the turn of this century is hardly different than at the beginning of the pandemic (Barbaro et al., 1998; Lanjewar et al., 1998). Specific data about HIV infection in heroin users has never been compiled. In San Francisco, at least, the experience has been that fewer than 10% of heroin abusers examined are HIV infected, and an even smaller percentage of those infected have lesions and opportunistic infections as a consequence of their disease. Any abnormalities detected at autopsy are likely to be incidental, unanticipated findings.

5.8.2.2 HIV-associated cardiovascular pathology

Seroprevalence rates vary greatly from location to location, ranging from as low as 13% for new intravenous drug users in Miami to over 70% of chronic users in Barcelona

Table 5.8.2.1.1 Types of Cardiac Lesions Found in Opiate Abusers

Disorder	Percentage
Cardiomegaly	68
Endocarditis (active or healed)	48
Coronary artery disease	21
Congenital	11
Acquired valvular disease	10
Myocardial disease	8

Note: These figures are based on the report by Dressler and Roberts (1989), published before HIV infection was widespread.

Table 5.8.2.2.1 Cardiac Findings in AIDS Patients at Autopsy, in Order of Frequency

1. Pericardial effusion
2. Right ventricular hypertrophy
3. Infiltrates
4. Opportunistic infection
5. Kaposi's sarcoma
6. Nonbacterial thrombotic endocarditis

Source: Adapted from Lewis (1989).

(Chitwood et al., 2000; Muga et al., 2000). The true percentage of intravenous heroin abusers who die from AIDS, rather than some complication of their drug abuse, is not known. Before the onset of the HIV pandemic, endocarditis was the only cardiac disorder unequivocally associated with intravenous opiate abuse. Unfortunately, the HIV pandemic began at almost the same time as the cocaine pandemic, and dual drug use is an increasingly frequent practice. It is often impossible to determine whether a specific abnormality detected in a heroin abuser's heart is related to HIV, or to simultaneous stimulant abuse, or both.

Pericardial effusion is the cardiac lesion most commonly seen in AIDS patients (Table 5.8.2.2). One-third to one-half of all patients dying of AIDS have effusions, with or without pericarditis (Lewis, 1989; Barbaro et al., 1998; Lanjewar et al., 1998). The etiology appears to be multifactorial. Effusions in the HIV-affected rarely require specific treatment or even produce symptoms, although patients with effusions appear to have a much worse prognosis than those without effusions (Chen et al., 1999).

In the past, the second most common cardiovascular abnormality detected in HIV-infected addicts was right ventricular hypertrophy (Blanchard et al., 1991; Rosales-Guzman et al., 1994). Right ventricular hypertrophy is not particularly surprising in drug abusers, who are likely to have both angiothrombotic lung disease from their drug abuse and AIDS-related fibrotic interstitial lung disease at the same time. This abnormality seems to have become much less common, perhaps because of the effective prevention and treatment of opportunistic pneumonia (Barbaro et al., 1998; Lanjewar et al., 1998). The apparent decrease in prevalence of pulmonary hypertension is somewhat surprising, given recent evidence suggesting that HIV infection itself predisposes to that condition (Mehta et al., 2000).

In Lewis' autopsy series of AIDS patients, mononuclear infiltrates were present in the myocardium of 10% of the patients, but none had evidence of healed or active myocarditis. Inflammatory infiltrates in the heart are now much more commonly reported, with incidence rates in excess of 50% in some series (Lanjewar et al., 1998). The infiltrates are composed predominantly of CD3+ and CD8+ lymphocytes, with positive staining for major histocompatibility Class I evident in 70% of the cases. Sequences of human immunodeficiency virus nucleic acid can be detected with *in situ* hybridization in the cardiomyocytes of most of these individuals (Barbaro et al., 1998).

Opportunistic infection, especially disseminated cryptococcosis, toxoplasmosis, cytomegalovirus (CMV) infection, and opportunistic tumors such as non-Hodgkin's lymphoma and Kaposi's sarcoma occur (Daisley and Charles, 1997; Barbaro et al., 1998; Sanna et al., 1998), but it is unusual for any of these disorders to produce symptoms referable to the cardiovascular system. These infections are almost always detected as incidental findings at autopsy.

Coronary artery disease is a relatively frequent finding in heroin-related deaths, and reports of myocardial infarctions in HIV-infected young people, especially those receiving protease inhibitor therapy, are increasingly frequent. Coronary artery disease in the HIV-infected could be related to any number of disorders associated with HIV infection, including insulin resistance, hypercholesterolemia, or fat redistribution syndrome (Passalaris et al., 2000). On the other hand, coronary artery disease in these individuals could also be a consequence of concurrent stimulant abuse, a practice known to be associated with accelerated coronary artery disease (Karch et al., 1995).

Coronary artery lesions in the HIV-infected have features intermediate between the lesions observed in common coronary atherosclerosis and the type of disease associated with chronic rejection of cardiac transplants. Thickening of the media and increased production of elastic fibers have both been demonstrated (Tabib et al., 2000). The etiology of these changes remains obscure, but intimal proliferation is the lesion traditionally associated with "chronic rejection," and the immune systems of these patients are clearly disordered (de Lorgeril et al., 1992).

5.8.2.3 Endocarditis

Infective endocarditis has changed very little in the last two decades (Netzer et al., 2000). After HIV infection, endocarditis is the only other cardiovascular disease where the incidence is clearly higher among intravenous drug abusers than in the population. Among intravenous drug users, most infections are still due to *S. aureus*, and the tricuspid valve is still the most commonly involved valve. However, infection with multiple Gram-negative organisms is increasingly common. (Reisberg, 1979). Surprisingly little research has been directed at explaining what places intravenous drug users at greater risk for valve infection. Autopsy studies indicate that most (>80%) vegetations occur on previously normal valves (Dressler and Roberts, 1989), but the results of echocardiographic studies suggest that the valves of intravenous heroin users, even those with no clinical evidence of endocarditis, are abnormal; small areas of thickening on both the mitral and tricuspid valves are often present (Pons-Llado et al., 1992). This finding is consistent with the notion that some type of endothelial trauma must occur to allow deposition of the microscopic thrombi which, in turn, constitute the first stage of infection.

The literature has always emphasized that addicts are prone to right-sided infection. While there is no question that the tricuspid and pulmonic valves are involved more often in addicts than in the general population, it is also true that in some series addicts, actually have left-side involvement more often than right (Hubbell et al., 1981; Dressler and Roberts, 1989). The origin of the infectious agent has also been a matter of some dispute. Because addicts seldom practice sterile techniques, the needles they use may be contaminated and the injected material may be unsterile. The injection site, especially if it is in the groin, may be colonized with pathogenic organisms. Thus, a number of possible sources for infection exist. With the exception of *Candida* infection (Drouhet and Dupont, 1991), studies have failed to link the heroin itself, or the paraphernalia used, to any particular infectious organism (Tuazon et al., 1974). More often than not, the infectious organism is derived from either the addict's normal surface flora (Hubbell et al., 1981) or from a pre-existing infection such as cellulitis or suppurative thrombophlebitis.

Platelet deposition, no matter what the cause, damages valvular epithelium, exposing the matrix of subendothelial connective tissue below, and allowing the further deposition of fibrin and platelet thrombi. Vegetations are friable, white or tan, and most likely to be found along the line of valve closure. Bacterial vegetations tend to arise on the atrial aspect of the atrioventricular valves and on the ventricular surfaces of the aortic and pulmonary

valves. With time, they may proliferate and involve the opposite side of the valve or spread to the chordae tendinae or onto the parietal pericardium. The lesions ulcerate, and the ulcerations seen in acute endocarditis tend to be larger and deeper than those associated with subacute disease (Silber, 1987).

To some degree, the size, color, and appearance of the vegetations depends on the type of infectious agent responsible. Fungal lesions tend to be larger and bulkier than bacterial vegetations and are more likely to cause valvular insufficiency and embolization. Streptococcal vegetations grow more slowly than staphylococcal vegetations, but they may get to be much larger (Ciliberto et al., 1999; Ellis et al., 2001). Vegetations much smaller than those seen with bacterial or fungal infection are seen at autopsy in approximately 2% of severely cachectic patients. The lesions are sterile, and the process of their formation is generally referred to as nonbacterial thrombotic endocarditis (NBTE; also marantic endocarditis) (Angrist and Oka, 1963). The same process also occurs in association with autoimmune disorders, but here, too, diagnosis during life is rare unless the verrucae embolize and cause a thromboembolic event (Reisner et al., 2000).

The verrucae of NBTE are composed of bacteria-free, amorphous material. Depending on how much fibrin has been deposited, the color of the vegetations can range from white to tan or gray. On microscopic examination, the lesions of marantic endocarditis are easily distinguished from those of infectious endocarditis; masses of fibrin, platelets, and polymorphonuclear leukocytes can be seen surrounding colonies of bacteria located directly on the surface of the valve. Necrotic areas of valve become surrounded with a mixed cellular infiltrate which often includes giant cells. In older lesions, capillary proliferation occurs, along with the formation of granulation tissue (Saphir et al., 1950; Saphir, 1960). Fibrous tissue eventually proliferates over the vegetations, and the necrotic material becomes organized and eventually endothelialized. Healed lesions are often calcified.

The pattern of valvular involvement is different in drug abusers than in the population at large, and so are the symptoms. In Dressler and Robert's series of 80 autopsied addicts with infectious endocarditis (Dressler and Roberts, 1989a), the tricuspid valve was involved almost half the time. But in the general population tricuspid valve involvement occurs less than 5% of the time in subacute cases, and less than 15% of the time in acute endocarditis (Lerner and Weinstein, 1966a,b,c; El-Khatib et al., 1976). Table 5.8.2.3.1 compares the frequency of involvement in addicts with the frequency seen in the general population. There is some evidence that the likelihood of infection depends upon the pressure to which

Table 5.8.2.3.1 Frequency of Valve Involvement in Addicts vs. General Population

Site	Addicts (%)	General (1989) (%)
Left side	41	85
Aortic	23	15–25
Mitral	19	30–45
Right side	30	5–20
Tricuspid	29	1–15
Pulmonic	1	<1
Right and left sides	16	5–10

Source: Data for addict population derived from Dressler and Roberts (1989); data for the general population derived from published clinical studies.

Table 5.8.2.3.2 Pathogens Reported in Addicts with Infectious Endocarditis, Compared with Pathogens Observed in Non-addicted Population

Pathogen	Addicts (%)	Non-addicts (%)
Streptococcus	15	65
Viridians (β-hemolytic)	<5	35
Group D	<5	25
Staphylococcus aureus	50–80	25
Pseudomonas aeruginosa	10–40	<5
Polymicrobial	10–20	<1

Source: Summary of data from published studies.

the valve is subjected (Lepeschkin, 1952), so the high incidence of low-pressure valve disease in addicts remains puzzling and unexplained. Equally difficult to explain is the fact that a significant incidence of right-side involvement has been reported in some non-drug-using populations (Grover et al., 1991).

There is no satisfactory explanation for why the spectrum of organisms attacking the right heart should be so different from, and so much more virulent than, the group of agents that infect the mitral and aortic valves. *Staphylococcus aureus* is the predominant organism infecting right-side valves, while 60 to 80% of the time the causative organism on the left is a *Streptococcus viridians* sp. (Weinberger et al., 1990). The predominant organisms in addicts and the general population are compared in Table 5.8.2.3.2.

Infection with multiple organisms is uncommon on the left, but polymicrobial involvement of the tricuspid valve is prevalent, especially among intravenous drug abusers. Until recently, polymicrobial infection was a distinctly rare entity. In one retrospective study of nearly 1000 patients seen from 1951 to 1966, only one case was found (Weinstein and Rubin, 1973). In more recent reports, the incidence has been closer to 8% (Crane et al., 1986). As many as seven different organisms may be involved at one time, and because many of these organisms are quite fastidious, all may not be diagnosed by routine laboratory methods (Adler et al., 1991).

Right-sided cardiac involvement results in symptoms that are more pulmonary than cardiac in nature. Dislodged vegetations frequently embolize to the lung, producing multiple segmental infiltrates, especially in the lower lobes (Chan et al., 1989). Tricuspid vegetations can, on occasion, grow quite large, and may even interfere with valve function. Papillary rupture, on the other hand, produces relatively few symptoms on the right because of the low intracavity pressure (Conway, 1969). Aneurysm of the sinus of Valsalva may result when infection dissects into the valve ring. This process is most often seen in cases of staphylococcal infection. Staphylococcal infections may also extend outward from the ring and, in addition to resulting in ring abscess, the infection may also spread to involve the interventricular septum (Conde et al., 1975; Rawls et al., 1968). Lethal arrhythmia can result. Extension of the infection outward may result in purulent pericarditis or even cardiac rupture. In fact, purulent pericarditis occurs in nearly 20% of all cases of endocarditis, even without the rupture of any large abscess (Silber, 1987). Smaller abscesses may be scattered throughout the myocardium, and even though abscess formation is more common in cases of acute endocarditis, it may be seen in subacute cases as well. Abscesses may be subendocardial or subpericardial but are most likely to be

found in the left ventricle (Arnett et al., 1976). A spectrum of other myocardial alterations short of frank abscess formation can also be seen. In acute cases, there may be cloudy swelling of the myocytes, hemorrhage, or even tiny areas of infarction. Small infarcts occur in subacute cases where small emboli obstruct distal branches of the coronary arteries (Saphir et al., 1950).

The peripheral sequelae of valve infection have changed little since Osler described them in the Gulstonian Lectures in 1885 (Osler, 1885). The most frequent complications associated with endocarditis in addicts are the same as those in the general population. Many of the extracardiac manifestations are the result of arterial embolization of the friable vegetations. Mycotic aneurysm is the result of septic emboli, most of which occur at the bifurcation of medium-size arteries (Katz et al., 1974). This process is especially common in the brain but can also occur elsewhere. In the kidneys, septic emboli can cause infarction, especially when *Staphylococcus* is the etiology. Glomerulonephritis is seen in more than half of the patients and is the result of immune complex deposition (Bell, 1932; Gutman et al., 1972). In addition to the classic focal embolic changes seen in the kidneys of patients with endocarditis, diffuse proliferative glomerulonephritis may also be seen. In these latter cases, there is strong evidence for an immune-related etiology. It may well be that other peripheral lesions, such as Roth's spots and even Osler's nodes, have an immune etiology (Bayer and Theofilopoulos, 1990).

If there is any suspicion that the patient was suffering from infectious endocarditis, aseptic techniques should be used at autopsy to ensure the collection of uncontaminated material. The major vessels should be clamped before removing the heart from the body. An area on the surface of the heart adjacent to the affected valve (e.g., entrance through the posterior right atrial wall would give access to the tricuspid valve) should then be seared and the center of the area incised with a sterile scalpel, allowing direct access to the valve, which can be sampled and cultured. If such an approach is not followed, the samples obtained may well be contaminated. In addition to routine Gram stains, slides should also be stained for fungi (Gomori stain) and for acid-fast organisms. Hearts should not be placed in formalin prior to sectioning (Atkinson and Virmani, 1991).

5.8.2.4 Other myocardial disorders

5.8.2.4.1 Myocardial fibrosis. Fibrosis is also a frequent finding in the hearts of drug abusers. Certain patterns of fibrosis play a role in the generation of malignant rhythm disorders and sudden cardiac death (Strain et al., 1983; Lecomte et al., 1993). Microfocal fibrosis is most typically seen in stimulant abusers (Rajs and Falconer, 1979; Tazelaar et al., 1987), where it is the result of healing contraction band necrosis. Given the increasing rate at which drug users combine both narcotic and stimulant drugs, the occurrence of myocardial fibrosis in opiate abusers probably is just a function of stimulant cardiotoxicity. On the other hand, healed endocarditis and healed myocarditis also cause fibrosis, as does poorly controlled hypertension with ventricular remodeling. Larger zones of fibrosis are likely to represent healed areas of ischemia infarction. Large zones of fibrosis could also be related to healed endocarditis, as emboli may cause infarction in some of the smaller coronary artery branches (Silber, 1987).

5.8.2.4.2 Myocardial hypertrophy. There is some evidence that myocardial hypertrophy is a concomitant of chronic heroin abuse (Willoughby et al., 1993). Cardiac enlargement in intravenous abusers with lung disease is to be expected; however, the findings of preliminary studies suggest that modest degrees of enlargement occur even in the

absence of lung disease. Here, too, the myocardial changes probably have more to do with concurrent abuse of stimulant drugs. Myocardial hypertrophy is a well-recognized complication of cocaine and methamphetamine abuse, and it is unlikely that concurrent use of heroin would do anything to change that process (Karch et al., 1995).

5.8.2.4.3 Coronary artery disease. Intravenous heroin abusers have abnormal, atherogenic lipid profiles (Maccari et al., 1991; Sztajzel et al., 1994). Whether the incidence of coronary artery disease in heroin addicts is any different from that in age-matched controls is not known. Dressler and Roberts (1989) found significant coronary artery disease (>75% narrowing) in 8% of their referral cases, but this observation has not been confirmed. In fact, no mention of coronary artery disease is made in any published autopsy series of heroin abusers (Halpern and Rho, 1966; Siegel et al., 1966; Louria et al., 1967; Froede and Stahl, 1971; Wetli et al., 1972). A possible relationship between HIV infection and accelerated coronary artery disease has also been postulated (Passalaris et al., 2000; Tabib et al., 2000).

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5.8.3 Pulmonary disorders

5.8.3.1 Noninfectious complications

5.8.3.1.1 Pulmonary edema. Illicit heroin users have no way of knowing how much heroin they are injecting. If the material they inject is less adulterated than usual, fatal respiratory depression may follow. Heroin purity on the street is highly variable, but if purity is less than 3%, withdrawal symptoms are likely. Addicts who have been abstinent

for some time are particularly at risk, as they will have lost their tolerance. This situation is not uncommon in addicts who have been incarcerated and then returned to the streets (Harding-Pink and Fryc, 1991).

Narcotic-related pulmonary edema was first observed by a Dr. Lee in New York in the 1850s. Lee described the simultaneous occurrence of cerebral edema and pulmonary congestion in a man dying from a laudanum overdose (Woodman and Tidy, 1877). Nearly 150 years later, the mechanism of narcotic-induced pulmonary edema remains unknown. It is generally presumed that pulmonary edema in heroin abusers is in some way related to respiratory depression and respiratory failure, although there are those who still adhere to the notion that narcotic-induced pulmonary edema is the result of some sort of allergic or anaphylactic reaction (Edston and van Hage-Hamsten, 1997, 1998; Dettmeyer et al., 2000). All opiates decrease the responsiveness of the respiratory centers to increased levels of PCO_2, and if enough narcotic is given, the respiratory drive disappears. In practice, postmortem examination will reveal pulmonary congestion of varying degrees, but not always florid pulmonary edema.

The edema fluid associated with narcotic overdose is rich in protein. Agonal respiratory efforts will cause the fluid to froth up, much like beaten egg whites. In extreme cases, congealed froth is seen in the mouth and nares. In one series, the average weights of the right and left lungs were 830 and 790 g, respectively (Levine and Grimes, 1973). In the case series described by Siegel et al. (1966), the average total was slightly lower (1400 g). Almost the identical result (1419 grams) was found in 154 heroin-related deaths investigated by the San Francisco Medical Examiner's office in 1999 (Karch, 2000).

Fluid accumulation is lobular in distribution, with areas of congestion and edema alternating with other areas of air trapping and acute emphysematous change. The posterior lower lobes are most severely affected, especially if gastric aspiration has also occurred. Depending on the severity of the process, histologic examination may reveal a spectrum of changes. In less severe cases, the only abnormality found will be widening of the interstitial spaces, especially around the bronchi and extraalveolar vessels (Pietra, 1991). In more extreme cases, the alveolar spaces are flooded with protein-rich fluid (Gottlieb and Boylen, 1974).

If there is enough time for hypoxic heart failure to occur, blood vessels in the nose and pharynx rupture, giving a pink tinge to the edema fluid. After 24 hours, hyaline membranes will be visible in the alveoli. They are composed of necrotic alveolar cell debris, mixed with the protein-rich edema fluid, deposited on the alveolar walls. This phase is followed by a recovery phase. During this final phase, the cut surface of the lung will be firm and brownish, suggesting the diagnosis of pneumonia. Type II alveolar cells and fibroblasts proliferate, and the fibrinous exudate in the alveoli is replaced by granulation tissue (Kringsholm and Christoffersen, 1987).

Studies of heroin users published in the older literature describe thickening of the alveolar septa, fibrosis, and hypercelullarity, with hemosiderin-laden macrophages often present in the alveolar walls and even in the lamina of the alveoli and respiratory passages (Rajs et al., 1984). At one time, it was thought that the presence of hemosiderin-containing macrophages was nearly diagnostic for chronic heroin use, but because so many heroin abusers also smoke "crack" cocaine, such conclusions are no longer warranted. Sputum from "crack" smokers is usually turbid, gray, or even black, and considerably darker than sputum seen in heavy tobacco smokers dwelling in the same urban environment. Microscopic examination of sputum from "crack" smokers will disclose excessive carbonaceous material in the cytoplasm of pulmonary alveolar macrophages and also in the extracellular compartment of sputum smears (Klinger et al., 1992). "Crack" smokers tend to have car-

bonaceous sputum and, not infrequently, emphysematous changes in their lungs. Carbon-laden macrophages can also be found in the pleural fluid of "crack" smokers who develop malignancy or HIV-related pulmonary disease (Singh et al., 1995), and small intrapulmonary hemorrhages are common. The pattern is readily apparent in microscopic sections, even before they are placed under the microscope; it is highly reminiscent of the pattern seen in "coal miner's lung." When the pattern of injury produced by cocaine smoking is superimposed on the pattern of injury produced by intravenous heroin abuse, the resultant picture is difficult to predict (Forrester et al., 1990; Bailey et al., 1994; Gallouj et al., 1999).

Why some individuals should develop florid pulmonary edema and others do not is a mystery. It has been suggested that heroin has direct toxic effects on pulmonary capillaries or even the heart, leading to hypoxic-induced heart failure (Menon, 1965). A role for altered capillary permeability is suggested by the fact that the protein content of the edema fluid is almost twice that of serum (Katz et al., 1972). Other theories that have been proposed include acute allergic reactions to heroin, the presence of contaminants in the heroin, causing histamine release, or some centrally mediated effect (Katz et al., 1972).

Alveoli normally stain negatively for laminin and type IV collagen, but in disease states, when membrane destruction is present, both compounds leach out. When stained with IgE antibodies, lung specimens from opiate overdose victims do not appear significantly different from controls, just the contrary to what would be expected if the edema was due to anaphylaxis (Dettmeyer et al., 2000). For the present, the most plausible explanation would appear to be one that was first proposed more than 30 years ago: respiratory depression leading to hypoxia, which in turn causes increased capillary permeability and fluid extravasation into the alveoli (Duberstein and Kaufman, 1971).

5.8.3.1.2 Needle and mercury emboli. Attempts at central vein injection may sometimes result in needle fragments embolizing to the lung. These events are usually not fatal, and the needle fragments may only be detected incidentally at autopsy. For example, one recent report described a cocaine-related death where a needle fragment was found protruding into the cavity of the right ventricle. Death was a consequence of cocaine toxicity, and the needle fragment was only an incidental finding (Thorne and Collins, 1998). Nonetheless, the x-ray appearance can be quite frightening (Lewis and Henry, 1985; Angelos et al., 1986; Brunette and Plummer, 1988; Gyrtrup et al., 1989; Hart et al., 1989; Stern and Steinbach, 1990; LeMaire et al., 1998).

In the late 1980s, several reports were published about drug users who were injecting mercury intravenously (De Ruggieri et al., 1989; Haffner et al., 1991). According to street lore, the injections increased athletic ability and sexual prowess. No recent reports and no autopsy studies have appeared since then. Chest x-rays of these individuals show striking metallic opacities outlining the pulmonary vascular bed and the apex of the right ventricle. Most of the mercury collects in the right ventricular cavity after injection, but a portion embolizes via the small pulmonary arteries The mercury spheres deposited in the right ventricle eventually penetrate into the myocardium, moving outward and causing a chronic and partly transmural inflammatory response.

5.8.3.1.3 Foreign body granulomas. Foreign particle embolization is frequent in intravenous drug abusers, but clinical symptoms are not. Granuloma formation is an inconsistent finding at autopsy (Halpern and Rho, 1966; Sapira, 1968; Gottlieb and Boylen, 1974; Glassroth et al., 1987). Granulomas form when drug users repeatedly inject themselves with aqueous suspensions of pharmaceutical preparations designed to be taken orally (Figure 5.8.3.1.3.1). Heroin has been available since the turn of the century, and

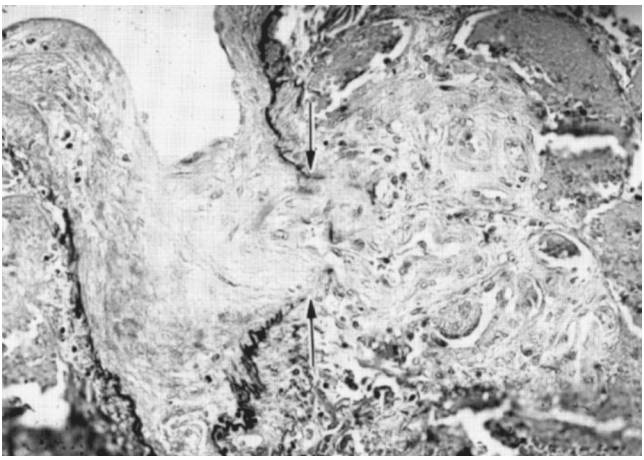

Figure 5.8.3.1.3.1 **Thromboembolic arteriopathy.** Repeated injection of particulate material can lead to pulmonary hypertension. Organizing and recanalizing thrombi in drug abusers can look very much like the plexiform lesions of primary pulmonary hypertension. The plexiform lesions of primary pulmonary hypertension, such as those shown here, are typically seen only at the branch points of stenotic small arteries. Lesions are composed of a complex network of small blood vessels and proliferating mytofibroblasts. (Courtesy of Giuseppe Pietra, Director, Division of Anatomic Pathology, Hospital of the University of Pennsylvania.)

morphine for nearly 200 years, but pulmonary granulomatosis in drug users was first described in 1950 (Spain, 1950). The time lapse suggests that the injection of oral medications is a relatively recent innovation.

In some cases, cotton fibers are the culprit. The cotton is introduced when addicts load their syringes by drawing up the liquid through a cotton ball; small fibers of cotton are drawn up at the same time. Most granulomas, however, are due to magnesium trisilicate (talc), because talc is widely used in the pharmaceutical industry as a filler. The amount of active ingredient in most pills can be quite small, so talc is added to create a pill of manageable size. When injected, talc particles become trapped in the pulmonary arterioles and capillaries, producing acute focal inflammation and thrombosis. The reported incidence of talc-containing granulomas ranges from 15% (Hopkins, 1972) to 90% in some series. The tissue reaction to cotton resembles the response to talc. If the injection of crushed pills is common, then so will be the incidence of foreign-body granulomas (Tomashefski and Hirsch, 1980; Tomashefski et al., 1981; Kringsholm and Christoffersen, 1987). Fungal spores can also cause granulomatous disease. The soil saprophyte *Scopulariopsis brumptii* was found to be the cause of hypersensitivity pneumonitis in at least one addict (Grieble et al., 1975), and analysis of confiscated heroin samples has shown the presence of many different fungal varieties.

Whether the offending agent is talc, cotton, corn starch, or cellulose (Table 5.8.3.1.3.1), the clinical course and pathologic findings are much the same. Trapped particles cause microthrombosis and granuloma formation. Some of the trapped material may migrate into the perivascular space, where more granulomas form. If the process is ongoing, a reduction in the size of the pulmonary bed occurs, and pulmonary hypertension can result. Associated anatomic changes include medial hypertrophy and eccentric/concentric intimal fibrosis. The tissue diagnosis can be confusing, because organizing and recanalizing thrombi seen in intravenous drug users can appear very much like the plexiform lesions

Table 5.8.3.1.3.1 Characteristics of Birefringent Materials Found in the Lungs of Intravenous Drug Users

Substance	Shape	Size (μm)	PAS Staining
Talc	Needle-shaped	5–15	Negative
Potato starch	Maltese cross, eccentric center	20–200	Positive
Maize starch	Maltese cross, concentric	10–30	Positive
Microcrystalline cellulose	Elongated rod	25–200	Positive
Cotton fibers	Irregular	Variable	Negative

Note: Talc and cellulose are frequently seen in conjunction with granulomatous reactions, but other agents are not.

Source: Adapted from Kringsholm and Christoffersen (1987).

of primary pulmonary hypertension. The two conditions can be distinguished by the fact that plexiform lesions are typically seen only at the branching points of stenosed small arteries (Pietra et al., 1989).

Microcrystalline cellulose, a depolymerized form of cellulose, is also used as a filler and binder in the manufacture of oral medications. Cellulose crystals measure anywhere from 20 to 90 μm and are a good deal larger than talc or cornstarch crystals. The larger size of these crystals explains granuloma formation in the larger elastic pulmonary arteries and even the right ventricle. Cornstarch granulomas are strongly associated with the injection of oral pentazocine and secobarbital preparations (Newell et al., 1988), which today is an increasingly uncommon practice. Cellulose granulomas can be identified by their distinctive Maltese-cross pattern (visible with a polarizing microscope), and by the fact that they stain as carbohydrates (Tomashefski and Hirsch, 1980). The presence of foreign bodies in the interstitium is consistent with a longstanding process. The presence of foreign material only in the media of vessels is consistent with more recent use.

5.8.3.1.4 Injuries of the great vessels. Adulterants and expients mixed with illicit heroin can provoke an inflammatory reaction; peripheral veins become sclerotic, and abusers must use central veins for access. The two most popular sites are the vessels of the groin and neck (the "groin hit" and the "pocket shot") (Lewis et al., 1980; Pace et al., 1984; Hillstrom et al., 1990; McCarroll and Roszler, 1991; Mackenzie et al., 2000). The neck vessels are especially difficult for the abuser to inject into and, for a fee, other addicts will do the injecting for them. The results are predictable. Pneumothorax is a frequent occurrence, as is hemothorax from laceration to one of the great vessels (Lewis et al., 1980; Douglass and Levison, 1986; Jackson et al., 1995). Pyohemothorax and pseudoaneurysm (Johnson et al., 1984; Navarro et al., 1984; Zorc et al., 1988; Zhao et al., 1998) are also seen. In Europe, the use of intercostal vessels is an occasional alternative to neck injections. Reported complications include both pneumothorax and infection (Gyrtrup, 1989). Vocal cord paralysis secondary to repeated neck injection has also been described (Hillstrom et al., 1990).

5.8.3.2 Infectious complications

5.8.3.2.1 Aspiration pneumonia. The combination of depressed cough reflex and decreased level of consciousness, in conjunction with a general tendency to retain secretions, favors aspiration (Cherubin et al., 1972). If aspirated stomach contents are of very

low pH, acute chemical pneumonitis will result. If there is much particulate matter present, then acute airway obstruction is possible. Pneumonitis is usually a result of infection with Gram-negative and anaerobic organisms (Warnock et al., 1972). Aspiration pneumonia in narcotics abusers is not any different from aspiration pneumonia in alcoholics or in patients debilitated by chronic disease.

5.8.3.2.2 Community-acquired pneumonia. Even before the HIV epidemic, intravenous drug abusers were at increased risk for pneumonia and for infections in general (Cherubin et al., 1972; Harris and Garret, 1972; Moustoukas et al., 1983; Scheidegger and Zimmerli,1989, 1996). If opiate users had normal immune function, which they do not (Novick et al., 1989), the injection of unsterilized material through contaminated syringes would still cause a transient septicemia. HIV-positive intravenous drug users are much more prone to develop community-acquired pneumonia and tuberculosis than are their HIV-negative counterparts, and when they do, their clinical courses are said to be more severe (Scheidegger and Zimmerli, 1996). Among HIV-infected patients, including those without AIDS, the increased rate of infection can be striking. In one study, the annual attack rate for *Streptococcus pneumoniae* was only 0.7–2.6/1000 in the general population, compared to 21/1000 in asymptomatic HIV-infected intravenous abusers (Selwyn et al., 1988). HIV-infected heroin abusers are more likely to develop empyema and empyema may even be the first evidence of infection in such individuals (Hernandez Borge et al., 1998). The rate of opportunistic lung infections among HIV-positive intravenous drug abusers is similar in frequency to that of other HIV-positive subgroups (Niedt and Schinella, 1985; Ambros et al., 1987). Eosinophilic pneumonia appears to be more common in cocaine users and "crack" smokers than in heroin addicts, but the process does occur. Diffuse pulmonary infiltrates with eosinophilic of bronchoalveolar fluid have been described, and appear to be the result of an IgE-mediated hypersensitivity reaction (Brander and Tukiainen, 1993). No new reports of this syndrome, however, have appeared for nearly a decade.

5.8.3.2.3 Fungal pneumonia. Pulmonary fungal infections occur even in HIV-negative intravenous drug users (Rosenbaum et al., 1974; Mellinger et al., 1983; Collignon and Sorrell, 1983). Street heroin is often contaminated with fungal species, and precipitins to *Aspergillus, Micropolyspora faeni,* and *Thermoactinomyces vulgaris* can, if sought, be found in the blood of many intravenous drug abusers (Smith et al., 1975). The preponderance of evidence suggests that most of the fungi found in illicit drug samples are there largely because of airborne contamination, introduced when the users prepared their drugs for injection. The presence of specific fungi cannot be used to identify the origin of a sample, although some types of heroin seem to contain more contaminants than others (Domínguez-Vilches et al., 1991).

Analysis of several outbreaks of fungal pneumonia among addicts suggests that the cause of infection was contaminated paraphernalia, including preserved lemon juice which is used to prepare the heroin injection (Clemons et al., 1991). Some types of heroin (Mexican Brown) are poorly soluble in water and can only be dissolved after they have been acidified. The two most popular agents for acidifying are lemon juice and vinegar. *Candida* species are present as contaminants of the lemon rind. Infected patients most often present with lobar pneumonia. In a high percentage of cases, peripheral nodules, with or without cavitation, may be seen. Lung abscess and empyema may also develop (Mellinger et al., 1982). Hilar and mediastinal adenopathy can be a prominent finding that resolves over the course of weeks or months. Pleural effusions are seen in about 20% of cases, and

pleural thickening may result (Lazzarin et al., 1985). DNA analysis has shown that all strains of *Candida* appear to be equally infective, and no particular genotype is linked with disease in the addict population (McCullough et al., 1998).

Disseminated *Candida* infections have a rapid onset, a few hours after injecting. The infection may be manifest as a self-limiting lobar pneumonia, or as a generalized infection with endocarditis, chorioretinitis, and hepatitis, with and without soft tissue abscesses. Occasionally the septicemia is manifested only as an isolated endophthalmitis (Dupont and Drouhet, 1985; Shankland and Richardson, 1988). Repeat showers of emboli cause mycotic aneurysms of the pulmonary arteries, but these are usually asymptomatic and are only incidentally found at autopsy. Histologic diagnosis can sometimes be made by examination of scalp biopsy specimens, which will show infiltration of the hair follicles with chronic inflammatory cells and *Candida albicans*.

5.8.3.2.4 Tuberculosis and melioidosis. The incidence of tuberculosis in both HIV-positive and -negative opiate abusers is increased. In one study, 10% of cases with suspected or proven tuberculosis seen in the Los Angles public health system were also found to have undiagnosed HIV infection (Lopez et al., 1998). Some evidence, however, suggests that the connection between heroin and tuberculosis has more to do with lifestyle than with any biological determinants; in a study of heroin users with tuberculosis treated in Barcelona, a history of prior imprisonment was found to be a much better predictor for infection than either concurrent HIV infection or number of years of heroin use (Manzanera et al., 2000). The clinical course and pathologic findings are the same for heroin users as for any other patients with tuberculosis. Pulmonary melioidosis (due to *Burkholderia pseudomallei*), which can resemble tuberculosis on x-ray, also occurs in narcotic addicts (Cooper, 1967). Melioidosis is an endemic tropical disease, but it is occurring with greater frequency in the developed world, with sporadic cases occurring in immigrants. There are, as yet, no reliable immunologic or serologic test kits, and diagnosis requires a combination of microscopy, sputum culture, and biochemical identification (Zysk et al., 2000).

5.8.3.2.5 Septic pulmonary emboli. Septic pulmonary emboli are not an infrequent finding in intravenous abusers. Recurrent emboli of infected material may be due to infected bone or soft tissue at the injection site, septic thrombophlebitis, or even endocarditis. The most probable source is vegetations on the tricuspid valve (Wendt et al., 1964). Recurrent septic pulmonary emboli should raise the possibility of tricuspid vegetations (Reiner et al., 1976; Aguado et al., 1990; Corzo et al., 1992).

5.8.3.2.6 Anterior mediastinitis. Mediastinitis secondary to soft-tissue infection in the chest wall occurs in HIV-positive heroin users. In one case, the initial infection was sternoclavicular; in another, infection was sternochondrial. In both cases, the infectious agent was *Staphylococcus aureus*, and in both cases the infection of the anterior mediastinum caused sepsis and vascular compromise (Dreyfuss et al., 1992). Soft-tissue infections of the chest wall are relatively common among intravenous drug abusers, but spread to the mediastinum is not, and no further cases have been described since the index cases were first reported. Invasion of the mediastinum in these cases almost certainly was a consequence of HIV infection.

5.8.3.2.7 Emphysema. Emphysematous changes are occasionally seen in the subset of intravenous abusers who inject medications meant for oral use. The process may involve

both the upper (Pare et al., 1979, 1989; Goldstein et al., 1986) and lower (Smeenk et al., 1990) lobes. Rarely, disease is panacinar (Groth et al., 1972). Typically, the upper lobes show the most damage. Intravenous drug abusers with emphysema are in their late 30s, which distinguishes them from those with emphysema due to smoking or α-1-antitrypsin deficiency, where victims tend to be much older. Emphysematous changes have always been more common in stimulant abusers than in individuals taking opiates (Schmidt et al., 1991; Guenter et al., 1981), but now that simultaneous abuse of both stimulants and narcotics is common practice it may be impossible to determine the etiology of the changes.

5.8.3.2.8 Cotton fever. "Cotton fever" is a benign syndrome occasionally seen in intravenous narcotic abusers (Thompson, 1978). Heroin injectors who filter their "fix" through a wad of cotton may be injecting themselves with limited amounts of endotoxin (Shragg, 1978; Harrison and Walls, 1990). Cotton plants are heavily colonized with Gram-negative bacteria, especially *Enterobacter agglomerans* (Rylander and Lundholm, 1978) Endotoxin released by *E. agglomerans* may activate pulmonary macrophages and neutrophils, and activation of those cells promotes the release of other chemicals, causing fever and leucokocytosis (Ferguson et al., 1993). The same symptoms occur in cotton workers who inhale the endotoxin, which floats freely in the air of cotton mills. There is no effective way to immediately identify patients who have injected themselves with limited amounts of preformed endotoxin and those who have actually inoculated themselves with *E. agglomerans* or other bacterial agents. Because the latter group is at risk for sepsis or endocarditis, prudence dictates that patients presenting with "cotton fever" should have blood cultures drawn and then be treated, at least initially, with empiric antibiotic therapy.

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5.8.4 Gastrointestinal disorders

5.8.4.1 Introduction

Liver disease has always been a common but relatively benign finding in intravenous heroin abusers. Infiltration of the portal triads, though nondiagnostic, is easily demonstrated in the livers of most chronic abusers, as is hepatic steatosis and limited portal fibrosis. With the advent of the hepatitis C epidemic, the situation is no longer quite so benign. In some parts of the U.S., most heroin addicts are infected with the hepatitis C virus. Chronic infection with that virus leads to cirrhosis and, in a small proportion of cases, to hepatocellular carcinoma. The widespread prevalence of this disease is almost certain to change the clinical picture of heroin addiction and heroin addicts.

5.8.4.2 Bowel disorders

Opiates that bind the μ receptor decrease gut motility and cause severe constipation or obstipation. The diagnosis of narcotism is easily made from the appearance of the colon at autopsy; it will be distended with hard feces. The other bowel disease associated with opiate abuse is the "body packer" syndrome. This disorder was first noted in a cocaine courier by Suarez in 1977 (Suarez et al., 1977), and most of the cases that have been reported continue to involve cocaine rather than heroin smuggling (Greenberg et al., 2000). Smugglers, known as "mules," ingest anywhere from 20 to 100 rubberized packets containing multiple-gram quantities of drug. At first, the packets were made from condoms, balloons, or the fingers of surgical gloves. Now more care is devoted to the packaging, not only because the packets occasionally rupture and kill the courier, but also because the earlier packets were too easy to see on x-ray (Krishnan and Brown, 1999). Detection can be avoided by minimizing the contrast difference between the packets and the surrounding feces. To this end, sophisticated smugglers may drink mineral oil to minimize the contrast between the packets and the bowel contents. Even if the packets are difficult to see with plain films, they can easily be demonstrated using CT scanning (Vanarthos et al., 1990). Urine testing, at least in the case of cocaine smugglers, is often positive even if none of the packets rupture; the rubber wrapping acts as a semipermeable membrane through which small amounts of the contents of the packet gradually diffuse and enter the bloodstream (Gherardi et al., 1990; Packer et al., 1991). In the absence of any case reports, the proportion of heroin smugglers with positive urine tests is not known.

5.8.4.3 *Liver disease*

The first paper suggesting the direct hepatotoxicity of heroin was published in 1935 (Baltaceano and Visilu, 1935), and it is true that when death is due to acute narcotic overdose, the liver is more often than not enlarged and congested (often weighing over 2000 g). However, the other abdominal organs are also likely to be congested, often in conjunction with pulmonary edema. It seems likely that congestion is the result of acute cardiac decompensation (although it is far from proven that heroin-induced pulmonary edema is a consequence of heart failure; Section 5.8.3.1.1).

Experimental models for heroin and opiate toxicity are virtually nonexistent; however, one study did review histologic and ultrastructural changes in liver sinusoid of otherwise healthy heroin users and found a significant increase in sinusoidal wall surface (Trigueiro de Araujo et al., 1993). The increase is due to hypertrophy of the sinusoidal cells and results in fibrosis within the space of Disse. It is not clear whether these changes represent damage or possibly some protective adaptation.

5.8.4.4 *Porta hepatitis adenopathy*

Enlargement of lymph nodes located in direct proximity of the liver is common and nearly diagnostic for chronic intravenous heroin abuse. The exact incidence of these changes has never been tabulated, but some have placed it at over 75% (Edland, 1972). The porta hepatitis, subpyloric and peripancreatic lymph nodes, the cystic node at the neck of the gallbladder, and other nodes located along the common duct may all be involved. Not infrequently, the gastroduodenal and pancreatoduodenal nodes will also be enlarged. These nodes are gray, firm, and sharply demarcated. The degree of enlargement may be striking. Nodes measuring as much as 2 cm across are not uncommon. Microscopic examination of these nodes shows only a nonspecific pattern of reticuloendothelial hyperplasia. A puzzling aspect of this abnormality is why, even though systematic autopsies have been done on opiate abusers for nearly 150 years, this common abnormality was not recognized until Siegel and Halpern published their paper in 1966 (Siegel et al., 1966), and their findings were reconfirmed later by Wetli et al. (1972).

There are at least three possible explanations for this type of adenopathy, all unproven. Node enlargement could be a reaction to the injection of particulate material. In one series, birefringent material was found in 39% of nodes from confirmed addicts (Table 5.8.3.1.3.1) (Kringsholm and Christoffersen, 1987). Another possible explanation is recurrent infection. Long before the existence of HCV was even recognized, histologic changes consistent with nonspecific reactive hepatitis were observed in more than half the known drug users coming to autopsy (Paties et al., 1987). Deep abdominal lymphadenopathy can also be seen in HIV infection, though usually only in individuals with overt AIDS and secondary malignancy (Subramanyam et al., 1985; Cassani et al., 1993). Finally, there is the possibility that morphine itself might exert some direct effect on lymph nodes, causing them to enlarge. Morphine is easily detectable in nodes draining the portal areas, and in most cases the concentration of morphine is greater in the nodes than it is in the blood. Lymph node morphine concentrations measuring anywhere from 300 to over 8000 ng/mL have been recorded (Nakamura and Choi, 1983).

Inflammation of the portal tracts is a constant finding in long-term intravenous drug abusers. In one series, the incidence was over 92% (Table 5.8.4.4.1) (Paties et al., 1987). The pattern of inflammation seen in addicts is commonly referred to as "triaditis," with a predominantly lymphocytic infiltrate that frequently also contain plasma cells. On occasion, neutrophils may also be present, but these infiltrates are usually devoid of eosinophils (Kaplan, 1963; Siegel et al., 1966; Edland, 1972).

Table 5.8.4.4.1 Frequency of Hepatic Lesions in 150 Randomly Selected Drug Addicts

Lesion	Incidence (%)
Steatosis	70
Portal fibrosis	47
Portal flogosis	93
Piecemeal necrosis	46
Lymphoid follicles	40
Plasma cells	34
Acidophil bodies	23
Viral antigens	16
Bile duct proliferation	6
Bridging necrosis	5
Granulomas	2
Birefringent material	<1
Mallory's hyaline	Absent

Note: Patients had a mean age of 23.3 years and were predominantly male (86%).

Source: Adapted from Paties et al. (1987).

Lobular inflammation is almost as common as "triaditis" (85%), but necrosis is less common (46%), and when it occurs, it tends to be widely scattered. The changes in addicts are easily distinguishable from those seen in alcoholics, as there are no centrolobular lesions, no Mallory's hyaline, and only rare neutrophils. True bridging necrosis is also uncommon. Infiltrates in areas of necrosis are composed mainly of monocytes. Steatosis, which earlier workers believed was uncommon, can be found over 70% of the time. The fatty accumulations may be microvesicular, macrovesicular, or mixed.

Hepatic foreign body granulomas are uncommon, as most injected contaminants are trapped in the pulmonary vascular bed and never enter the systemic circulation. Whether or not birefringent material will be found in the liver or hepatic nodes depends in large part on the population being studied. If the population of addicts is injecting pills meant for oral consumption, then the probability of finding birefringent material is greater. Of course, foreign bodies can be widely disseminated when a septal defect and a shunt are present, and users with widespread systemic granulomas have been reported occasionally (Riddick, 1987).

5.8.4.5 Hepatitis

Liver disease is a common finding in narcotic abusers. In Paties' series of 150 addicts (Paties et al., 1987), changes consistent with chronic active hepatitis were found in 24% of the cases, and acute hepatitis was diagnosed in 12%. Most of these individuals had immunohistochemical evidence of one or more viral antigens. In acute cases, scattered foci of parenchymal cell loss with acidophilic necrosis and swelling along with proliferating reticuloendothelial cells and mononuclear infiltrates can be seen. During the last 10 years, the prevalence of both hepatitis B and C, not to mention HIV, in intravenous drug abusers has increased drastically.

5.8.4.5.1 Hepatitis A virus. The prevalence of hepatitis A virus (HAV) is much lower than that of hepatitis B virus (HBV) or hepatitis C virus (HCV). Only 125,000 to 200,000 new cases are reported in the U.S. each year, with fewer than 100 HAV-related deaths. HAV is transmitted via the fecal oral route; there is no evidence of increased risk among drug abusers, and chronic HAV infection does not occur (Advisory Committee on Immunization Practices, 1999). Epidemiological survey results indicate that perhaps one third of Americans have serologic evidence of past infection, with major outbreaks of infection occurring once every decade (the last such outbreak was in 1989). HAV infection does not produce any unique histologic features (Kryger and Christoffersen, 1982).

5.8.4.5.2 Hepatitis B virus. Estimates suggest that more than 350 million people worldwide are chronic HBV carriers. The prevalence of chronic HBV infection varies widely, from rates of greater than 8% in Africa and Asia to less than 2% in Europe and the U.S. In areas where the infection rate is very high, infection is usually transmitted from mother to child at birth. In the U.S., the main routes for transmission are high-risk sexual activity and intravenous drug abuse. In San Francisco, nearly one-third of intravenous drug users under the age of 30 reported sharing needles, and nearly two-thirds reported having more than two sexual partners in the previous month; only 10% reported having received vaccinations for hepatitis B infection (Seal et al., 2000). Estimates suggest that less than a third of the chronically infected go on to develop progressive liver disease, cirrhosis, and primary liver cancer (Maddrey, 2000).

Approximately 2.1% of patients with chronic HBV develop cirrhosis each year. The annual incidence of hepatocellular carcinoma is only 0.1% in asymptomatic patients, rising to 1% in patients with chronic HBV, and increasing still further to 3–10% when cirrhosis is present. Many otherwise healthy HBV-infected patients first come to medical attention only after they have become infected with a different virus, such as hepatitis. The combined infection places them at greatly increased risk of fulminant hepatic failure. For reasons that are not clear, HCV superinfection may lead to negative HBV tests (HBsAg positivity) (Chu, 2000).

No histopathologic differences have been observed between patients with HBV and HCV — not in the severity of inflammatory activity, degree of architectural damage, or appearance of the bile ducts (Thorne et al., 1982). It is not possible to distinguish with certainty patients with a hepatropic virus from those with nonalcoholic hepatic steatosis. More than a third of cases have steatosis, and 80% have some evidence of necrosis (Goldstein et al., 1995).

5.8.4.5.3 Hepatitis C. It is estimated that more than 170 million individuals worldwide are infected with HCV. Although HIV is the most widely publicized virus associated with drug abuse, the rate of infection for HCV is significantly higher than the annual incidence of HIV, which ranges from less than 1% to greater than 50% (Denis et al., 2000; Freeman et al., 2000; Fuglsang et al., 2000; Hagan and Des Jarlais, 2000; Touzet et al., 2000).

Most of the time, infection with the HCV virus leads to chronic hepatitis. Infection follows an indolent course, and clinically apparent cirrhosis occurs only in a minority of cases unless concurrent infection with HBV is also present, in which case the probability of becoming symptomatic greatly increases. HCV infection is the most common cause of fibrosing liver disease (Rockey, 2000). A number of histologic features are said to be characteristic, but not pathognomonic, for the diagnosis of HCV. These include the presence of lymphoid follicles in the portal tracts, bile duct lesions, fatty metamorphosis, and Mallory body-like condensations in the cytoplasm of the hepatocytes.

The early stages of HCV infection do not produce unique histologic changes, and they may even resemble the changes seen in an unrelated disorder, nonalcoholic steatohepatitis. In addition to fatty change, a mixed cellular inflammatory infiltrate may extend across the lobule, with evidence of hepatocyte injury and fibrosis (Neuschwander-Tetri, 2000). Similar alterations were first noted in intravenous heroin abusers more than 25 years ago and recognized in stimulant abusers a decade later.

The etiology of nonalcoholic steatosis is thought to be two different types of mitochondrial dysfunction: mitochondria lose their normal ability to metabolize fats properly, and they overproduce reactive oxygen species. β-oxidation of fatty acids can be impaired by a disparate group of drugs, including ethanol, aspirin, valproic acid, ibuprofen, or zidovudine (Pessayre et al., 1999). Fat begins to accumulate in liver cells, while the concurrent overproduction of free oxygen species causes necrosis, inflammation, Mallory's bodies, and fibrosis. Liver damage in the addict population has always been attributed to a combination of lifestyle (smoking, alcohol consumption, malnutrition) and possibly some toxic effects exerted by the drugs injected. The effects of commonly abused drugs on mitochondria, if any, have never been evaluated. Worse still, the types of lesions seen in drug abusers and in patients with HCV are also relatively common in obese individuals and in patients with diabetes. These conditions cannot be distinguished anatomically (Sorrell and Mukherjee, 1999; Sorbi et al., 2000).

Long-term infection with HCV may lead to the occurrence of hepatocellular carcinoma. These tumors generally arise in older patients and involve only those who have already progressed from steatosis and mild fibrosis to frank cirrhosis. When carcinoma does occur in the HCV-infected, it seems to be less aggressive than in other individuals. Typically, the tumor grows as a single hepatic nodule for several years before generating satellite or distant tumor nodules (Colombo, 1999). Evidence suggests that treatment of HCV patients with interferon attenuates their risk of developing carcinoma (Colombo, 1999; Okuda, 2000).

The only tests for HCV currently approved by the Food and Drug Administration (FDA) are those that measure anti-HCV antibodies, which are detectable in >97% of those infected. Such tests do not distinguish among acute, chronic, or resolved infections. In order to make the diagnosis of active infection, supplemental tests are required. At present, the recombinant strip immunoblot assay (RIBA™) is the most widely used of these tests; however, polymerase chain reaction (PCR) assays have a lower limit of detection (100 to 1000 viral genome copies per milliliter), and are diagnostic for chronic HCV more than 95% of the time (Halfon et al., 1997; Brojer et al., 1999).

5.8.4.6 HIV infection

The gastrointestinal tract is a less common target for HIV involvement than either the brain or respiratory tract (Jellinger et al., 2000). For a variety of reasons, however, nearly two-thirds of AIDS patients do, in fact, have hepatomegaly and/or abnormal liver function, and fewer than 15% of HIV-infected patients have histologically normal livers at autopsy (Trojan et al., 1998). Hepatic abnormalities may be a consequence of alcoholism or previously existing viral hepatitis, or they may even be a manifestation of opportunistic infections or opportunistic tumor. Hepatic disorders in the HIV-infected can also be a complication of sepsis, malnutrition, and even drug therapy (Schneiderman, 1988). The longer an individual has had AIDS, the higher the probability that histologic changes will be seen in the liver. Opportunistic infections that have been reported include *Mycobacterium avium-intracellulare*, which causes multiple granulomas obstructing the terminal branches of the biliary tree (Glasgow et al., 1985); cytomegalovirus; *Cryptococcus neoformans;* and type 2

herpes simplex virus, to name but a few (Schneiderman, 1988; Ainsworth et al., 2000; Limaye et al., 2000; Sheikh et al., 2000; Small et al., 2000; Suh et al., 2000). The incidence of extracerebral protozoal and bacterial infections and even tumors such as Kaposi's sarcoma has significantly decreased since the mid-1990s (Jellinger et al., 2000).

Interestingly, HIV-infected patients, like anabolic steroid abusers, may develop peliosis, a condition characterized by the presence of many small, cystic, blood-filled areas, usually in the liver but occasionally in the lungs or other organs. Blood-filled lesions are randomly scattered throughout the liver, often in association with foci of hepatocellular necrosis. The condition was first recognized in conjunction with tuberculosis, but the connection with anabolic steroid abuse has been recognized for some time (Taxy, 1978; Bagheri and Boyer, 1974). Peliosis is the result of infection with *Bartonella quintana*. Bacteria may or may not be visualized, but the causative organism can be identified by PCR. The infection can be eradicated by treatment with erythromycin (Santos et al., 2000). Peliosis is closely related to bacillary angiomatosis, which, unlike peliosis, usually only occurs in individuals with HIV infection (Leong et al., 1992). *Bartonella henselae* is responsible for bacillary angiomatosis, and this disorder is also responsive to treatment with erythromycin.

5.8.4.7 Amyloidosis

Intravenous drug abusers with hepatic amyloid often are HIV infected. When hepatic amyloid deposition occurs in heroin and cocaine abusers, it is almost invariably a consequence of the chronic suppurative skin lesions, a result of poor hygiene and repeated subcutaneous heroin injection. In heroin addicts, the type of amyloid deposited is unpredictable and of no diagnostic value, and the pattern of deposition is not helpful in identifying the origins of the process (Osick et al., 1993).

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5.8.5 Renal disease

5.8.5.1 Introduction

Chronic intravenous narcotic use can result in renal disease, although the factors determining individual susceptibility remain poorly understood, and it is not always clear whether the drug injected or some other factor is responsible. In the U.S., focal segmental glomerulosclerosis was once the most frequent cause of nephrotic syndrome in addicts, but this disease has never been seen outside of the U.S., and its incidence in the U.S. has decreased markedly over the last decade (Friedman and Tao, 1995). In some populations of drug users, renal amyloidosis is the predominant histopathologic lesion. In Europe, chronic glomerulonephritis is more likely to be encountered (Dettmeyer et al., 1998). Table 5.8.5.1.1 lists the more common renal disorders that have been identified in narcotic abusers.

Table 5.8.5.1.1 Renal Disorders Associated with Opiate Abuse

Focal glomerulosclerosis
Membranoproliferative glomerulonephritis
Renal amyloidosis
Necrotizing angiitis with renal involvement
Interstitial nephritis
Acute tubular necrosis due to rhabdomyolysis

5.8.5.2 Acute renal failure and nontraumatic rhabdomyolysis

Rhabdomyolysis accounts for much of the renal disease seen in addicts. It was first observed in narcotic users over 30 years ago (Richter et al., 1971), and cases have been reported regularly since then (Hamilton et al., 1972; Koffler et al., 1976; Akmal and Massry, 1983; Blain et al., 1985; de Gans et al., 1985; Curry et al., 1989; Otero et al., 1992; Melandri et al., 1996; Klockgether et al., 1997; Kumar et al., 1999; Riggs et al., 1999; Deighan et al., 2000; Rice et al., 2000). Rhabdomyolysis is caused by a combination of factors, including hypotension, fluid imbalance, and pressure necrosis. The result is muscle destruction and liberation of myoglobin into the bloodstream. However, as Richter et al. (1971) observed, the syndrome can occur in patients who are neither comatose nor subject to muscle compression; in those cases, it seems likely that mycotoxic adulterants play a role (de Gans et al., 1985; Melandri et al., 1991). Whatever the etiology, rapid onset of oliguria is followed by azotemia, acidosis, hypophosphatemia, hyperuricemia, and all the other electrolyte and chemical disorders associated with renal failure. Because the condition is rarely fatal, these patients do not come to autopsy or even biopsy. There is no reason to suppose that the histologic changes are in any way different from those encountered in cases due to traumatic rhabdomyolysis.

5.8.5.3 Secondary amyloidosis

The first reports of renal amyloidosis in heroin abusers were published in 1978 (Jacob et al., 1978). Since then it has become apparent that the incidence of renal amyloid in heroin addicts is significantly higher than the incidence of amyloid, found at autopsy, in the general population (Dubrow et al., 1985). There is very little evidence that the incidence of this disorder has increased over the last decade. Amyloid deposits are more commonly found in the kidneys of older, long-term abusers. Amyloid deposition results in massive proteinuria, with or without azotemia. Over 90% of addicts with renal amyloid will have clinical evidence of repeated skin infections with suppurative cutaneous lesions (Meador et al., 1979; Menchel et al., 1983; Neugarten et al., 1986). Most of the reported cases of renal amyloid in heroin abusers have been from New York City, raising the possibility that some local practice has a role. It has been suggested that subcutaneous injecting, and the inevitable chronic skin infections that result, are the cause (Campistol et al., 1988). Renal amyloid is hardly unique to heroin users, and a proven mechanism in these other patients is still wanting (Maury and Teppo, 1982). Routine light microscopy with hematoxylin eosin, or PAS staining, shows large amounts of eosinophilic material within the glomerulus. Confirmation that the material is in fact amyloid can be obtained by Congo red staining or by using polarizing microscopy. Amyloid has a typical apple-green birefringence. Electron microscopy shows amyloid fibrils.

Table 5.8.5.4.1 Differentiating HAN from HIV

Heroin-Associated Nephropathy (HAN)	Human Immunodeficiency Virus (HIV)
Mesangial hypercellularity	Mesangial hypocellularity
Interstitial infiltrates present	Interstitial infiltrates absent
Interstitial fibrosis prominent	Interstitial fibrosis absent

5.8.5.4 Heroin-associated nephropathy and other glomerular disorders

In the early 1970s, reports began to appear describing a relentlessly progressive variety of nephrotic syndrome. It was unresponsive to therapy and terminated in renal failure within a few months to a few years (Rao et al., 1974; Cunningham et al., 1983; Dubrow et al., 1985). The syndrome occurred only in heroin abusers. The predominant histologic alteration in these individuals was focal segmental glomerulosclerosis (Grishman et al., 1976). By the mid-1990s, however, new cases stopped appearing (Friedman and Tao, 1995). Though it has never been proven, many believe that kidney failure in these individuals was an immune-mediated process. They suggest that new cases were no longer appearing because the purity of the heroin supply had improved so drastically that street heroin no longer contained whatever compound it was that was initiating the immune process.

By the mid-1980s, it became apparent that HIV infection, even in the absence of opiate abuse, could cause a picture very similar to that seen in heroin-associated nephropathy (HAN). Without actually demonstrating the presence of virus, distinguishing HAN from HIV may be impossible; however, the kidneys of heroin abusers usually have evidence of marked interstitial fibrosis with interstitial infiltrates of lymphocytes and plasma cells. In addition, Bowman's capsule may be markedly thickened. By contrast, the focal segmental glomerulosclerosis that occurs in HIV patients is usually devoid of cellular infiltrates, and HIV patients generally do not have interstitial fibrosis. The results of animal studies suggest that the glomerular and renal epithelial cells are the primary targets of HIV-1 pathogenesis in the kidney, and that the essential pathologic process involves dysregulation of the epithelial cell cycle, with increased proliferation, apoptosis, cellular dedifferentiation, and altered cellular polarity (Barisoni et al., 2000). Even though HAN- and HIV-related nephropathy are clearly separate diseases, distinguishing between the two with routine light microscopy may not be possible, but electron microscopy is usually diagnostic (Table 5.8.5.4.1) (Genderini et al., 1990).

Cases of HAN have never been reported from Europe, but renal disease among European heroin users is not rare. A retrospective study of 179 forensic autopsies disclosed that slightly less than two-thirds of the decedents had nonlymphocytic membranoproliferative glomerulonephritis, and half of the specimens contained deposits of IgM antibody but none showed any evidence of focal glomerulosclerosis. In any individual case it is impossible to say whether IgM antibody deposits are a response to infection with HCV, or HBV, or to some toxic adulterant mixed with street heroin (Dettmeyer et al., 1998). Whatever the cause, progression of the lesions ultimately leads to glomerular destruction and symptomatic renal disease. Advanced lesions consist primarily of intracapillary deposits of eosinophilic, PAS-positive material involving isolated or multiple segments of the glomerulus.

Other infectious diseases can also involve the glomerulus, either directly or indirectly. Many heroin injectors with endocarditis will have focal or diffuse glomerulonephritis as a result of circulating antigen–antibody complex deposition (Rao et al., 1974). The deposition of immune complexes causes diffuse proliferative changes and even classic crescent formation. Most reported cases are in the older literature and occurred in individuals with staphylococcal endocarditis (Louria et al., 1967; Gutman et al., 1972). The true incidence of glomerulonephritis in addicts has never been established, but reports are uncommon. In Sapira's (1968) autopsy study, the incidence of chronic glomerulonephritis in known addicts was 8%. That value may no longer apply today. More recent experience suggests that the incidence of acute disease may be much lower. In most cases of endocarditis, renal embolization with infarction is probably more likely than immune complex deposition. In either case, these lesions rarely cause significant disease.

Infections with methicillin-resistant *Staphylococcus aureus* release bacterial superantigens which may in turn cause acute glomerulonephritis. Hepatitis B and C infections may also cause glomerulopathy. Membranous nephropathy associated with chronic hepatitis B surface antigenemia is a well-recognized entity (Cunningham et al., 1983). Chronic HCV infection, thought to be present in up to 80% of chronic intravenous drug injectors, may be associated with mixed cryoblobulinemia which may in turn result in glomerulonephritis (Ramos et al., 1994; Bakir and Dunea, 1996).

5.8.5.5 Necrotizing angiitis

A polyarteritis-like syndrome in intravenous drug abusers was first described by Citron et al. (1970); medium-sized and small arteries in most organs, as well as the arterioles in the brain, were involved. The elastic arteries, capillaries, and veins were all spared. Acute fibrinoid necrosis of the media and intima was observed, along with prominent infiltrates of eosinophils and lymphocytes. Occlusive thrombi were also present. The subacute process was marked by intimal proliferation and luminal narrowing, with saccular aneurysms, especially at vessel bifurcations. Very little evidence suggests that such a disorder ever occurs in opiate abusers, or even that it occurs in today's amphetamine abusers. Most of the patients described by Citron were intravenous amphetamine abusers, or polydrug abusers taking combinations of amphetamine with other drugs. Of the patients Citron studied, none who used only heroin developed the syndrome. No reports in heroin users have appeared since. Unfortunately, this entity remains in the literature and is frequently invoked to explain otherwise puzzling symptoms or outcomes.

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5.8.6 Neuropathology

5.8.6.1 Introduction

When the first reports of heroin toxicity were published at the turn of the century, opiates were thought to be neurotoxic (Creutzfeldt, 1926; Nissl, 1897). Fatty degeneration, particularly of neurons in the deeper layers of the frontal cortex and Ammon's horn, was thought to be diagnostic for morphinism. Subsequent studies have shown that the changes observed were either nonspecific or artifactual. Decades later, it was argued that heroin abusers were uniquely prone to infarction of the basal ganglia (Jervis and Joyce, 1948; Strassmann et al., 1969; Hall and Karp, 1973). The nonspecific nature of this finding is also now appreciated. With the exception of perivascular pigment deposition within macrophages, which probably is the result of repeated intravenous injection of foreign material (Figure 5.8.6.1.1) (Gray et al., 1992), no one lesion is diagnostic for narcotic abuse, at least not at the light microscopic level. Newer, noninvasive imaging techniques have disclosed a host of abnormalities, but none of these is apparent grossly or with the light microscope. When abnormalities are visible, they are almost always a consequence of some infection process acquired during the process of heroin injection. The better-known neuropathologic complications of narcotic abuse are listed in Table 5.8.6.1.1.

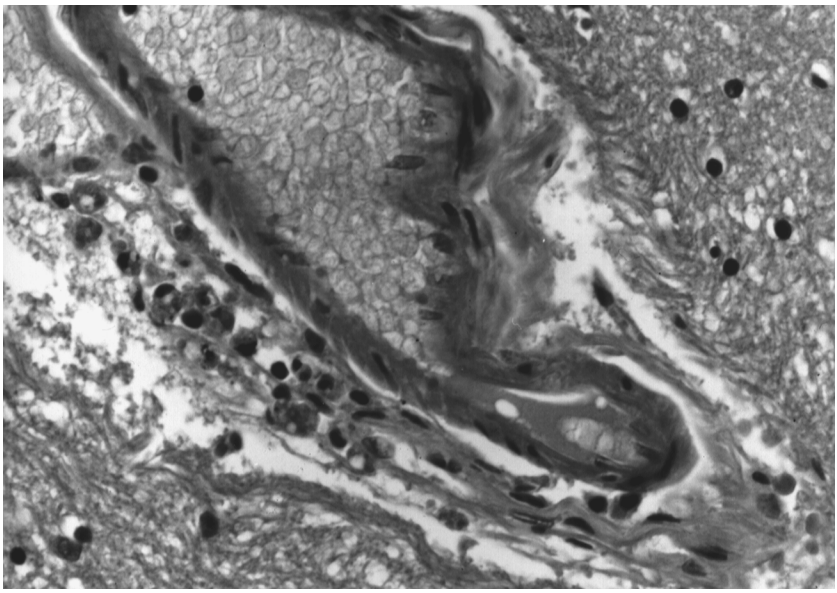

Figure 5.8.6.1.1 **Hemosiderin-laden macrophages.** Micrograph from brain of HIV-negative heroin addict. Similar cells are often seen in the lungs. In both locations, they appear to be the result of repeated intravenous injections of particulate matter. (Courtesy of Professor Francoise Gray, Department de Pathologie Hôpital Henri Mondor, Gretiel, France.)

Table 5.8.6.1.1 Neuropathologic Complications of Narcotic Abuse

1. Hypercapnic hypoxia
   a. Cerebral edema
   b. Venous congestion
   c. Focal hemorrhage
2. Infectious
   a. Complications of endocarditis
   b. Complications of HIV infection
      i. Encephalopathy
      ii. Opportunistic infections
      iii. Opportunistic tumors
   c. Phycomycosis
3. Spongiform encephalopathy
4. Transverse myelopathy
5. Peripheral neuropathy
6. Rhabdomyolysis
7. Stroke
8. Necrotizing angiitis
9. Parkinsonism

5.8.6.2 Hypoxic encelopathy

Deaths from acute opiate toxicity are usually associated with cerebral edema, meningeal congestion, and flattening of the gyri (Adelman and Aronson, 1969; Strassmann et al., 1969; Pearson et al., 1972; Levine and Grimes, 1973; Metter, 1978). As a rule, these deaths occur so rapidly that morphologic evidence of cellular injury is not apparent. With longer periods of survival, characteristic patterns of tissue necrosis emerge. The injuries seen are not so much a result of hypoxia but rather a result of the arterial hypotension that ensues because of the hypoxia (Brierley, 1972).

In almost all cases there will be terminal changes such as nerve cell ischemia and vascular congestion (Slayter, 1862; Gray et al., 1992), but under certain circumstances the pattern of injury may reveal a great deal about the clinical events that preceded death. A major abrupt decrease in systemic blood pressure typically produces necrosis in the arterial boundary zones between the major arteries. The area most frequently involved is the parieto-occipital region. If the drop in blood pressure is more gradual and of longer duration, then laminar necrosis of the calcerine cortex may be seen. This lesion is also prominent in the deeper layers of the cerebellum.

A pattern of continuous necrosis, often accentuated in arterial border zones, may also be observed. The Purkinje cells of the cerebellum are particularly vulnerable to injury, as are the cells of Sommer's sector, located in the hippocampus (Adams et al., 1966; Brierley, 1972). Some time must elapse before these patterns become apparent. If death occurs within 3 to 6 hours, the probability of detecting anything but chronic changes is small. With the passage of more time, typical eosinophilic degenerative changes become apparent in scattered neurons. The cells of the caudate and putamen may or may not be involved. If changes are to be detected in those nuclei, then sampling from multiple sites will be required.

These gross findings are not inconsistent with more recent single photon emission computed tomography (SPECT) studies of opiate addicts, where baseline perfusion reductions are apparent in the frontal and parietal cortices, while at the same time flow to the

thalamus is increased. When these same individuals are given naloxone, cerebral perfusion to these areas decreases (Krystal et al., 1995; Wang et al., 1997).

Chronic hypoxic episodes from repeated drug overdoses predictably result in necrosis and scarring of the hippocampus. However, the diagnostic value of this observation is limited by the fact that most heroin abusers today are in fact polydrug abusers. For example, hippocampal atrophy is common in alcoholics, particularly women (Agartz et al., 1999), as is reduced cross-sectional area of the corpus callosum (Pfefferbaum et al., 1996). These acute lesions may be superimposed on pre-existing chronic or subacute changes. Thus, zones of parietal-occipital necrosis may be seen along with areas of laminar necrosis, suggesting an initial acute hypotensive episode followed by prolonged hypotension and decreased cerebral flow. This type of pattern is not uncommon in heroin addicts.

5.8.6.3 Infectious diseases

5.8.6.3.1 Complications of endocarditis. Narcotics abusers get infectious diseases because of their unhealthy lifestyles, because their injection techniques are not sterile, because chronic opiate use causes immunosuppression, and occasionally because the heroin they are injecting is contaminated (Hagmann, 2000). Some very bizarre infections, such as aspergillosis (Morrow et al., 1983), nocardia (Hershewe et al., 1988), phycomycosis (Adelman and Aronson, 1969; Kasantikul et al., 1987), chromoblastosis (Kasantikul et al., 1988), and mucormycosis (Masucci et al., 1982) have been reported. Generally, these exotic infections are not major causes of morbidity. On the other hand, septicemia, endocarditis, and even necrotizing fasciitis are becoming more common, and all three disorders may have neurologic sequelae. In fact, the incidence of neurologic complications from subacute endocarditis has changed hardly at all since the introduction of antibiotics (Ziment, 1969).

Vegetations on the aortic and tricuspid valves can shed, producing disseminated microabscesses throughout the central nervous system. Small lesions center around septic emboli that lodge in terminal vessels, producing cerebral infarction (Louria et al., 1967; Dreyer and Fields, 1973; Grindal et al., 1978). In more severe cases, foci of metastatic suppuration may be seen throughout the leptomeninges. Intracranial hemorrhage secondary to the rupture of mycotic aneurysms can occur, but even today such events remain relatively uncommon (Jones and Siekert, 1968, 1989; Adelman and Aronson, 1969; Jones et al., 1969; Gilroy et al., 1973). The main sites of bacterial infection are the capillaries and small venules. They are usually surrounded by perivascular collections of polymorphonuclear leukocytes. As a rule, microabscesses do not produce severe or focal symptoms, and their presence may often be masked by other more obvious disease processes (Biller et al., 1986).

5.8.6.3.2 Complications of HIV infection. Even with the introduction of effective antiretroviral therapy, HIV-infected intravenous drug abusers still can be expected to have central nervous system abnormalities detectable at autopsy. The lung is the organ most frequently involved (84% of all cases demonstrate pulmonary pathology), but the incidence of brain involvement is not much lower (63%) (Masliah et al., 2000). AIDS-associated disorders can be divided into four groups: (1) AIDS encephalopathy, due to the direct effects of the virus itself; (2) opportunistic viral, fungal, parasitic, and bacterial infections; (3) opportunistic neoplastic processes, particularly primary brain lymphoma; and (4) HIV-related lymphocytic meningitis.

Several large autopsy studies have shown that within the last several years the frequency of opportunistic infections, such as cytomegalovirus, *Pneumocystis carinii* pneumonia, and *Mycobacterium avium* complex, have all decreased. Conversely, rates for bacterial

infections have increased, while the rate of fungal infection has remained unchanged (Jellinger et al., 2000; Masliah et al., 2000). The advent of effective retroviral therapy seems to have had little or no impact on the frequency of non-Hodgkin's lymphoma, a disorder which is now increasingly common. The frequency of Kaposi's sarcoma involving the brain remains unchanged since the start of the HIV pandemic, and HIV encephalitis continues to be detected in at least 25% of the cases.

The most frequently seen abnormality in the brains of AIDS patients is atrophy with diffuse or focal lesions in the white matter (Mossakowski and Zelman, 1997). Pallor of the myelin can be seen, and necrosis is prominent in the centrum semiovale. Diffuse or focal neuronal loss in the caudate and putamen may also occur (Navia et al., 1986a; Petito et al., 1986). In cases where diffuse white matter damage is present, multifocal microgranulomatous lesions and multinucleated giant cells can be seen. Immunohistochemical techniques will almost invariably demonstrate the presence of the virus itself (Budka, 1991). The severity of cortical atrophy appears to be related to the level of viral load in the CSF, suggesting that active HIV-1 replication in the CNS may account for the atrophy that is readily apparent on CT scanning (Brouwers et al., 2000).

Cytomegalovirus infection is common in HIV-infected patients. Evidence of infection is apparent in one-quarter of all autopsied AIDS cases (Petito et al., 1986). Cytomegalovirus has a tropism for both neuronal and glial cells. After a viremic phase, the virus may reach the brain, where it usually causes mild infection, but may on occasion be manifest as severe encephalitis. Many HIV-infected patients have minimal symptoms during life. Infection is evidenced histologically by the presence of microglial nodules, and the virus can be detected with immunohistochemical techniques (Sinclair et al., 1994), although today the diagnosis of central nervous system CMV infection is based upon the detection of CMV DNA in cerebrospinal fluid by means of PCR (Iten et al., 1999).

Toxoplasmosis infection is much less common than CMV infection, but it is more likely to produce symptomatic disease (Navia et al., 1986b). In life, the diagnosis is often difficult to make. CT scanning may or may not show hypodense lesions with ring contrast enhancement. In one recent series of HIV-infected patients, Tl-201 SPECT was used to accurately differentiate primary brain lymphoma from other causes of focal CNS lesions, with both false-positive and false-negative results occurring at a fairly high rate. The combination of Tl-201 SPECT with serum toxoplasma IgG measurement improves diagnostic accuracy, but still not to the level of certainty desired (Skiest et al., 2000). The findings at autopsy depend on how long the disorder has been present, whether or not it has been under treatment, and what other opportunistic diseases are also present (Martinez et al., 1995; Mossakowski and Zelman, 1997).

Early in the disease process, poorly demarcated foci of necrosis with surrounding edema and mixed inflammatory infiltrates can be observed. Evidence of arteritis may or may not be present. The diagnosis of toxoplasmosis is confirmed by the demonstration of extracellular tachyzoites and bradyzoite-containing cysts. In longer standing cases, organization of the necrotic material occurs, and well-demarcated areas of coagulation necrosis can be seen. In longstanding cases, cysts and tachyzoites may be very difficult to find (Huang and Chou, 1988; Bjerkas and Presthus, 1989; Bjerkas, 1990).

The principal opportunistic neoplasm seen in AIDS patients is high-grade B cell lymphoma. Primary CNS lymphoma has a strong association with Epstein–Barr virus (Yu et al., 1996), and is thought to occur in as many as 20% of HIV infected patients (Ciacci et al., 1999). The diagnosis is often difficult to make, especially in individuals already suffering from opportunistic infections (So et al., 1986; Gill et al., 1985). Diffusely infiltrating masses may be seen that are indistinguishable from any other sort of glioma. Tumor masses are

most often localized in the cerebral hemispheres, especially within the basal ganglia and periventricular regions, less frequently in the brain stem and cerebellum. Some of these tumors selectively involve leptomeninges, but in most cases leptomeningeal infiltrations are present alongside the tumor in the cerebrum. Not uncommonly, features of various opportunistic infections may be seen superimposed on the tumor, with multinuclear giant cells or even CMV inclusion evident within the mass of the tumor (Zelman et al., 1998).

5.8.6.3.3 Primary phycomycosis. Fungal brain infection is usually associated with poorly controlled diabetes or the presence of some disorder, such as leukemia that depresses immunity. A handful of reports have linked phycomycosis to intravenous drug abuse, usually in heroin users (Adelman and Aronson, 1969; Hameroff et al., 1970; Chmel and Grieco, 1973; Masucci et al., 1982; Kasantikul et al., 1987; Micozzi and Wetli, 1985). Infection begins in the nasal cavities, then invades the turbinates and the veins that drain them, extends into the paranasal sinuses, and eventually reaches the orbit. In other instances, the infection reaches the brain by a hematogenous route. It may be that the brain supplies a particularly conducive environment in which the fungus can grow. Whatever the route of infection, the result is edema, proptosis, and ultimately destruction of the trigeminal and facial nerves. At least in drug addicts, the disease follows a fulminant course. Most patients die within two weeks of onset. Diagnosis in life may require brain biopsy, because fungi are not detected in the cerebrospinal fluid. CT scanning may be suggestive, but it is not diagnostic. Lesions are usually multiple and symmetric, and involve the basal ganglia. Material removed at surgery or autopsy is composed of aggregates of macrophages, lymphocytes, and multinucleated giants cells. Even routine H & E staining will show the broad, branching, nonseparate fungal mycelia (Schwartz et al., 1982).

5.8.6.3.4 Spongiform leukoencephalopathy. The classification of this disorder is somewhat obscure. It has never been established whether its etiology is toxic or infectious (Figure 5.8.6.3.4.1). In 1982, an epidemic outbreak of spongiform leukoencephalopathy occurred in The Netherlands (Wolters et al., 1982; Haan et al., 1983). Nearly 50 patients were involved, and the only factor common to all those affected was that they were addicts who smoked heroin. In most cases, the disorder ran a two- to three-month course. In the initial stages, motor restlessness and apathy, with obvious cerebellar signs, rapidly gave way to hypertonic hemiplegia or even quadriplegia. In some cases, patients developed myoclonic jerks or choreoathetoid movements. Onset of hemiplegia seemed to mark a turning point in the progression of the disease. Half of the patients stabilized or improved while the other half progressed to a final, fatal stage with central pyrexia, spastic paresis, and akinetic mutism. These individuals died of respiratory failure. Since then, other cases have occurred in England, Germany, and Spain (Haan et al., 1983; Schiffer et al., 1985; Hugentobler and Waespe, 1990; Sempere et al., 1991; Roulet et al., 1992; Tan et al., 1994; Stoltenburg-Didinger et al., 1995; Celius and Andersson, 1996; Chang et al., 1997; Kriegstein et al., 1997; Rizzuto et al., 1997; Nuytten et al., 1998; Weber et al., 1998; Chen et al., 2000). In 1997, the first cases were reported in the U.S., and additional cases have been reported since then (Kriegstein et al., 1997, 1999).

All of the patients in the original series reported from The Netherlands had obvious edema with flattening of the convolutions and brain weights of 1380 to 2560 g. In all cases, microscopic examination showed damaged white matter filled with vacuoles. In some areas, the vacuoles had coalesced to form larger cavities. Around the cavities could be seen a fine network of attenuated myelin. The number of oligodendroglia was reduced,

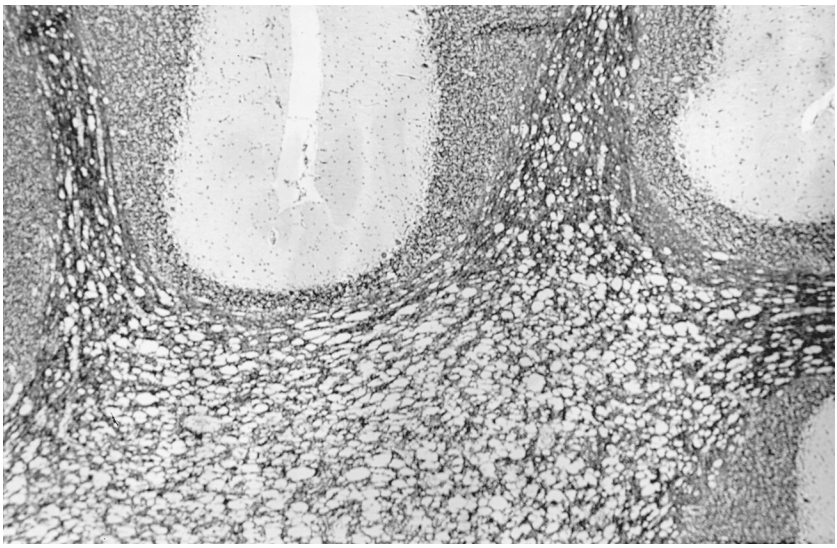

Figure 5.8.6.3.4.1 **Spongiform leukoencelopathy.** This degenerative brain disorder is seen only in heroin smokers. In some areas, vacuoles have coalesced to form larger cavities. Around the cavities is a fine network of attenuated myelin. No myelin breakdown products are evident and inflammatory cells are also absent. (Courtesy of Dr. E. Ch. Wolters, Academisch Ziekenhuis, Vrje Universiteit, The Netherlands.)

but no myelin breakdown products were evident. Inflammatory cells were also absent. Electron microscopy done in several cases showed multivacuolar degeneration of the oligodendroglia, with swollen mitochondria and distended endoplasmic reticulum. Light microscopic examination did not disclose it, but the electron micrographs showed abnormalities of the myelin lamellae and axoplasm, which also contained swollen, abnormal mitochondria. Magnetic resonance studies have demonstrated the presence of elevated lactate concentrations in white matter, raising the possibility that the underlying abnormality in these individuals may be mitochondrial dysfunction (Kriegstein et al., 1999). Toxicologic evaluation of all patients has been unremarkable. Chemical analyses of samples of local heroin used by the addicts showed only the usual adulterants: caffeine, lidocaine, procaine, phenobarbital, and methaqualone. None of these agents has ever been shown to be neurotoxic.

The changes in these individuals are easily distinguishable from those seen in AIDS-associated progressive multifocal leukoencephalopathy (PML), a disorder that may be present in 10% or more of autopsied patients with AIDS (Aksamit et al., 1990). This disorder may constitute the only abnormality present in the brain, or it may be seen in conjunction with other HIV-related opportunistic infections and/or neoplastic lymphoma. Before the AIDS epidemic PML was rare, usually seen only in association with leukemia and lymphoma. PML is due to infection with JC virus, a papova virus that most are exposed to in childhood (Sweeney et al., 1994; Berger and Major, 1999).

Demyelination with oligodendroglial and astrocytic pathology is always evident. Changes tend to be widespread with predominant oligodendroglial abnormalities (Mossakowski and Zelman, 1997, 2000). Rarely, changes may be very localized. Intense demyelination occurs, resulting in tissue destruction and cavitation. Typical microglial nodules are inevitably present, as are impressive infiltrates of macrophage and lymphocytes. For

reasons that are unexplained, these changes are confined to the cerebral hemisphere and cerebellum (Berger and Major, 1999). Changes in the cerebellum can be very striking, and some have suggested that it represents a different form of disease (Kuchelmeister et al., 1993). Changes also occur in the microvasculature, including mural thickening, pleomorphism of the endothelial cells, and prominent perivascular collections of HIV-positive monocytes and multinucleated cells. Even with treatment, survival in patients with AIDS-associated progressive multifocal leukoencephalopathy is poor, with a 6-month survival rate of under 10%.

5.8.6.3.5 Transverse myelitis. This rare entity was first described in 1926. Its etiology also remains undetermined, but its occurrence has been noted in conjunction with a heterogeneous group of disorders, including viral infections, AIDS, systemic lupus erythematosus, smallpox vaccination, trauma, extreme physical exertion, and heroin abuse. The association with heroin abuse was first noted in 1968 (Richter and Rosenberg, 1968). Since the index report, transverse myelitis has been reported on a number of occasions (Schein et al., 1971; Thompson and Waldman, 1970; Rodriguez et al., 1971; Pearson et al., 1972; Hall and Karp, 1973). The incidence of this disorder is not very high and, in spite of the increased availability of heroin, does not seem to be increasing; only five new case reports have been published since 1995 (Yang et al., 1995; Bernasconi et al., 1996; Sverzut et al., 1998; Derkinderen et al., 2000; McCreary et al., 2000).

The patients first described by Richter had not been taking heroin for a number of months, and they developed neurologic symptoms only after they began injecting heroin again. In all of the cases, onset of symptoms was quite rapid, ranging anywhere from a few hours to a few days. Victims developed flaccid paralysis and complete sensory loss ascending from the lower extremities to thoracic or even cervical levels. In the addict subpopulation, at least, fairly rapid improvement seems to be the norm, though residual deficits usually are seen. Myelography in acute cases is unremarkable (Arlazoroff et al., 1989). The few cases that have been studied with modern imaging techniques have all shown infection to be the cause (spinal cord abscess, spondylodiscitis, and epidural abscess), but in the few cases where autopsy has been performed the only findings have been extensive but nonspecific necrosis. Cerebrospinal fluid analysis has also been unremarkable, and it does not seem that infection is the only etiology.

Transverse myelitis was initially thought to be the result of anterior spinal artery occlusion, but when more cases were studied it became evident that the circulation in other territories could also be involved. Even ventral pontine disease has been observed (Hall and Karp, 1973) which, when it occurs, is usually the result of an isolated vascular accident within the spinal cord. In the case of narcotic abusers, it is not clear whether that accident is the result of thromboembolic phenomena, some sort of inflammatory vascular disease, or a toxic manifestation due to some contaminant injected along with the heroin. Because it is clear that heroin administration decreases blood flow to specific areas of the brain (Wang et al., 1997), the possibility exists that similar decreases might occur in the spinal cord but for the present, at least, the conclusion remains speculative, supported only by animal studies (Fuller and Stein, 1991).

5.8.6.3.6 Peripheral neuropathy. Peripheral nerve lesions occur in addicts for a number of reasons. Unsterile injections may lead to local infection with nerve involvement, as can the injection of toxic adulterants. Neuropathy associated with rhabdomyolysis is a well-recognized entity. Nerve injury may be an indirect result of elevated compartment pressure or a direct result of ischemia that can occur if compartment pressures rise high

enough. Unperceived pressure or traction can also cause plexus or peripheral nerve injuries, even without muscle swelling (Kaku and So, 1990). Evidence suggests that at one time or another, all of these mechanisms come into play (Penn et al., 1972; Schreiber et al., 1972; Richter et al., 1973; Gille et al., 1995; Sheehan and Jabre, 1995; Diaz Guzman et al., 1996).

In addition, HIV-positive patients are subject to peripheral and autonomic neuropathies, probably due to direct invasion by the virus, though it has also been suggested that an autoimmune etiology might be possible (Villa et al., 1990, 1992). Nerve injuries in narcotic addicts have been documented with electrophysiologic testing, but no autopsy studies have been carried out (Akmal and Massry, 1983). The mechanism in these cases has never been elucidated, but toxic or allergic reactions seem likely candidates because there have been cases of lumbar plexus neuropathy where pressure or traction obviously are not factors (Challenor et al., 1973; Greenwood, 1974; Jacome, 1982).

5.8.6.3.7 Rhabdomyolysis. Heroin had been available for nearly 70 years before anyone observed that heroin abuse occasionally gave rise to acute myoglobinuria (Richter et al., 1971; Schreiber et al., 1971; Penn et al., 1972; Greenwood, 1974; Grossman et al., 1974; Koffler et al., 1976; D'Agostino and Arnett, 1979; Cone et al., 1982; Jacome, 1982; Nicholls et al., 1982; Gibb and Shaw, 1985; Hecker and Friedli, 1988; Strohmaier and Friedrich, 1991a,b; Yang et al., 1995; Melandri et al., 1996; Klockgether et al., 1997; Kumar et al., 1999; Riggs et al., 1999; Deighan et al., 2000). The incidence of rhabdomyolysis in heroin users is not known with any precision, but judging by the number of cases reported in the literature, rhabdomyolysis may be occurring more often than is generally appreciated.

In some instances, the cause of muscle injury is obvious: pressure necrosis from the weight of the patient's own body while the individual is lying comatose (Schreiber et al., 1971), but few of the reported cases can be explained in this fashion (Chan et al., 1995). Cases with unequivocal evidence of concurrent cardiac necrosis, where the etiology could hardly have been pressure necrosis, have been reported (Schwartzfarb et al., 1977; Wynne et al., 1977; Scherrer et al., 1985; Melandri et al., 1996). In such cases, a direct effect of heroin or of an adulterant seems to be responsible.

The notion that heroin is directly myotoxic is supported by animal studies showing degenerative changes in rat soleus muscle after intraperitoneal heroin administration (Pena et al., 1993). Lesions produced in this model included hypercontraction of muscle fibers and disruption of the sarcoplasmic reticulum. Eosinophils were frequently observed around the degenerating fibers, suggesting that muscle destruction might be the result of a hypersensitivity reaction. Rhabdomyolysis has also been reported after rapid opioid detoxification with subcutaneous naltrexone maintenance therapy, although the possible mechanisms in that case are not known (Chanmugam et al., 2000).

Patients usually complain of muscle weakness, pain, and swelling that begin several hours to several days after using heroin. The muscles of the lower limbs are involved more often than those of the upper limbs. Associated neurologic complaints and neuropathies of various sorts have been reported in conjunction with heroin-induced rhabdomyolysis (Amnueilaph et al., 1973; Finelli and Taylor, 1977), although it should be noted that not all neuropathies in heroin users are a consequence of rhabdomyolysis. The presence of symmetric brachial neuropathy should raise the suspicion of lead poisoning, a rare consequence of using contaminated heroin (Antonini et al., 1989).

The diagnosis of rhabdomyolysis in these cases is usually suggested by the presence of muscle swelling and elevated creatinine phosphokinase levels. However, muscle swelling need not always be evident, and the presence of myoglobin in the serum is an

unreliable indicator at best, because myoglobin is rapidly cleared from the plasma. Early on, laboratory tests will disclose marked elevations of creatinine phosphokinase and aldolase. Some individuals may complain of dark urine, and about half will go on to develop full-blown renal failure, with typical laboratory findings. More recently, ultrasonography has been employed as a diagnostic tool (Steeds et al., 1999). Even early in the course of the disease, sonography may reveal multiple hyperechoic areas within the muscle — a pattern consistent with recent injury.

5.8.6.3.8 Stroke. Stroke occurs in heroin users, but in spite of very substantial increases in the number of heroin abusers, the number of case reports has not increased proportionally. In most cases, the etiology is obscure. Twenty years ago it was thought that the re-exposure of addicts to heroin after a period of abstinence might lead to vascular hypersensitivity reactions (Rumbaugh et al., 1971), but the theory has never been substantiated.

Necrotizing angiitis (see below) can certainly cause cerebral infarction (Citron et al., 1970), but there is rarely evidence for this disorder, and the few cases that have been reported have been almost exclusively in methamphetamine abusers (Toffol et al., 1987; Chevalier et al., 1995). The apparent decline in the number of cases of necrotizing angiitis, even among methamphetamine abusers, suggests that when cases did occur they may have been the result of some toxic contaminants mixed with the heroin (Citron et al., 1970). Cases rarely come to autopsy, but one of the few published case reports described necrosis of the elastica and smooth muscle layers without any accompanying leukocytotic infiltration of the blood vessel walls, but involving virtually all of the major cerebral vessels (Shibata et al., 1991). As often as not, angiographic studies in heroin-abusing stroke victims will be normal (Herskowitz and Gross, 1973).

Table 5.8.6.3.8.1 lists additional mechanisms that can cause stroke in opiate abusers. The same mechanisms that cause stroke in stimulant abusers could also cause stroke in opiate abusers but vasospasm seems unlikely in opiate users, as opiates share no common pharmacologic mechanisms with stimulants and do not (except for pentazocine) cause elevations in circulating catecholamines. A likely mechanism in many cases of stroke is positional vascular compression. The most recently published case involved a 35-year-old addict with dense hemiparesis. Regional flow studies demonstrated severe hyperemia of the entire carotid territory on the affected side, but normal vessels on angiography. Such localized hyperemia is often seen following restoration of flow in stroke patients and after cerebral spasm (Caplan et al., 1982). Generalized hyperemia is more likely to be observed after global ischemia. Stroke in these patients may be the result of an unfortunate set of

Table 5.8.6.3.8.1 Possible Etiologies for Stroke in Opiate Abusers

Thromboembolism
Thrombocytopenia
Vasculitis
Septic emboli
Hypotension
Secondary to arrhythmia
Secondary to decreased cardiac output
Secondary to peripheral vasodilation
Positional vascular compression

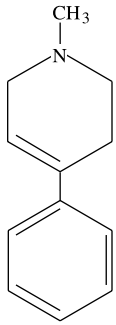

Figure 5.8.6.3.9.1 **MPTP.** 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) molecule.

circumstances. Large doses of narcotic lead to hypotension, decreased respiration, and generalized cerebral ischemia. If the carotid artery is then compressed by lying in the wrong way, perfusion might be lowered beneath some critical level, and stroke could occur in an already ischemic brain (Olson and Winther, 1990). In the absence of experimental evidence, such an explanation is speculative, but it could well account for an occasional infarct.

Hemorrhagic stroke in heroin abusers is the result of a deranged clotting mechanism, as might be encountered in cases of fulminant hepatitis or in individuals with AIDS-associated thrombocytopenia (Brust and Richter, 1976; Chevalier et al., 1995). Rupture of a mycotic aneurysm or underlying AV malformation is also possible but still uncommon enough to be reportable (Dreyer and Fields, 1973; Jensen et al., 1990; Bartolomei et al., 1992; Brust, 1993; Niehaus and Meyer, 1998). This is in contrast to hemorrhagic stroke in cocaine users, where victims commonly bleed from a pre-existing malformation or aneurysm.

5.8.6.3.9 Parkinsonism. MPPP is a potent meperidine analog. When it is synthesized by clandestine chemists, inattention to detail occasionally results in the production of a byproduct known as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Figure 5.8.6.3.9.1). MPTP is itself nontoxic, but astrocytes oxidize MPTP to a pyridinium metabolite (MPP+) that can damage neuronal cells. Dopaminergic neurons are particularly vulnerable to MPTP toxicity because they accumulate MPP+ and retain it for prolonged periods. Two pathways of astrocytic MPP+ formation have been identified, one utilizing monoamine oxidase (MAO) and the other requiring the presence of transition metals, though experimental studies suggest MAO plays a minor role in human MPTP toxicity (Di Monte et al., 1996; Przedborski and Jackson-Lewis, 1998). Whatever the metabolic route, it results in selective destruction of dopaminergic neurons in the substantia nigra and the globus pallidus (Jenner, 1998; Kramer et al., 1998).

If taken in sufficient quantity, MPTP can produce all the classic symptoms of parkinsonism including resting tremor, rigidity, bradykinesia, and postural instability. At least three isolated outbreaks of recognized MPTP toxicity have been reported. The first reported case occurred in 1979 (Davis et al., 1979). A graduate student who had been synthesizing and intravenously injecting MPPP for a period of six months made the mistake of modifying his methods. Shortly afterward, he developed symptomatic Parkinson's disease. Later analysis by authorities disclosed that the student had in fact produced a mixture of MPPP and MPTP. His symptoms responded well to treatment, but he died of an unrelated drug overdose some two years later. Detailed neuropathologic examination of his brain disclosed degenerative changes within the substantia nigra that were confined

to zona compacta. A marked astrocytic response and focal glial scarring were present along with abundant collections of extraneuronal melanin pigment.

A second cluster of patients was reported in 1983. Four patients bought what they thought was "synthetic heroin" and within a matter of days developed striking features of parkinsonism. Analysis of material injected by these individuals showed they had been using mixtures of MPTP and MPPP (2.5–3.2% MPTP, 0.3–27% MPPP) (Langston et al., 1983). Since the original report, 22 additional cases with less florid symptoms have been identified, all stemming from exposure to product from the same clandestine lab that had been operating in Northern California (Tetrud et al., 1989). The results of follow-up epidemiological studies indicate that during the three-year period from 1982 to 1985, over 500 individuals were exposed to MPTP, probably all from the same clandestine lab (Ruttenber, 1991).

Additional cases stemming from exposure to products from other sources were reported in 1983 and 1984, and continue to be reported episodically (Kramer et al., 1998). The first of these was in a non-drug-abusing chemist exposed to MPTP at work. He developed classic symptoms of parkinsonism that responded to treatment. The most recent reported case was in a polydrug-abusing chemist who responded to initial treatment but died of unrelated causes two years later. This individual preferred to snort his drug, but his parkinsonian symptoms were no less severe than those of the intravenous users. When he accidentally drowned, examination of his brain was perfunctory, and the substantia nigra was never even examined (Wright et al., 1984).

Other than the fact that different age groups are involved (average age in the 30s vs. average age in the 60s), there is little to distinguish parkinsonism occurring after MPTP exposure from parkinsonism in the general population. Initial symptoms may be mild or quite severe, though some evidence suggests that tremor is somewhat less common in the drug abusers. It is an open question whether additional new cases are likely to be encountered. Only sporadic seizures of samples containing MPTP have been reported. The most recent was in 1985, the same year that production of MPTP was made illegal. A closely related analog of MPTP called PEPTP (1,2-phenylethyl-1,2,5,6-tetrahydropyridine) can be generated as a byproduct of PCP production and may well possess the same neurotoxicity as MPTP, but no cases of parkinsonism attributable to PCP contamination have been reported to date.

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5.8.7 Hormonal and immune alterations

Heroin abusers are subject to a number of hormonal alterations, mostly involving sexual and reproductive functions. Studies have demonstrated decreased levels of both testosterone and leutinizing hormone, with testicular atrophy and impotence (Mirin et al., 1980; Mendelson and Mello, 1982). Opiates induce hyperprolactinemia in both experimental animals and in chronic opiate abusers (Tolis et al., 1978). Compared to non-drug-using controls, long-term heroin users have decreased levels of parathyroid hormone and decreased levels of testosterone. As a consequence, they have abnormal bone and mineral metabolism, with decreased vertebral bone density (Pedrazzoni et al., 1993). The etiology of these changes is not at all clear, but there is some evidence that opiates may act directly on the pituitary. When compared to controls, the response of β-endorphin and adrenocorticotropic hormone (ACTH) to metyrapone administration in addicts is significantly blunted, suggesting that the chronic stimulation of opiate receptors in some way impairs the function of the anterior pituitary gland (Vescovi et al., 1990). This notion is also supported by the observation that pituitary volume in healthy men addicted to heroin

Table 5.8.7.1 Immune Abnormalities in Opiate Abuser

Depressed E-rosette formation (*in vitro*)
Depressed cutaneous sensitivity
Depressed mitogenic response
Elevated CD4 cells
Elevated CD4/CD8 ratio
Elevated levels of CD4 receptor
Elevated neopterin levels
Elevated soluble interleukin-2 receptors
Elevated γ-interferon levels

Source: Adapted from Pillai et al. (1991).

and cocaine when assessed by magnetic resonance imaging (MRI) is nearly twice as great as the volume observed in healthy controls (Teoh et al., 1993).

Host resistance to most pathogens is reduced by opiate abuse (Table 5.8.7.1). Long before the advent of HIV, heroin addicts were known to have higher rates of opportunistic infection and cancer than the population at large (Sapira, 1968; Harris and Garret, 1972). Studies done in the early 1900s proved that morphine acts directly on lymphocytes (Atchard et al., 1909; Terry and Pellens, 1928). With the advent of intravenous narcotic abuse, long before the advent of HIV, other abnormalities of the immune system were also recognized. These included generalized lymphadenopathy (Halpern and Rho, 1966), elevated serum immunoglobulins (Kreek et al., 1972), lymphocytosis (Sapira, 1968), and abnormal T-cell rosette formation (McDonough et al., 1980).

It has become increasingly evident that morphine alters the immune response of most of the major cell types in the immune system including depression of natural killer (NK) cell activity, depressed T-cell function (manifested by either inhibition or induction of delayed-type hypersensitivity reactions), altered cytotoxic T-cell activity, and abnormal T-cell antigen expression. (Eisenstein and Hilburger, 1998).

Morphine downregulates phagocytic cell function in both human peripheral blood mononuclear cells (PBMCs) and human polymorphonucleocytes. Not only does exposure to morphine inhibit phagocytosis, but it also disrupts chemotactic responses and interleukin production and inhibits the generation of activated oxygen intermediates and activation of the arachidonic acid cascade. How all these actions are accomplished is not known, but the existence of an *in vivo* neural-immune control mechanism seems to be increasingly likely (Weber and Pert, 1989; Roy, 1996; Eisenstein and Hilburger, 1998).

The lifestyles of addicts are partially responsible for some of the immune abnormalities that have been observed. Chronic infection with viruses other than HIV may also contribute. The prevalence of hepatitis B and C infection is increasing worldwide (Kassem et al., 2000; Khan et al., 2000). Hepatitis C is now the most common chronic bloodborne infection in the U.S. (Anon., 1998), and infection with this virus is associated with a number of nonspecific immune changes (Dalekos et al., 1993).

In addition to the indirect control of mast cell function by cytokine release, opiates can also bind directly to specific receptor sites on the mast cell membranes (Fjellner and Hagermark, 1982). One result of such binding is histamine release that can lead to bronchospasm, hives, and flushing. Opiate-induced histamine release has occasionally been referred to as "pseudoallergy." IgG-class antibodies to morphine and other opiates have been demonstrated in humans, but it is not known if these antibodies have any clinical

significance (Biagini et al., 1992). IgM antibodies specific for morphine and codeine have also been demonstrated. In two studies, IgM antibodies were detected in 50 to 60% of addicts tested (Gamaleya et al., 1993a,b). Most addicts have elevated serum immunoglobulins, especially IgM, but IgE-type opiate antibodies have not been identified, at least not in humans. The immunoglobulin elevations are thought to be a consequence of the repeated injections of antigenic material (Cherubin and Millian, 1968; Vogel et al., 1970). The changes revert when heroin use is discontinued (Cushmanet al., 1970) unless, of course, chronic HCV infection has supervened.

Some *in vitro* evidence suggests opiates as cofactors in HIV infection (Gamaleya et al., 1993a,b). Comparisons of HIV seronegative intravenous narcotic users with seronegative, rehabilitated methadone users and normals have shown that natural killer activity is significantly reduced in the heroin users when compared to activity measured in methadone maintenance patients and controls. Measurements made in these same individuals show higher absolute numbers of CD2, CD3, CD4, and CD8+ cells (Novick et al., 1989). Other measurements in heroin users have also confirmed the presence of increased numbers of CD4+/T cells. Because the CD4 antigen is the receptor that HIV requires to gain entrance to T cells, the presence of increased numbers of CD4 cells in narcotic abusers may favor HIV infection (Pillai et al., 1991).

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5.8.8 Bone and soft tissue disorders

5.8.8.1 Introduction

Fibrous myopathy is a known complication of chronic pentazocine abuse and meperidine abuse (Levin and Engel, 1975; Rousseau et al., 1979; Yamanaka and Parsa, 1985; Kim, 1987; von Kemp et al., 1989; De Schepper and Degryse, 1990), and evidence suggests that it may also be associated with repeated injections of heroin (Mastaglia, 1982). Heroin use is also associated with decreased serum osteocalcin concentrations, and reduced osteocalcin production is a marker of decreased osteoblastic activity. Female heroin users infected with the HIV virus experience significantly worse osteoporosis than HIV-infected women who are not heroin users (Teichmann et al., 2000). In fact, most bone and soft tissue disorders seen in opiate abusers are infectious in origin and are the main reason that drug abusers are hospitalized (Cherubin et al., 1972; White, 1973). Directly or indirectly, especially if HIV and HIVC infections are included, infectious complications also account for the majority of deaths. Exotic infections such as malaria and tetanus, which were common 40 years ago, have been replaced by endocarditis, hepatitis, and AIDS, but it is the more mundane conditions such as cellulitis, soft tissue abscess, and septic thrombophlebitis that most often bring the abusers to medical attention.

5.8.8.2 *Bone and joint infections*

In most instances, the source of bone and soft tissue infections is either the solution used to dissolve the drug or the abuser's own skin flora (Tuazon et al., 1974). Once introduced into the body, infection may spread locally or hematogenously. The pattern of sites most frequently infected, and the organism responsible for the infection, appear to be changing. In the past, the skeletal sites most frequently infected were the vertebral column and sternoarticular joints (Goldin et al., 1973; Gifford et al., 1975; Bayer et al., 1977; Waldvogel and Papageorgiou, 1980; Friedman et al., 1981; Brodaty et al., 1983; Gillis et al., 1990; Brancos et al., 1991; Covelli et al., 1993). In more recent studies the extremities, especially the left knee (Chandrasekar and Molinari, 1987), were found to be involved much more than the sternoarticular joint. The shift seems to be due to the fact that more addicts are injecting themselves in the groin and the fact that infection is most likely to occur in the structures closest to the injection site. Because most individuals are right handed, the left side is most frequently injected.

In early studies, *Pseudomonas aeruginosa* was responsible for most (more than 80%) of the joint and bone infections in intravenous drug abusers (McHenry et al., 1975; Waldvogel and Papageorgiou, 1980), but any number of organisms may be responsible. Infectious discitis caused by *Enterobacter cloacae* has been described in both HIV-positive and -negative intravenous drug users (Marce et al., 1993). Infections with *Candida* are increasingly frequent, but *Candida* infection appears to be just as common in addicts without HIV as it is in those with HIV (Lafont et al., 1994; Jensenius et al., 1999; Derkinderen et al., 2000).

Heroin users occasionally develop osteomyelitis of the cervical spine (Silvani et al., 1987; Endress et al., 1990), an infection that almost never occurs in non-drug abusers. More often than not, the infectious agent is *Staphylococcus*, introduced when addicts inject into the great veins of the neck (Endress et al., 1990). In life, CT scanning will show an inflammatory reaction about the carotid sheath, with prevertebral soft-tissue masses adjacent to the areas of bone destruction.

Candida bone infections, on the other hand, almost never involve the cervical spine. While such infections may occur in intravenous abusers, they are more commonly seen in immunnosuppressed patients in general, and those with indwelling catheters in particular (Andermahr et al., 1998; Williams et al., 1999; Eisen et al., 2000). Just why the blood supply should favor the lower lumbar spine is not obvious, but almost all cases of *Candida* osteomyelitis have involved the lower lumbar area. The reason appears to be that infection spreads into the endplate of the vertebral body, which is supplied by ventral branches of the spinal arteries. *C. albicans* is usually the responsible agent (Almekinders and Greene, 1991; Lafont et al., 1994), but the more exotic infections also must be considered (Owen et al., 1992; Eisen et al., 2000).

The prevalence of tuberculosis is increased in heroin users, especially those who are HIV seropositive. Extrapulmonary involvement, with or without obvious lung lesions, is seen in 15% of cases (Alvarez and McCabe, 1984), and in many of those the extrapulmonary site involved is osteoarticular, usually the vertebral bodies and their intervertebral discs. Involvement of the bony arch usually produces a compression syndrome. Fortunately, involvement of the vertebral arch is rare, but it has been reported in intravenous heroin users (Mallolas et al., 1988). Pott's disease is a rarity, but it does occur. Clinically, tuberculous osteomyelitis of the spine can be distinguished from pyogenic or fungal by its less indolent onset. Patients with Pott's disease can be expected to present with fever, back pain, weight loss, and night sweats. They also are much more likely to have apparent urologic abnormalities, which are uncommon with pyogenic or fungal vertebral infection (Forlenza et al., 1979).

5.8.8.3 Soft tissue infections

Though skin and soft tissue infections are common among intravenous abusers, there is nothing to distinguish their appearance from similar lesions in non-drug users. The bacteriology of these infections is somewhat controversial, with conflicting results being reported from different centers. In one series, most infections were polymicrobial, and only 19% had isolates of *S. aureus*, the remainder being anaerobes, including clostridia and *Bacteroides* spp. (Webb and Thadepalli, 1979). Other series have also described polymicrobial infections, with *S. aureus* present in almost every case, along with enteric Gram-negative aerobes and oropharyngeal organisms (Orangio et al., 1984). In more recently published series, *Streptococcus* seems to be as common as any of the more unusual agents (Hoeger et al., 1996; Mackenzie et al., 2000). *E. corrodens,* a Gram-negative anaerobe, part of the normal flora in the mouth, is occasionally seen when addicts use their saliva to dilute or dissolve their drug for injection (Brooks et al., 1974; Zumwalt and Franz, 1983). Femoral drug injection is associated not only with infection and bacteremia, but also with illofemoral thrombosis (Mackenzie et al., 2000).

5.8.8.4 Fibrous myopathy

Woody infiltration, cutaneous ulcers, and abnormal pigmentation can be seen surrounding areas of repeated pentazocine injection. Clinically, the syndrome is marked by limitation of motion, neuropathic symptoms, and even muscle and joint contractures (Levin and Engel, 1975; Oh et al., 1975; de Lateur and Halliday, 1978; Rousseau et al., 1979; Adams et al., 1983; Kim, 1987; Wagner and Cohen, 1991; Kim and Song, 1996; Sinsawaiwong and Phanthumchinda, 1998). The contractures and neuropathic symptoms are secondary to nerve damage and reflex sympathetic dystrophy (Roberson and Dimon, 1983; Hertzman et al., 1986).

The syndrome may be the result of a foreign body reaction, with crystallization of the drug within the muscle (Levin and Engel, 1975; Oh et al., 1975). This possibility is suggested by the fact that birefringent crystals have been demonstrated in the areas of most intense induration (Adams et al., 1983). Myocytes are destroyed and replaced with dense, fibrotic tissue. Inflammatory infiltrates may or may not be present. Dystrophic calcification may be so marked that it sometimes can be detected by CT scanning or sonography. In areas where pentazocine for injection is no longer generally available, this syndrome has disappeared.

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chapter six

Disassociative anesthetics

The three agents described in this chapter, phencyclidine (PCP), ketamine, and γ-hydroxybutyric acid, are all hallucinogens. Compared to heroin and cocaine they are neither popular nor widely abused. Only 98 PCP-related deaths were reported in the 1999 Drug Abuse Warning Network (DAWN) survey, and even fewer were attributed to ketamine (21 deaths) and γ-hydroxybutyrate (GHB) (no mentions); however, evidence indicates that interest in the three drugs is increasing. The Emergency Room component of the 1999 DAWN report lists 2973 GHB-related visits, compared to only 55 in 1994. Ketamine-related visits have increased from 19 in 1995 to 396 in 1999 (SAMHSA, 2001). But, except for massive doses of PCP that cause rhabdomyolysis and death and large doses of GHB that can cause transient (but potentially fatal) respiratory paralysis, the principle toxic effects exerted by these drugs are psychiatric.

All three agents are classified as dissociative anesthetics; when patients are given PCP or ketamine they remain conscious but exhibit no apparent response to surgical pain. The same is also true of GHB. None of the three causes muscle relaxation. As a consequence, when any of these drugs are used as anesthetics, other anesthetic agents must be administered concurrently. In spite of the similar effects produced by these agents, they are all quite different from each other and from other hallucinogens such as LSD.

Methamphetamine and PCP both induce psychotic states that closely resemble schizophrenia, as can ketamine (Krystal et al., 1994). Some speculate that this ability to produce schizophrenic-like psychosis has something to do with PCP's ability to differentially affect dopamine transmission (Griffiths et al., 1999). Others point out that both PCP and ketamine disrupt *N*-methyl-D-aspartate (NMDA)-type glutamanergic transmission. In animal studies, drugs that normalize NMDA function (specifically, glycine and glycine transport agonists) reverse the schizophrenic symptoms (Javitt et al., 1999).

The mechanism for the behavioral changes observed with GHB appears to have nothing at all to do with the NMDA receptor. Instead, it seems to involve both the γ-aminobutyric acid (GABA) receptor and dopamine metabolism. GHB binds to a GHB-specific receptor and, in addition, to a subtype of GABA receptor referred to as $GABA_B$ (Benavides et al., 1982; Snead, 1996). Documented effects of $GABA_B$ agonists include increased synthesis and increased release of dopamine (Spano et al., 1971; Cheramy et al., 1977).

6.1 Phencyclidine (PCP)

6.1.1 Incidence

Phencyclidine (PCP), or PCP in combination with another drug, was the 34th most frequent cause of drug-related deaths in both the 1998 and 1999 DAWN surveys. In 1999, 98 such deaths were reported, amounting to 0.84% of the drug-related deaths reported to the government that year. PCP use is, in fact, not very frequent. In the first half of 1999 there were 2154 emergency room visits for treatment of PCP-related illness, 10,447 for methamphetamine, and 84,320 for cocaine-related illness (a ratio of nearly 40:1). Mentions of PCP and PCP in combination with other drugs began to decline in 1996 and have been stable since then, with no change in 1997 or in the first half of 1998 (Kissin et al., 2000).

6.1.2 Epidemiology

According to the most recent National Household Survey, 3.0% of the population in 1997 and 3.5% in 1998 had used PCP sometime during their lifetimes. The rate of use was similar among older age groups (26–34 years and 35 years and older), and somewhat lower among younger people (1.2% among 12- to 17-year-olds and 3.0% in young people ages 18 to 25 years) (Greene et al., 2000). The fact that the Drug Enforcement Agency (DEA) does not even tabulate PCP seizures in any of its publications (see, for example, the *DEA Briefing Book* prepared for the Office of Congressional and Public Affairs in October 1999), suggests that, in the U.S. at least, production of and interest in this drug continue at a very low level.

6.1.3 History

Phencyclidine (1-(1)-phenylcyclohexyl piperidine, or PCP) was discovered by pharmacologists at Parke-Davis in 1956 (Greifenstein et al., 1958). It was first sold as an intravenous anesthetic called Sernyl® (Collins et al., 1960). In recommended doses, PCP produces neither respiratory nor cardiovascular depression and, at least in animals, is devoid of cellular toxicity (Chen and Weston, 1960). Use in humans had to be discontinued when it was discovered that 10 to 20% of patients given PCP became delirious and/or unmanageable for many hours after surgery (Greifenstein et al., 1958). In 1978, PCP was transferred to Schedule II under the Controlled Substance Act, and legal production was discontinued in 1979.

Recreational abuse was first reported in California during the late 1960s, but the drug soon developed a reputation for causing antisocial, violent behavior (Fauman et al., 1976). Abuse was prevalent during the 1970s and early 1980s, but illicit use of PCP has markedly decreased over the last two decades.

6.1.4 Physical constants

Phencyclidine, 1-(1-phenylcyclohexyl)piperidine, has a molecular weight of 243.39, and the formula is $C_{17}H_{25}N$. The hydrochloride has a melting point range of 234 to 236°C. It is water soluble, with a pKa of 8.5. It is a tertiary amine, and the most important physical property of PCP, at least as far as toxicity is concerned, is its lipid solubility. PCP is extremely lipophilic and is rapidly shifted from the bloodstream into adipose tissue and the brain (Budavari et al., 1996).

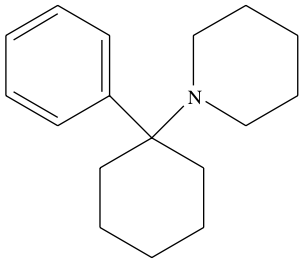

Figure 6.1.5.1 **Phencyclidine molecule.** The preferred route in clandestine labs starts with condensation of 1-phenylcyclopentylamine with pentamethylene dibromide. Ethyl ether and other volatile solvents used in the process give off a distinctive odor that often gives away the location of the laboratory.

6.1.5 Clandestine laboratories

The synthetic route preferred by clandestine chemists is condensation of 1-phenylcyclopentylamine with pentamethylene dibromide (Figure 6.1.5.1) (Kalir et al., 1969). Other routes are possible, and piperidine, the central ingredient, is not as strictly controlled in Europe as in the U.S. The direct conversion of piperidine to PCP is becoming an increasingly popular approach (the piperidine ring is the central core of the PCP molecule). The synthesis is simple, and the economics attractive. Given an average street dose of 1 to 10 mg, 1 kg of piperidine can be converted to anywhere from 100,000 to 1,000,000 doses of street drug (INCB, 1999).

Many different PCP derivatives have been produced, some psychoactive and some not. The resultant psychological effects are at least partly related to how well the synthetic derivatives bind the sigma receptor (Loustau-Then et al., 1997; Moriarty et al., 1998). Some of these derivatives are used in positron emission scanning in order to help localize sigma receptors and to study the effects of prolonged drug use.

Bulk phencyclidine is sold either in liquid or powder form. Street drug may be anywhere from 50 to 100% pure. The ethyl ether and other volatile solvents used in the production process give off a distinctive odor that often gives away the location of the laboratory. The fumes are also quite explosive, making illicit PCP production a risky affair.

Initially, most of the PCP supply in the U.S. was manufactured by Los Angeles-based street gangs, whose affiliates would then distribute the drug around the country. Increasingly, production is being taken over by Mexican "super labs," operated by Mexican gangs that operate out of Southern California, using precursors that are much more easily obtained in Mexico. Six clandestine PCP laboratories were seized in 1993, compared to four in the preceding year, and 21 in 1988. Seizures of clandestine PCP laboratories are now distinctly rare events.

6.1.6 Routes of administration

Phencyclidine can be smoked, snorted, injected, or swallowed. Results of animal studies indicate that the effects produced are essentially the same whether the drug is smoked or taken intravenously (Meng et al., 1996). That observation probably explains why smoking PCP has become the preferred route of administration. Cigarettes soaked in PCP were very popular during the 1980s. In some areas of the country, PCP-laced cigarettes were called "Sherms," because the cigarette preferred for soaking purposes was produced by the Nat

Sherman Tobacco Company. The term may still be in use, but the website of the Office of National Drug Control Policy (www.whitehousedrugpolicy.gov/drugfact/terms/type_pcp.html) lists more than 100 different synonyms ranging from ace, ameba, and angel dust to *yerba mala* (Spanish for marijuana soaked in PCP), zombie weed, and zoom.

Parsley leaves soaked in PCP are occasionally substituted for marijuana leaves, with little apparent difference in result. Studies on human volunteers who smoked 100 μg of (^{3}H)-phencyclidine indicate that most smoked PCP is absorbed. Peak blood levels occur 15 to 20 minutes after smoking, but a second peak occurs slightly later, suggesting delayed release from the lungs. The maximum concentration achieved in this particular smoking study was 1.5 ng/mL. The mean half-life of the smoked PCP was 24 hours ± 7 hours (Cook et al., 1982). Oral absorption is nearly as good as intravenous administration. Volunteers given 1 mg orally had average PCP concentrations of 2.7 ng/mL. Plasma concentrations after 1 mg given intravenously were 2.9 ng/mL.

Peak plasma levels after oral dosing occur at 2.5 hours, although levels are near maximal at 1.5 hours. After both oral and intravenous administration, a 1- to 2-hour plateau period follows, during which plasma levels remain relatively stable (Cook et al., 1983). Skin absorption does occur and can result in positive urine tests, possibly at levels exceeding National Institute on Drug Abuse (NIDA) cutoffs. In one study, a crime lab chemist was found to have a PCP level of 28 ng/mL (Pitts et al., 1981). Just how relevant all of these measurements are to the problems of clinical intoxication is not entirely clear. The amount used for the volunteer studies was probably very small when compared to the amounts taken by abusers. When PCP was first introduced as a legal anesthetic, sophisticated techniques for measuring blood levels were not available. Now that such techniques exist, ethical considerations prevent the administration of PCP in quantities that accurately reflect street practices.

6.1.7 Metabolism

The mode of action of PCP is highly dependent on the amount of drug taken (Gao et al., 1993) and on where in the brain it is exerting its effects. PCP is a noncompetitive antagonist of glutamate-type NMDA receptors (Su, 1991; Su et al., 1991); it binds to its own receptor in the NMDA channel when given in low doses. This may explain why low doses produce only mild inebriation. At higher doses, PCP acts as an indirect agonist at sigma sites, and can produce long-lasting psychotic episodes.

In many ways, PCP's effects resemble those of methamphetamine. The resemblance is explained by the fact that both PCP and methamphetamine block dopamine uptake. On a weight-per-weight basis, PCP is nearly as potent a re-uptake blocker as methamphetamine. And, like methamphetamine, PCP also causes the release of stored catecholamines, but in this respect, at least, it is much less potent than methamphetamine (Johnson and Jones, 1990; Yang et al., 1991).

In the rat model, PCP has a biphasic course of action. High doses lead to an initial increase in brain glucose metabolism at 3 hours, followed by decreased glucose utilization at 24 hours, and a return to normal at 48 hours. Low doses of PCP cause no initial changes in glucose metabolism, but at 24 hours glucose uptake is depressed and remains so for some time (Gao et al., 1993). PCP also inhibits ATP-sensitive K^+ channels in both heart and brain, increasing the inward Ca^{2+} current and blocking the outward K^+ current (Kokoz et al., 1994).

Even though PCP has marked neuroprotective effects (Olney et al., 1987), the mechanism by which it protects neurons has never been established. Clinical trials in humans

with PCP-like drugs have been universally disappointing, in spite of clear protective effects exerted by PCP and by PCP-derivatives such as MK101 in experimental animals.

Phencyclidine attaches to sigma receptors throughout the body, not just those found in the central nervous system but also on membranes from endocrine, immune, and peripheral tissues (Su, 1991). Sigma stimulation is thought to be responsible for many of the unpleasant side effects associated with opiate use and could possibly explain why *in vitro* studies have shown that lymphocyte function is depressed after exposure to relatively low doses of PCP (Thomas et al., 1993). In addition to PCP, cocaine, pentazocine, dextromethorphan, and even anabolic steroids all bind sigma receptors, which may explain certain similarities in the behavioral effects of these drugs.

It was not appreciated until quite recently that PCP is toxic to certain portions of the nervous system, specifically the limbic system. In animals, treatment with PCP induces apoptosis of striatal neurons, particularly neurons that project to the globus pallidus. The mechanism by which cell death is induced is not clear, but animals that display this sort of neural damage also show evidence of early gene activation (c-*fos*), a process that has come to be associated with apoptosis (Griffiths et al., 1999).

In cases of PCP overdose, death appears to be a consequence of respiratory and cardiac depression. In the dog model of extreme PCP intoxication, respiratory failure is followed by a combination of hypoxia, hyperpyrexia, and acidosis. If the animals are paralyzed, convulsions and hyperthermia are prevented but respiratory and cardiac depression still occur. At the highest doses, death seems to be entirely due to myocardial depression (Davis et al., 1991). These results can be extrapolated to humans only with great caution, because reports of massive overdose (blood concentration > 1800 ng/mL) in humans do not mention myocardial compromise (Jackson, 1989).

Phencyclidine is extensively metabolized, and less than 10% is excreted unchanged in the urine (Cook et al., 1981; Woodworth et al., 1985). Because it is so lipid soluble, its volume of distribution is probably the highest of any abused drug, somewhere between 5.3 and 7.5 L/kg (Baselt and Cravey, 1995). The portion that remains circulating in the blood is highly protein bound (60–70%), although just which proteins are involved is not clear; less than one quarter is bound to albumin (Busto et al., 1989). Recovery of PCP and its metabolites in urine and feces is incomplete. Hydroxylated derivatives, accounting for less than 50% of a total dose, can be recovered from the urine. At the same time, unchanged PCP can be found in saliva and sweat, suggesting that some elimination may occur by these routes (Cook et al., 1983).

Phencyclidine is metabolized by hydroxylation on position 4 of the cyclohexane ring and/or on the piperidine moiety. Both of the resulting metabolites are pharmacologically inactive. The metabolites then undergo glucuronidation and are excreted in the urine. Because PCP is a weak base, acidification of the urine enhances its excretion. In the past, individuals with PCP overdoses were given ammonium chloride or ascorbic acid in hopes of increasing excretion and minimizing toxicity. This approach was eventually found to be ineffective. On the other hand, continuous gastric suction has proved a useful treatment because PCP is excreted into the stomach, setting up a pathway for gastroenteric recirculation (Aniline and Pitts, 1982).

The window for detection of PCP in the urine is variable. In experimental animals the half-life for PCP is only 3 to 5 hours (Woodworth et al., 1985), but in humans it is much longer. After oral administration, PCP's terminal half-life may approach 24 hours, which means that PCP should still be detectable in the blood for 5 days, and for at least as long in the urine. NIDA cutoffs require a urine concentration of at least 25 ng/mL before a measurement may be reported as positive.

Table 6.1.7.1 Blood and Tissue Levels in 70 Fatal Cases of PCP Intoxication

Blood (ng/mL)	Urine (ng/mL)	Liver (ng/mL)	Bile (ng/mL)	Brain (ng/mL)	Kidney (ng/mL)
100–2400	100–7600	100–7820	100–1690	30–710	400–900

Source: Adapted from Budd and Liu (1982).

6.1.8 Tissue concentrations

Concentrations of PCP measured during clinically apparent intoxication and also at autopsy have been extensively reported. Intoxication in humans is not apparent when blood levels are less than 3 ng/mL, but otherwise clinical correlations between blood levels and physical findings, except for systolic blood pressure, are generally poor (Bailey, 1978). In 70 cases where PCP was deemed a factor in the death, blood concentrations in 90% of the decedents ranged from 10 to 300 ng/mL (Table 6.1.7.1) (Budd and Liu, 1982). In a smaller series of five PCP-related deaths and ten cases of intoxication, concentrations at autopsy ranged from 8 to 2100 ng/mL. Plasma concentration in the ten individuals with clinical evidence of intoxication were lower, ranging from less than 10 up to 812 ng/mL (Bailey, 1978). A case report from 1989 described a man who swallowed two balloons full of PCP and promptly lapsed into a coma. The particulars of the case were unknown until the man passed the two balloons, one of which was ruptured, while he was still comatose, on day 11 of his hospitalization. The maximum blood level on the third hospital day was 1879 ng/mL. His blood level at the time he passed the two balloons was not recorded, but the level in his cerebrospinal fluid was 245 ng/mL, and the blood level the day before was nearly 1000 ng/mL (Jackson, 1989).

The PCP blood concentrations may be affected when other drugs are taken at the same time. In a dog model of PCP intoxication, concurrent administration of PCP with marijuana resulted in higher blood and brain PCP concentrations than when PCP was given alone. Alcohol, on the other hand, does not exert this effect (Godley et al., 1991). This synergy may explain why PCP and marijuana are frequently detected in the same urine specimens. PCP appears in saliva, and saliva concentrations appear to correlate well with blood levels (McCarron et al., 1984; Kidwell et al., 1998).

6.1.9 Interpreting blood and tissue concentrations

Blood and urine measurements of PCP are of historical interest only. They prove that the individual in question did, at one time, take PCP. The clinical and forensic importance of isolated blood and urine levels is impossible to determine. PCP is rapidly extracted from the blood by brain and fatty tissues and then slowly released back into the circulation. In one animal study, PCP levels in adipose tissue were 13 times higher than brain levels and 20 times higher than blood levels (James and Schnoll, 1976). Continued slow release from fat depots can occur over an extended period of time. PCP also makes its way back into the circulation after being reabsorbed from the gastric contents and entering the small bowel. Measurable levels may persist for months (Aniline and Pitts, 1982). NIDA guidelines calling for screening and confirmation tests with a 25-ng/mL cutoff significantly reduce the time frame for detectability. If the cutoff was reduced by one-half, the period during which PCP could be detected might be lengthened by a period of weeks!

Controlled studies on the limits of detection have not been published, but in one case report a police chemist who had daily contact with PCP still had a blood level of 70 ng/mL six months. After leaving the laboratory (Aniline and Pitts, 1982). PCP remains stable in stored urine specimens for long periods of time with almost no change in PCP concentration after three months of cold storage, and one-half of the initial concentration of PCP was still present after six months (Hughes et al., 1991). Because PCP is no longer sold either as a human or veterinary anesthetic, its presence can only be explained by illicit use.

Episodes of fatal PCP intoxication, as opposed to homicides and trauma deaths where PCP is an incidental finding, are uncommon (Noguchi and Nakamura, 1978; Budd and Lindstrom, 1982; Poklis et al., 1990; Li and Smialek, 1996). Tolerance to PCP is seen in animals, and almost certainly in humans. It has been argued that tolerance in humans is proven by the fact that blood levels in patients dying directly from the effects of PCP overlap with the blood levels seen in victims of accidental deaths (Poklis et al., 1990). This same phenomenon can be seen in cocaine-related deaths and probably in all other stimulant-related fatalities. A further problem in PCP-related fatalities is the very great volume of distribution of the drug. At any given instant, almost all of the PCP in the body is found in tissues, not circulating in the blood. If, after death, even a small percentage of the PCP found in tissues was to redistribute into the blood (which it almost certainly would do), then the blood level measured in a postmortem sample might be many times higher than the actual plasma concentration in the immediate antemortem period. Maternal–fetal relationships have not been studied in depth, but the few papers that have been published have shown not only that PCP crosses the placenta with ease, but also that the fetus concentrates the drug and usually has higher levels than the mother (Aniline and Pitts, 1982).

6.1.10 Toxicity by organ system

6.1.10.1 Neurologic disorders

Autopsy studies make no mention of unique neuropathologic changes. Whether this reflects a lack of toxicity or just a limited number of observations is not clear. Most PCP-related deaths occurred before it was known that PCP induced cell apoptosis. Indeed, most of the deaths occurred before the process of cell apoptosis was even recognized (neurons programmed to self-destruct can be recognized by condensed and fragmented cell chromatin contained within an intact cellular membrane) (Raff et al., 1993).

All of the arylhexylalkyamines that have been tested, including MK-801, ketamine, and tiletamine, produce acute changes in rat brains. Vacuolization of neurons in the posterior cingulate and retrosplenial cortices can be seen within 4 hours of subcutaneously injecting 1 mg/kg of PCP. Some evidence suggests that the changes resolve and tolerance to the effects develops with repeated usage (Olney et al., 1989; Gao et al., 1993). Evidence also indicates that PCP, but not MK-801, can cause damage to Purkinje cells of the cerebellar virmus (Nakki et al., 1995). It is conceivable that these transient changes could account for behavioral disorders that are seen in human PCP users. There is no proof, however, one way or the other. Fatal status epilepticus has been reported (McCarron et al., 1984; Kessler et al., 1974), which is puzzling, because PCP and related compounds such as MK-801 have anticonvulsant properties (Balster, 1987). One contributing factor may be the ability of phencyclidine to block the action of calcium ATPase in both the heart (Section 8.1.11.2) and the brain (Pande et al., 1999).

6.1.10.2 Cardiovascular disease

Most of the studies on the cardiovascular actions of PCP were done more than 30 years ago, using experimental animals given very large doses by continuous infusions. Under those conditions PCP increases heart rate, cardiac output, blood pressure, and temperature (Hackett et al., 1981). More recent *in vitro* and animal studies have shown that, even in low doses, PCP inhibits the calcium-dependent ATPase located in cardiac sarcoplasmic reticulum. That action effectively disrupts intracytasolic calcium homeostasis and decreases cardiac output (Pande et al., 1998). The differences between the old and new studies are probably just a reflection of the dose used; massive infusions of PCP activate sympathetic mechanisms that would more than make up for any calcium-mediated decrease in cardiac output. Altered myocyte calcium concentrations should result in recognizable lesions (contraction band necrosis), but such lesions have not been reported in either human PCP users or experimental animals.

6.1.10.3 Renal disorders

In one series of 1000 PCP-intoxicated patients, 2.2% had rhabdomyolysis, and three of these patients had renal failure that required dialysis (McCarron et al., 1981a,b). Most renal failure has occurred in deeply comatose patients with convulsions (Cogen et al., 1978; Hoogwerf et al., 1979; Fallis et al., 1982).

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6.2 Ketamine

6.2.1 Incidence

Ketamine abuse occurs, but not very often. The Medical Examiner component of the 1999 DAWN report contained 21 ketamine mentions. An insignificant increase from 3 to 16 deaths was reported in 1997, placing ketamine in the number 71 position on the DAWN list and accounting for 0.18% of all drug-related deaths reported to the federal government that year (Kissin and Ball, 2000).

6.2.2 Epidemiology

No mentions of ketamine appeared in the Emergency Room component of the 1993 DAWN survey, and only 19 episodes were mentioned in 1994. The report for 1999, however, contains 396 mentions, compared to 5126 LSD mentions and 2850 emergency room visits related to use of MDMA (Garfield et al., 2000). Even on the club scene, ketamine is not a widely abused drug.

6.2.3 History

Ketamine was first introduced as an anesthetic agent in 1965 (Domino et al., 1982). It is classified as a dissasociative anesthetic with a structure and actions closely related to those of PCP. Even though it was used for many users as an anesthesia adjunct (Ketalar®, Parke-Davis), in 1999 the DEA placed ketamine, including all of its salts, isomers, and salts of isomers, into Schedule III of the Controlled Substances Act (21 U.S.C. 801 et seq.). It continues to be sold in the U.S. as a veterinary anesthetic under the names Ketajet®, Ketaset®, and Vetalar®. Although it appears that Ketalar® is no longer sold in the U.S., it is widely sold in Europe and even offered for sale in the U.S. by Internet pharmacies.

6.2.4 Physical constants

Ketamine, α(±)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone, has a formula of $C_{13}H_{16}ClNO$, a molecular weight of 237.73, and a pKa of 7.5 (Figure 6.2.4.1) (Budavari et al., 1996). It is water and lipid soluble (10 times the lipid solubility of the widely used anesthetic thiopentone). Ketamine has a chiral center at the C-2 carbon of the cyclohexanone ring, allowing the existence of both (+) and (–) isomers. Veterinary ketamine preparations are supplied as mixtures containing equal amounts of both isomers.

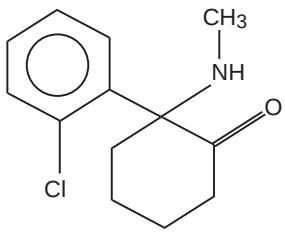

Figure 6.2.4.1 **Ketamine molecule.**

6.2.5 Clandestine laboratories

Ketamine used in the recreational drug market is illegally diverted from legitimate suppliers. Commercial anesthetic products are allowed to evaporate and the crystals are scrapped into a fine powder, then packaged. No clandestine ketamine laboratory has ever been discovered in the U.S.

6.2.6 Routes of administration

Ketamine can be administered by almost any route, depending on the intent. In addition to intramuscular and intravenous routes, epidural and intrathecal administration has been used but with somewhat ambiguous results. In one study, 50 mg of ketamine given intrathecally provided adequate anesthesia, but it was of short duration (Bion, 1984). Other studies have shown that epidural morphine was more effective and longer lasting than ketamine (Kawana et al., 1987). Oral administration is also possible and, because of first-pass effects and the formation of norketamine, anesthetic effects are observable at lower blood concentrations. Rectal administration has a more rapid onset, and has been used as an induction agent in children (Idvall et al., 1983). When used as a recreational drug, ketamine is usually insufflated. Bioavailability and blood concentrations in this setting have not been determined.

6.2.7 Metabolism

Ketamine's mode of action is still not known with certainty, probably because so many different mechanisms are involved. Even at subanesthetic doses ketamine is a potent analgesic, and the analgesic effects can be explained by the ability of ketamine to bind opiate receptors. But, like PCP, ketamine blocks the NMDA receptor, a receptor classified by some as a subtype of the sigma opiate receptor. Still, other research points to possible effects on muscarinic and opioid receptors, not to mention voltage-dependent ion channels, particularly L-type calcium channels (Wong and Martin, 1993).

Bioavailability is high after either intravenous or intramuscular injections, which is one of the factors that makes this agent so attractive for use in the battlefield setting. When taken orally, first-pass effects result in lower blood concentrations but, somewhat surprisingly, more rapid onset. The explanation has to do with hepatic formation of norketamine, an active metabolite with approximately one-third the activity of the parent compound. Ketamine is metabolized in the liver by the P-450 system, mainly to norketamine. Norketamine is then hydroxylated, conjugated, and excreted in the urine. The cyclohexanone ring undergoes oxidative metabolism (Adams et al., 1981; Reich and Silvay, 1989).

6.2.8 Pharmacokinetics

Given the high degree of lipid solubility of ketamine, its large volume of distribution (between 3 and 5 L/kg) is hardly surprising (Baselt and Cravey, 1995). The elimination half-life is 2.17 hours (Domino et al., 1984). The pharmacokinetics in children is not very different than in adults, although children do form more norketamine (Grant et al., 1983).

6.2.9 Tissue concentrations

Oral doses of 5 mg/kg result in analgesia and blood concentration of 400 ng/mL 30 minutes afterward (Grant et al., 1981). Intravenous doses only half as great result in plasma

concentrations more than twice as high (Wieber et al., 1975). Ketamine plasma concentrations in recovering alcoholics induce symptoms very similar to those seen after giving ethanol. Chronic alcohol consumption is thought to increase NMDA receptor function and to partially account for the seizures and other evidence of neurotoxicity seen in chronic alcoholics (Fidecka and Langwinski, 1989). In 20 detoxified alcoholics, an intravenous dose of 0.1 mg/kg produced peak ketamine concentrations of approximately 75 ng/mL after 80 minutes. When the dose was increased to 0.5 mg/kg, peak concentrations occurred at the same time but were much higher (400 ng/mL) (Krystal et al., 1998).

6.2.10 Interpreting blood concentrations

In general, plasma concentrations of 400 ng/mL or more are associated with analgesia, and concentrations of greater than 1000 ng/mL with anesthesia. Compared to other anesthetic agents), ketamine appears to possess little intrinsic toxicity. In a recently published review of 87 ketamine-positive deaths occurring over a two-year period almost all of the positive test results were found in hospitalized patients following surgical procedures or burns, and in no single case could death could be attributed to intoxication with ketamine (Gill and Stajic, 2000). A 1994 report may or may not be relevant. It describes a homicide committed by injecting a man with a massive amount of ketamine (Licata et al., 1994). The resultant blood concentration was 27.4 μg/mL; urine, 8.51 μg/mL; bile, 15.2 μg/mL; brain, 3.24 μg/mL; liver, 6.6 μg/mL; and kidney, 3.38 μg/mL. Given the extreme lipophilicity of this drug, the relatively low brain concentration (at least when compared to the other tissues) suggests that death must have been very rapid. On the other hand, norketamine was detected in all samples, proving that the decedent had lived long enough to metabolize at least some of the drug.

6.2.11 Toxicity by organ system

Although ketamine is classified as a "dangerous drug," it has quite an extraordinary safety record. A 1996 study on the use of ketamine as an anesthetic in the developing world surveyed 122 physicians, operating in less-than-ideal circumstances, about their experience with ketamine in more than 12,000 patients. Pulse oximetry was used in fewer than 10% of the cases, and intermittent vital signs taken in less than half. One unexplained pediatric death occurred during an unmonitored, unobserved ward recovery, and an adult suffered cardiac arrest after a failed intubation attempt. Apnea, possibly related to ketamine, was reported in ten patients, and laryngospasm in six. Similar experiences were reported by the Red Cross in its field hospitals (Lenz et al., 1985). Even in the case of a substantial overdose, the main effect seems to be prolonged sedation. Green et al. (1999) described nine cases of inadvertent ketamine overdose in children. Three of the children received 5 times the recommended dose, five received 10 times the ordered dose, and one child was given a dose 100 times greater than ordered (all by intravenous or intramuscular route). All nine experienced prolonged sedation (3 to 24 hours). Except for prolonged sedation, no adverse outcomes were noted.

6.2.11.1 Neurologic disorders

Ketamine dependence has been reported, particularly among hospital workers with ready access to the drug (Ahmed and Petchkovsky, 1980; Jansen, 1990, 1993). Ketamine has the advantage, at least so far as hospital workers are concerned, of a short half-life and relatively rapid renal clearance, making detection less likely (Moore and Bostwick,

1999). Intrathecal and epidural ketamine is sometimes used in the management of chronic pain, generally without significant side effects (e.g., no respiratory depression or urinary retention) (Yaksh, 1996). Small doses, on the order of 50 mg, produce complete pain relief for at least one hour. Large doses result in longer pain-free periods. However, there is at least one report of isolated lymphocytic vasculitis of the spinal cord, presumably related to ketamine administration (Stotz et al., 1999). Intrathecal ketamine therapy is usually reserved for terminal patients, so the true incidence of this complication remains unknown.

6.2.11.2 Cardiovascular disease

Ketamine is used for anesthesia induction in trauma victims because, unlike other anesthetic agents, ketamine causes an increase in blood pressure, and the increase may be of considerable magnitude (Tanaka and Nishikawa, 1994). The mechanism has always been presumed to involve activation of the sympathetic nervous system and release of catecholamines. Experimental proof was recently provided by a study of hearts taken from rabbits that had been repeatedly anesthetized with a mixture of ketamine and xylazine (an agent without effects on the sympathetic nervous system). Histologic examination of the animals' hearts showed the classic finding of microfocal fibrosis (Marini et al., 1999), an abnormality strongly associated with chronic catecholamine excess (Krystal et al., 1998).

6.2.11.3 Hematologic disorders

In small doses, ketamine attenuates the cytokine response to cardiac surgery. As blood circulates through the bypass pump, there is activation of the inflammatory pathways. One recent study measured blood concentrations of interleukin-6 (IL-6) after giving 0.25 mg/kg of ketamine along with a general anesthetic. Normally, IL-6 concentrations begin to rise immediately after surgery, returning to baseline after eight days, but this rise never occurred in the ketamine-treated patients (Roytblat et al., 1998).

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6.3 γ-Hydroxybutyrate (GHB)

6.3.1 Incidence

The true extent of GHB use within the U.S. is not known. The Medical Component of the 1999 DAWN report does not include any GHB-related deaths, and only one such death was reported to the government between 1992 and 1995 (Kissin and Ball, 2000). However, interest in this drug is increasing. In 1994, only 55 emergency room visits were attributed to GHB use, but by the end of 1999 nearly 3000 such visits had been reported (Kissin et al., 2000). GHB would not be detected by any of the standard screening tests available at

hospital emergency rooms and is not part of standard postmortem toxicology screens. Even when GHB is detected in postmortem blood specimens its significance is difficult to interpret, because GHB forms spontaneously after death. The mere presence of GHB is not proof that death was a consequence of GHB ingestion, or even that it was consumed. This fact is still not generally appreciated by many coroners and toxicologists, so it may well be that the incidence of GHB deaths (as opposed to emergency room visits by living patients) has been, and continues to be, higher than it appears.

6.3.2 Epidemiology

When questioned, almost all of the GHB users report that they were taking GHB for "recreational" purposes. Nearly two-thirds of GHB-related emergency room visits are due to "overdose," and one-third to "unexpected" reactions. Nearly 60% of emergency room visits involved the use of multiple other drugs, usually GHB in combination with ethanol (76%), cocaine (6%), marijuana (5%), and MDMA (4%) (Woodworth and DEA, 1999). The DEA reports that at least 100 illicit GHB laboratories have been raided since 1997.

6.3.3 History

γ-Hydroxybutyrate was first synthesized by French researchers attempting to create a GABA analog that could freely cross the blood–brain barrier (Tunnicliff, 1997). GHB turned out not to be a true GABA agonist, but it is a naturally occurring (Bessman and Fishbein, 1963) inhibitory neurotransmitter (Berthier et al., 1994). Because GHB rapidly crosses the blood–brain barrier, sedation is the almost immediate result. European surgeons began using GHB as an anesthetic adjunct in the early 1960s, but GHB does not produce analgesia, so opiate administration is also required for effective anesthesia (Kleinschmidt et al., 1998). Because the use of additional drugs is required and because large doses of GHB cause seizure-like activity (Dyer, 1991), GHB anesthesia never really became popular, even though some European neurosurgeons still resort to it on occasion. Paradoxically, it appears that low doses of GHB may exert anti-epileptic effects (Maitre et al., 1990). GHB is also sometimes used, like propopfol, to maintain long-term sedation of ventilated patients (Kleinschmidt et al., 1997).

During the late 1960s, Europeans experimented with GHB in the treatment of a variety of syndromes but without any great clinical successes, except perhaps in the treatment of some sleep disorders and alcoholism (Mamelak et al., 1986; Poldrugo and Addolorato, 1999). Clinical trials using GHB to treat opiate addiction and cocaine are ongoing (Gallimberti et al., 1993; Martellotta et al., 1998). In 1990, the U.S. Food and Drug Administration (FDA) placed GHB in its orphan drug program, a decision that led to research on the use of GHB in a number of apparently unrelated areas, especially resuscitation. The results of animal studies suggest that GHB reduces oxygen requirements, which means GHB could potentially increase survival in patients with myocardial infarction and stroke (Khokhlova et al., 1978), and improve the success rate in organ transplantation (Li et al., 1998).

γ-Hydroxybutyrate first became popular as an abused drug in 1977 when Japanese researchers observed that taking GHB could stimulate the release of human growth hormone (Takahara et al., 1977). The observation was of mild interest to the medical community but of very great importance to weight lifters and body builders who were convinced, quite correctly, that treatment with growth hormone could increase strength and endurance (Neely and Rosenfeld, 1994). During most of the 1990s GHB and γ-butyrolactone, which is

readily converted to GHB, were easily obtained at health food stores and gyms (Anon., 1999). The lactone is a widely used solvent, found in such diverse products as engine degreasers and nail polish, and it can be obtained almost anywhere. GHB is a Schedule III drug, meaning that suppliers can be prosecuted under federal law. Sometime during the early 1990s GHB made the transition from gyms and health clubs to bars and dance clubs, where it became popular as a mild intoxicant (Anon., 1997; Williams et al., 1998).

More than 20 states regulate GHB more strictly than is required by federal law. Some states (Georgia, Hawaii, Illinois, Louisiana, Michigan, and Rhode Island) have gone so far as to classify GHB as a Schedule I drug. In Florida and California, GHB is a Schedule II drug. Other states, such as New Jersey, have made it illegal to manufacture GHB. Just how much good this legislation will accomplish is an open question. γ-Butyrolactone is universally available and readily converts to GHB once it enters the body. Control of its production and sale is virtually impossible.

γ-Hydroxybutyrate has been increasingly implicated as an agent in drug-facilitated sexual assault (Anon., 1997). The true incidence of such assaults is not known for two important reasons: GHB has a very short half-life, and it produces amnesia. An ongoing surveillance program has analyzed more than 3000 urine specimens collected from alleged rape victims examined within 72 hours of the incident. Specimens were frozen and then shipped to a central laboratory for analysis. Approximately half of the specimens analyzed in the survey tested negative for all drugs. Of those that did contain drugs, 4% were positive for GHB compared to over 40% positive for alcohol (El Sohly and Salamone, 1999).

6.3.4 Chemical constants

The formula of GHB, 4-hydroxybutanoic acid (or hydroxybutyric acid or 4-hydroxybutyrate), is $C_4H_8O_3$, and it has a molecular weight of 104.11 (Figure 6.3.4.1) (Budavari et al., 1996). GHB is usually synthesized as sodium or potassium salt. The volume of distribution is small, approximately 0.4 L/kg. GHB is said to have a salty or soapy taste. GHB is thermally unstable and reverts to the lactone when it is heated. Analysis and identification are complicated by the fact that GHB has no distinctive chromatographic properties and no distinguishable ultraviolet characteristics.

6.3.5 Clandestine synthesis

γ-Hydroxybutyrate is easily produced by the hydrolysis of γ-butyrolactone. In theory, GHB can be produced either by acid or base cleavage, but most of the formulas circulated on the Internet and most of the recipes disseminated in "underground" magazines use base cleavage for the primary reaction (Suner et al., 1997). The difficulty with this approach is that too much sodium hydroxide may be used, leading to a corrosive mixture that can produce burns and erosion of the lips, mouth, and esophagus. One of the most widely used formulas instructs would-be producers to heat one quart of γ-butyrolactone to its

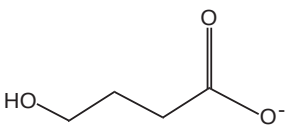

Figure 6.3.4.1 **GHB molecule.**

boiling point and then add one pound of sodium hydroxide crystals. The instructions say that the resultant solution should then be neutralized to a pH of between 6 and 7. If the instructions are actually followed, a 50% GHB solution is produced which, in turn, is diluted to give a 20% solution. One teaspoon of this 20% solution will contain 1 g of GHB (Sanguineti et al., 1997).

6.3.6 *Routes of administration*

According to anecdotal police reports, when GHB is used to facilitate sexual assault it is often placed in a used Visine® container or some other small squeeze bottle. Predators can then quickly and surreptitiously introduce GHB into an intended victim's drink. Investigators should look for such containers at the scene. GHB ingestion by anything but the oral route has not been reported.

6.3.7 *Metabolism*

Endogenous GHB is produced from GABA, which is first converted by GABA aminotransferase to succinic semialdehyde (Figure 6.3.7.1) (Roth and Giarman, 1969). The semialdehyde is then converted to GHB by an $NADP^+$-dependent reductase (Anderson et al., 1977). In animal species, several different forms of this enzyme have been identified (Hearl and Churchich, 1985). Metabolic breakdown is accomplished by oxidation back to succinic semialdehyde, which is then shunted into the Krebs cycle (Doherty and Roth, 1978). In the fetus, GHB dehydrogenase converts succinic semialdehyde to succinic acid (Kaufman et al., 1979). In adults, it appears that GHB–ketotranshydrogenase is responsible for the conversion (Nelson and Kaufman, 1994). There is no evidence for *in vivo* conversion of GHB to GBL (Ferrara et al., 1993). A rare genetic disease is recognized in

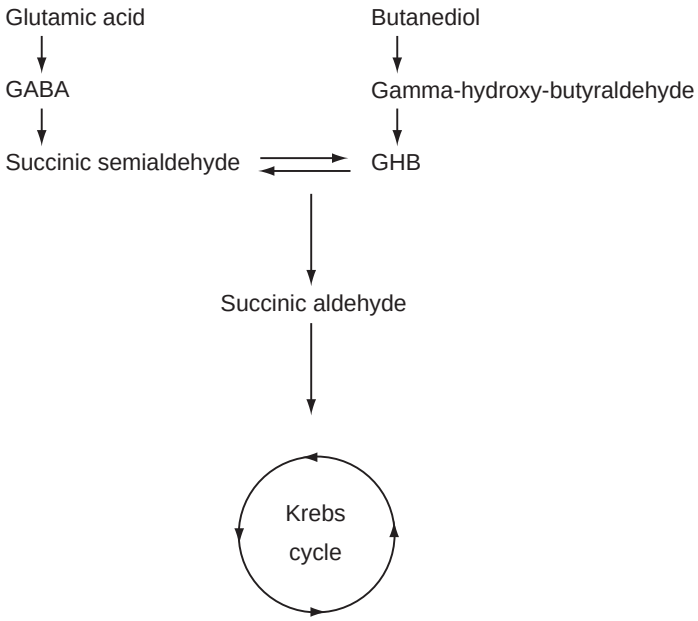

Figure 6.3.7.1 **Production of GHB.**

which GHB accumulates because of a deficiency of brain succinic semialdehyde dehydrogenase (Jakobs et al., 1984; Rating et al., 1984).

6.3.8 Pharmacokinetics

Absorption and disposition kinetics have been studied in eight healthy male volunteers following oral administration of single doses of 125, 250, and 500 mg/kg. GHB does not bind to plasma proteins to any significant degree. Peak plasma concentrations, when normalized to the lowest dose given, decrease significantly as dose increases. This observation suggests that both the oral absorption and the elimination of GHB are capacity-limited processes; the greater the dose, the slower the absorption and the longer the elimination period.

Peak plasma GHB concentrations occur 20 to 40 minutes after oral administration. Plasma samples collected from patients being treated either with 250 or 500 mg/day had mean peak concentrations of 550 μg/mL (range, 240–880 μg/mL) and 900 μg/mL (range, 510–1580 μg/mL). Multiple dose regimens do not lead to GHB accumulation. Peak urine concentrations occur within 4 hours of ingestion (Ferrara et al., 1993). Pharmacokinetic parameters in healthy volunteers are essentially the same as those in alcohol-dependent patients with compensated alcoholic liver disease (Palatini et al., 1993). Based on the findings of several different studies, the half-life of GHB in humans is approximately 20 minutes, with a clearance rate of 14.0 mL/min/kg (Dyer, 1991). No drug is detectable in the blood after 8 hours, and none in the urine after 12 hours (Hoes et al., 1980). All of these parameters are based on measurements made when GHB is the only drug given. Although case reports are few, it appears that most GHB users often imbibe ethanol at the same time. That practice may be dangerous, because in animal studies high concentrations of either drug affect the metabolism of the other. When large doses of GHB are given, ethanol elimination is reduced (Hoes et al., 1981), an effect that would almost certainly lead to higher ethanol concentrations and probably to increased GHB toxicity.

6.3.9 Tissue concentrations

γ-Hydroxybutyrate appears almost immediately in the plasma and saliva of healthy volunteers given 100-mg/kg doses of drug, but no correlation between plasma and saliva concentrations was observed. In urine specimens collected from living non-GHB-using donors, the detection of anything more than negligible GHB concentrations is distinctly uncommon (Fieler et al., 1998). GHB is not likely to be detected in the blood of the living unless GHB has been ingested. Fieler et al. (1998) found no GHB in blood or urine samples taken from 20 living non-GHB users, and no GHB was demonstrated in urine samples obtained at autopsy from 25 non-GHB users. However, blood from these same 25 postmortem cases had GHB concentrations ranging from 0 to 168 mg/L.

Couper and Logan (2000) found GHB in 10 of 12 urine samples from non-GHB users, with a median concentration of 5.4 mg/L. Stephens and Baselt (1994) reported that GHB concentrations were undetectable in 14 of 17 urine specimens from nonusers, with values ranging from 5.1 to 9.5 in three cases.

Depending on the time elapsed after ingestion, blood concentrations of GHB measured during life may be very high. Couper and Logan (2000) found concentrations of 3.2 mg/L in the blood of a sexual assault victim, concentrations of 33 and 34 mg/L in two DUI cases, and levels of 130 and 221 mg/L in two overdose victims who were successfully resuscitated. The corresponding urine concentrations in the two overdose

victims were 16,000 mg/L and 22,000 mg/L. Stephens and Baselt (1994) measured a somewhat lower GHB concentration of 1975 mg/L in a man found asleep at the wheel of his car with the motor running. These values are comparable to those seen when GHB is used as an anesthesia adjunct; plasma concentrations of 260 mg/L are associated with deep but reversible coma (Helrich et al., 1964). In six published case reports where death was attributed to GHB intoxication, blood concentrations have ranged from 98 to 596 mg/L (Chin et al., 1992; 1998; Li et al., 1998; Engelsen and Christensen, 1999; Nordenberg, 2000).

6.3.10 Interpreting tissue concentrations

γ-Hydroxybutyrate blood concentrations depend on the postmortem interval, the type of preservative, length of storage, storage temperature, and possibly even the analytical method used. Furthermore, the evidence is quite overwhelming that GHB forms in blood as a postmortem artifact. The evidence for postmortem formation in urine is somewhat less clear, but if it does occur the amounts formed are generally much less than in postmortem blood. Without a history of witnessed ingestion, the detection of GHB in postmortem blood is without significance. The diagnosis of GHB-related death, or even the use of GHB during life, should not be made on the basis of a single isolated blood measurement. High postmortem blood concentrations do not prove that the drug was taken, though low urine levels may mean just that. Similarly, the absence of GHB in the urine of a sexual assault victim 24 hours after the event does not mean that GHB was not administered. Conversely, if seizures and respiratory arrest occur after the witnessed ingestion of GHB and no other anatomic cause is apparent, then the absolute amount of GHB detected would seem to matter very little to the final diagnosis.

6.3.11 Toxicity by organ system

6.3.11.1 Clinical considerations

γ-Hydroxybutyrate is a central nervous system depressant, but it has a complicated mode of action which is not entirely understood. GHB disrupts several different neurotransmitter systems at the same time (Tunnicliff, 1997). It binds to a GHB-specific receptor and also to a subtype of GABA receptor referred to as $GABA_B$ (Benavides et al., 1982; Snead, 1996). Documented effects include both increased synthesis and increased release of dopamine (Spano et al., 1971; Cheramy et al., 1977).

The dose–response curves in humans and animals are quite similar and demonstrate a very narrow therapeutic index. Low doses, on the order of 50 to 100 mg/kg, produce mild agitation and excitement. Doses of 100 to 200 mg/kg induce euphoria and probably hallucinations. At doses much above 200 mg/kg, users become unresponsive. Seizures occur in the 400- to 800-mg/kg range, as does respiratory arrest. The most unique aspect of GHB intoxication is its very brief duration. A number of case reports describe deeply comatose patients, requiring ventilator support, who wake after only a few hours, extubate themselves, and simply walk out of the emergency room (Dyer, 1991; Chin et al., 1992; James, 1996; Louagie et al., 1997).

Recreational GHB users who overdose usually present at emergency rooms with obtundation, mild hypothermia, and asymptomatic bradycardia. Emesis is very common, but, when large series of such patients are reviewed, clinical aspiration is uncommon (Chin et al., 1998). If enough GHB has been ingested (>500 mg/kg), victims may require temporary respiratory support.

Case reports suggest that chronic use of GHB can lead to addiction and result in withdrawal syndrome (Winter, 1981; Colombo et al., 1995). However, the reinforcing effects of GHB in rhesus monkeys are far from impressive, suggesting that this particular drug has, at most, a very low potential for addiction (Woolverton et al., 1999).

Except for death from respiratory depression, few medical complications are recognized. What few data are available have been provided in abstracts presented at toxicology meetings, with very little published in the peer-reviewed literature. Most reported deaths have been in polydrug users, for whom it is quite possible that some other drug or drug interaction may have been the cause of death. Similar considerations apply to the solitary case of Wernicke–Korsakoff psychosis that was reported in a GHB user (Friedman et al., 1996).

6.3.11.2 Organ toxicity

γ-Hydroxybutyrate is not known to produce any specific pathologic lesions. GHB-related deaths, however, almost invariably occur in polydrug users; therefore, postmortem examination is likely to reveal the typical anatomic changes associated with polydrug abuse. Ethanol is frequently detected, and it may in fact contribute to toxicity). Hepatic steatosis is common in drug users, but the etiology is multifactorial.

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chapter seven

Anabolic steroids

7.1 Incidence

The 1999 Drug Abuse Warning Network (DAWN) report makes no mention of steroid-related deaths (Kissin and Ball, 2000). Steroid abuse is not tracked as a separate category in the mid-year 1999 preliminary DAWN report on emergency room visits (Ball et al., 2000), and the National Household Survey on Drug Abuse does not include anabolic steroids in the list of drugs surveyed (Greene et al., 2000).

7.2 Epidemiology

The real incidence of steroid abuse in general, and as a cause of medical problems in particular, is difficult to evaluate. Results of the National Household Survey on Drug Abuse indicate that more than 1,000,000 Americans are current or former users, with more than 300,000 having used steroids within the last year. The median age for users is 18 years. Older steroid abusers are more likely to be using other drugs as well (Yesalis et al., 1997).

A survey of varsity high school football players in the midwestern U.S. found that 6.3% of 873 interviewed students admitted they were current or former anabolic steroid users. The average age at time of first use was 14 years, but 15% had taken steroids before the age of 10. Almost half of those surveyed indicated that they could, if they so desired, easily obtain a supply of these drugs (Stilger and Yesalis, 1999).

Of 13,355 Australian high school students completing a drug use survey, 3.2% of the boys and 1.2% of the girls admitted to having used steroids on at least one occasion (Handelsman and Gupta, 1997). Prevalence appears to be very low in Canada; of 754 athletes surveyed, only 0.09% admitted to using steroids in the previous year, compared to 20% reporting use of marijuana or hashish (Spence and Gauvin, 1996). Single case reports of steroid-related deaths and vascular disease are becoming more common, but research papers describing medical complications in a large series of steroid abusers have yet to be published. This observation suggests that the incidence of steroid-related disease is still extremely low.

7.3 History

Anabolic steroids are synthetic compounds structurally related to testosterone, the male sex hormone. Testosterone has two different effects on the body: it promotes the development of secondary male sexual characteristics (androgenic effects), and it accelerates muscle growth (anabolic effects). The hormonal basis for male sexual characteristics was discovered by Berthold in 1849, when he observed that the male characteristics of roosters disappeared after they were castrated. These characteristics reappeared when the testes were implanted into the rooster's abdomen. Berthold correctly deduced that the testes were secreting something into the blood that controlled the development of male sexual characteristics.

In 1930, another scientist who worked at the same medical school in Göttingen where Berthold made his original discovery succeeded in isolating 15 mg of an anabolic compound from 25,000 L of policemen's urine. The compound was named androsterone for three reasons: it was virilizing (thus *andro,* the Greek word for male), the nucleus of its molecule was like that of cholesterol ("ster"), and it contained a ketone group ("one"). A few years later testosterone was crystallized from bull testes, and its chemical structure was characterized (Kochakian, 1990).

When testosterone was finally synthesized in the 1940s, it became apparent that the positive effects of testosterone on nitrogen balance and muscle growth could partially be separated from its androgenic effects. In the process of trying to separate the androgenic from the anabolic effects, it was observed that substitutions at the 17 position of the testosterone molecule produced compounds that could be taken orally and had anabolic effects but with only a fraction of the androgenic effects of testosterone. Further manipulations of the testosterone molecule at the 17 position have led to the production of a series of "anabolic" steroids that are active when taken orally (Figure 7.3.1).

Nandrolone remains the most popular of the oral anabolic agents, both among athletes and cattlemen attempting to increase profit yield. In the early 1990s competitive athletes stopped using nandrolone not because it was ineffective, but because it remained in the body for long periods of time and was too easily detected. Current International Olympic Committee (IOC) regulations set a urine concentration limit of 2 ng/mL; however, the urine concentration in non-steroid abusers never exceeds 0.6 ng/mL. A loophole in the regulations of most international sporting organizations allows athletes to exceed these limits and not be disqualified. Nandrolone precursors, 19-norandrostenedione and 19-norandrostenenediol, are available in many health food stores and are perfectly legal. Once in the body, these compounds are rapidly converted into nandrolone (Lee et al., 1991).

When large numbers of athletes began testing positive, the regulations were rewritten so that precursors were also disallowed. Because both of these nandrolone precursors are legal, any athlete testing positive was able to state legitimately (though hardly sincerely) that he or she had not used a prohibited substance. The other defense for a positive nandrolone test was innocent ingestion by consuming meat from cattle that had been illegally given steroids to promote growth. While seemingly farfetched, innocent ingestion from dietary sources is possible. Meat from noncastrated male pigs normally contains 19-norandrosterone, and consumption of boar meat can cause positive urine tests in humans (Le Bizec et al., 2000). Similar findings have been demonstrated after consumption of lamb (Vandenbroeck et al., 1991) and cows (de Brabander et al., 1994). Trace contamination of the androstenedione sold in health food stores seems to be the most likely explanation for many of the positive tests. Contamination of androstenedione with 19-norandrostenedione is sufficient to cause positive urine test results for 19-norandrosterone, the standard marker for nandrolone use (Catlin et al., 2000).

Figure 7.3.1 **Anabolic steroids.** When these agents first became available, they were often used for indications that are no longer considered acceptable today. This advertisement is from a 1961 issue of *JAMA*.

7.4 Steroid abuse

No agent is purely anabolic. All so-called "anabolic steroids" exert androgenic effects, and the only difference between agents is the ratio of anabolic to androgenic effects that are produced. When commercially prepared anabolic steroids became available just prior to World War II, they were used to promote healing and speed recovery. It soon became apparent that these drugs also had the ability to alter mood, and they were used to treat

Table 7.4.1 Commercially Available Steroid Preparations

Injectable agents
Delyestryl injection (BTG Pharmaceuticals)
Oral agents
Androl-50 tablets (unlimited)
Oxandrine® tablets (BTG Pharmaceuticals)
Testred® capsules (ICN Pharmaceuticals)
Winstrol® tablets (Sanofi Winthrop Pharmaceuticals)
Transdermal agents
Androderm® Transdermal System CIII (Watson)
Androgel® (Unimed)
Transderm® Transdermal Systems (Alza Corporation)

depression (Ehrenreich et al., 1997). It is alleged that steroids were given to German storm troopers to increase both strength and hostility.

The notion that steroids might improve physical performance is attributed to Boje, who first published his ideas in 1939 (Boje, 1939). Table 7.4.1 lists the anabolic steroids most commonly abused today. The black market for these drugs is thriving, with much clandestine production and importation. Since the dissolution of the former Soviet Union, a number of laboratories in the component republics have started producing steroids (along with other drugs) intended for European and U.S. black markets. Analyses of confiscated samples have shown wide variations in steroid content. Many products are falsely labeled.

Athletes use steroids because they believe steroids will improve their performance. Specifically, it has been claimed that steroid use (1) increases lean body mass, (2) increases strength, (3) increases aggressiveness, and (4) leads to a shorter recovery time between workouts. Evidence supports all of these claims, particularly the increase in strength (Plymate and Friedl, 1992); however, steroid abusers routinely take doses of anabolic agents well in excess of those that any physician could ethically administer, and it is certainly possible that if enough testosterone has been taken, violent behavioral changes could occur, especially if a pre-existing psychiatric disorder is present.

The various approaches to taking steroids are referred to as stacking, cycling, and pyramiding. Stacking is the practice of using several different steroid preparations at once in the hope that maximal anabolic effects will be achieved, while at the same time the androgenic effects are minimized. Cycling describes a pattern of usage where combinations of drugs are taken in alternating 6- to 12-week cycles; the rationale here is that the practice will prevent tolerance from occurring. Pyramiders start with low doses of the drug and gradually increase the amount of drug taken over several weeks, tapering off entirely before a competition. Not uncommonly, serious steroid abusers combine all three approaches.

Ethical considerations prevent physicians from participating in "megadose" steroid studies; however, that was not always the case. During the Cold War, within the sporting community, steroid abuse by East German athletes was considered a given. No one had any idea how widespread the practice actually was until Werner Franke, a cell biologist at the German Cancer Research Center in Heidelberg, obtained copies of *Stasi* (state secret police) files and brought them to the West. He was assisted in this venture by his wife, who was a former Olympic competitor (Franke and Berendonk, 1997).

According to the documentation supplied by Franke and Berendonk, the extent of the problem was far greater than anyone had ever believed. *Stasi* records show that hundreds of doctors, scientists, and coaches were involved, all participating in a classified, state-sponsored program known as State Plan 14-25. Athletes were treated with steroids from 1974 to 1989, often without their knowledge, and the responses to treatment were measured. Much of the testing was carried out in East Germany's State Anti-Doping Laboratories, one of only a handful of such laboratories approved by the IOC. In fact, the laboratory functioned as a "doping" laboratory. Excretion times were plotted for each athlete so that their coaches would know how long before a competition they would have to stop administering steroids.

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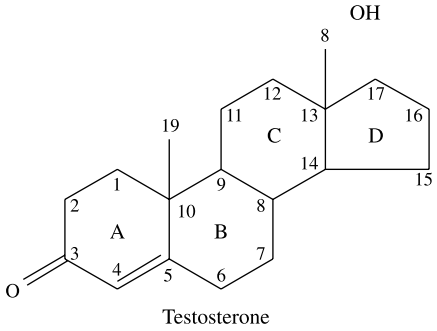
7.5 Pharmacology

7.5.1 Synthesis and metabolism

Testosterone is synthesized both by the testes and the adrenal glands, but only about 5% originates in the adrenals. Testosterone is a 19-carbon molecule synthesized from cholesterol that is originally produced from acetate stored in the testes, not from circulating cholesterol bound to low-density lipoprotein. Conversion from cholesterol to pregnenolone occurs in the mitochondria. From there the pregnenolone is transported to the endoplasmic reticulum, where it is converted to testosterone in a three-step process. Once produced, testosterone is immediately released into the circulation. It is estimated that a normal adult male produces 6 mg of testosterone per day (Miller, 1988).

Once testosterone is released into the bloodstream, approximately 50% circulates tightly bound to sex-hormone-binding globulin (SHBG), a glycoprotein produced in the liver (Harman et al., 2001). Much smaller amounts circulate loosely bound to albumin. The bond between albumin and testosterone is so weak that, for practical purposes, it can be considered unbound. Free testosterone seems to enter cells by simple diffusion. Once testosterone enters a cell it binds to a steroid receptor in the cytosol, which is then transported to the nucleus where it initiates DNA transcription. Testosterone bound to SHBG is so tightly bound that it probably never enters cells. Changes in the concentration of SHBG must be considered when measuring total testosterone blood levels, because they may drastically affect the observed half-life of the drug. Half-life values reported in the literature have ranged anywhere from 10 to 100 minutes (Kumar et al., 1997).

When testosterone is given orally, nearly half of it is metabolized on the first pass through the liver, so very large oral doses are required to produce any therapeutic effect (Figure 7.5.1.1). Agents such as methyltestosterone are not as extensively metabolized by the liver and can be taken orally. In the liver, testosterone is transformed into a series of 17-ketosteroids. The latter are excreted in the urine along with much larger amounts of 17-ketosteroids produced in the adrenal cortex. Testosterone is excreted mainly in the urine



Testosterone

Figure 7.5.1.1 **Testosterone.** Testosterone is rapidly degraded by the liver when it is given orally. Modifications at the 17 position, such as esterification of the β hydroxyl group, prevent hepatic breakdown and allow the drug to be given orally.

(>90%), either as the glucuronic or sulfuric acid conjugates. Approximately 6% is excreted unconjugated in the feces, and small amounts of glucuronide may appear in the bile. Less than 250 μg/day of testosterone appears unchanged in the urine. For testing purposes, most programs monitor the ratio of testosterone to epitestosterone in the urine. In healthy young men, this ratio is known to be less than 2:1, but the IOC accepts any value of less than 6:1 as normal.

7.5.2 Aging effects

Longitudinal and cross-sectional studies have shown that testosterone levels decrease as men age. The decrease is often greater than it appears because at the same time that testosterone concentrations are decreasing, levels of SHBG are increasing. The net effect is that even less free testosterone is available. The rate of decline appears to be quite variable and difficult to estimate because there is no accepted definition of what constitutes a "normal" testosterone concentration. For the purposes of replacement therapy, which is becoming a subject of increasing interest, most investigators define a "normal" testosterone in an aging man as being equivalent to whatever is considered the lower level of normal for a healthy young man (Bhasin et al., 1998; Tenover, 1998).

7.5.3 Legitimate clinical indications

As far as the Food and Drug Administration (FDA) is concerned, the only legitimate indication for testosterone treatment in men is replacement therapy when, for whatever reason (trauma, congenital), there is testicular failure and hypogonadism. In addition to parenteral testosterone, two different transdermal delivery systems and a testosterone-containing gel are now available (Testoderm®, Androderm®; AndroGel®). The Drug Enforcement Agency (DEA) classifies all of the testosterone-containing products as Category III restricted drugs.

Androgens are occasionally used to treat women who have metastatic breast cancer involving bone. Steroids classified as anabolic agents such as stanozolol (Winstrol®) are indicated only for use in the treatment of hereditary angioedema. Compounds that exert both androgenic and anabolic effects are also indicated for the treatment of deficient red blood cell production (acquired aplastic anemia and myelofibrosis), although this indication has largely been abandoned because erythropoietin (EPO) is so much more effective. Methyltestosterone is also sold in combination with estrogens (Premarin®) for the relief of symptoms associated with menopause.

Testosterone is not a wonder drug, but regular treatment with exogenous testosterone can reverse some of the alterations normally associated with aging, such as central, as opposed to peripheral, fat deposition (Katznelson et al., 1998; Elbers et al., 1999) and further changes in body fat distribution (Forbes et al., 1992), bone mass, muscle mass, and lean body mass (Lexell, 1995). Not only does muscle mass decrease with age, but so does the number of muscle fibers. The amount of creatinine excreted in the urine is a good indirect indicator of muscle mass and muscle creatinine content. Between the ages of 20 and 90 years, urinary creatinine excretion decreases by nearly two-thirds (Tzankoff and Norris, 1978). That observation alone may explain the increasing number of older runners with very impressive competition times who are later detected using steroids.

7.6 Steroid-related disorders

7.6.1 Liver disease

The incidence of liver disease in patients taking androgen hormones is said to be higher than for the general population and includes hepatic adenomas, cholestasis, peliosis, nodular regenerative hyperplasia, and hepatocellular carcinoma. However, causation has been very difficult to establish. Elevated amino transferase activity has also been observed in steroid-abusing athletes, but because exercise itself can be associated with some enzyme changes (depending on when the sample is drawn in relation to exercise), it is difficult to be sure if any connection exists at all (Graham and Kennedy, 1990; Dickerman et al., 1999). Similar doubts exist about other disorders (hepatic adenoma, peliosis hepatis) said to be related to anabolic steroid abuse.

7.6.1.1 Peliosis hepatis

This obscure disorder has been recognized for well over 100 years. It is characterized by the presence of scattered small, cystic blood-filled lakes scattered throughout the liver. Some of the cysts may be lined with epithelium, while others are not (Kalra et al., 1976). These collections of blood are often located adjacent to zones of hepatocellular necrosis. The lungs may also be involved in the same process, as may the entire reticuloendothelial system. Lesions have been described in the spleen, lymph nodes, and bone marrow (Taxy, 1978).

The connection between anabolic steroids and peliosis was first noted in 1952 (Taxy, 1978), and has been reconfirmed in many additional reports. In one series of 38 patients with peliosis, 27 had hematological disorders and all 27 had been treated with 17 α-alkyl-substituted steroids (Boyer, 1978). In an autopsy study of patients with aplastic anemia, one-third of the patients treated with steroids had peliosis. Only 3% of the patients who had not been treated with steroids developed peliosis (Wakabayashi et al., 1984). All of the steroid-peliosis case reports have involved 17-alkylated androgens. Peliosis related to the use of testosterone or its esters has never been reported.

Peliosis is easily diagnosed by ultrasonography as well as by conventional x-ray CT scans and magnetic resonance imaging (Parmar et al., 2000; Supe et al., 2000). But because most individuals with peliosis are asymptomatic, the probability that they will be scanned is very small. Patients with peliosis occasionally bleed to death from these lesions (Nadell and Kosek, 1977; Boyer, 1978; Taxy, 1978) or die of hepatic coma. Because most deceased patients with peliosis were gravely ill with other disorders, it is difficult to determine what caused the fatal event. More recently, peliosis has been described in AIDS patients, where the lesions may be confused with Kaposi's sarcoma (Czapar et al., 1986; Trojan et al., 1998; Gazineo et al., 2001).

Early researchers thought that peliosis was a congenital disease (Zak, 1950), but cows with peliosis (known as St. George's disease) can be cured simply by a change of pasture (Graham and Kennedy, 1990). In fact, a heterogeneous group of agents have been implicated. Many cases, particularly those occurring in the immunosuppressed, are infectious in origin. Bacillary angiomatosis and bacillary peliosis, opportunistic infections caused by *Bartonella henselae* and *B. quintana,* involve skin and bone as often as the liver. *B. quintana* and related organisms such as *B. henselae* (the same organism thought to be responsible for cat scratch disease) can be identified with polymerase chain reaction (PCR) techniques, either in skin or liver specimens. If the diagnosis can be made, infection will respond to long-term antibiotic treatment (Leong et al., 1992; Santos et al., 2000). Whether chemically induced cases without underlying infection ever occur is unclear.

7.6.1.2 Cholestasis

The 17-α-alkyl-substituted steroids can cause cholestatic jaundice. Bile accumulates in the canaliculi but without evidence of inflammation or necrosis (Foss and Simpson, 1959; Westaby et al., 1977; Lucey and Moseley, 1987). The frequency with which cholestasis occurs in testosterone abusers is not known. Different estimates place the incidence of cholestasis at anywhere from less than 1% to at least 17% (Plymate and Friedl, 1992). Several deaths from cholestatic jaundice have been attributed to steroids, but they occurred in elderly, debilitated patients, and the evidence of causality is far from convincing (Plymate and Friedl, 1992).

Tissue culture studies show that 17-α-alkylated steroids such as methyltestosterone, oxymetholone, and stanozolol are directly toxic to hepatocytes, but nonalkylated steroids such as testosterone cypionate, 19-nortestosterone, testosterone, and estradiol are not (Welder et al., 1995). At the same time, the results of animal studies suggest that P-4503A underexpression may play a role in toxicity, and that the activity of this particular cytochrome is, in turn, a function of bile composition (Paolini et al., 2000). Many drugs can affect bile composition, and it may be that the expression of specific human cytochromes is the final common pathway leading to cholestasis. A solitary case report, published in 1994, described severe cholestasis and jaundice in a user of non-C17-alkylated steroid (testosterone propionate), raising the possibility that cholestasis may not be confined only to users of oral agents (Yoshida et al., 1994).

7.6.1.3 Hepatic tumors

A clear association exists between the use of C17-alkylated androgens and the occurrence of hepatic tumors. Hepatocellular adenomas, similar in many ways to the adenomas that arise in the livers of women taking birth control pills, are not uncommon even in men who are not steroid abusers. Judging from the number of reports, the incidence is 1 to 3% among the 17-alkylated androgen users (Friedl, 1990). Like peliosis, hepatocellular adenomas are usually silent; patients with adenomas only come to medical attention when the adenomas rupture and cause hemoperitoneum, or are incidental findings at autopsy (Lesna et al., 1976; Boyd and Mark, 1977; Hernandez-Nieto et al., 1977; Paradinas et al., 1977; Taylor et al., 1984; Creagh et al., 1988). Liver function tests may be normal in asymptomatic cases (Westaby et al., 1983), and the distribution of these lesions is such that even if their existence is suspected, percutaneous biopsy may miss the lesions (Bagheri and Boyer, 1974).

Adenomas have the same appearance in men treated with androgens and women taking birth control pills. In either case, the adenoma is composed of sheets of cells that look like normal hepatocytes. There are, however, some differences. One important difference is that androgen-related adenomas tend to be larger. Adenomas in steroid users range in size from a few millimeters to several centimeters in diameter. Androgen-related adenomas often form bile-containing acini, and absent a history of androgen abuse, acini formation is usually considered to be histologic evidence of malignancy.

Adenomas in steroid users may also display other features that are suspect for malignancy, such as bizarre nuclei and even rare mitoses (Creagh et al., 1988). The benign nature of most of these lesions is confirmed by their sharply demarcated margins, their failure to metastasize, the absence of demonstrable alphafetoprotein, and the absence of associated cirrhosis (the most frequent setting for hepatocellular carcinoma). The fact that adenomas regress when androgens are discontinued also argues against their malignant nature (Friedl, 1990). Nonetheless, hepatocellular carcinoma has been diagnosed in individuals taking C17-substituted androgens (Overly et al., 1984), so the possibility for conversion from adenoma to carcinoma cannot be ruled out (Boyd and Mark, 1977).

Rarely, nodular hyperplasia may result in portal hypertension, even in the face of a normal biopsy (Stromeyer and Ishak, 1981). As a consequence, bleeding esophageal varices may occur (Winwood et al., 1990).

7.6.2 Cardiovascular disease

Given the very large number of people thought to be taking anabolic steroids, the number of reported cardiovascular complications is remarkably small. Myocardial infarction with sudden death (McNutt et al., 1988; Luke et al., 1990; Lyndberg, 1991; Ferenchick and Adelman, 1992; Kennedy et al., 1993; Dickerman et al., 1995; Hausmann et al., 1998; Fineschi et al., 2001), arrhythmias (Sullivan et al., 1999), and stroke have all been described in young steroid abusers (Frankle et al., 1988; Lommi and Harkonen, 1991; Akhter et al., 1994; Lisiewicz et al., 1999), but in a given case it may be impossible to determine whether or not steroid abuse actually was responsible (Fineschi et al., 2001).

Anabolic androgens directly affect myocyte, growth, metabolism, and programmed cell death. Myocardial hypertrophy is easily produced in the rat model of steroid toxicity (Tseng et al., 1994) and has been documented in controlled trials of steroid-abusing weight lifters (Dickerman et al., 1998; Sader et al., 2001). Myocardial hypertrophy, from whatever cause, is accompanied by remodeling and fibrosis; either can provide the substrate for arrhythmic sudden death (Zipes and Wellens, 1998). In animal models, new capillary formation does not keep pace with steroid-induced myocyte hypertrophy (Tagarakis et al., 2000). Thus, at the cellular level, even in the absence of significant disease of the epicardial vessels and even in the absence of extreme exertion, the myocardium of steroid abusers may be relatively ischemic, and ischemia could account for many of the reported episodes of sudden death in steroid abusers.

Anabolic steroids exert conflicting effects on coagulation. Receptor densities for the thromboxane A2 receptor are increased (Halushka et al., 1995; Higashiura et al., 1996), but so is antithrombin III production (Bonithon-Kopp et al., 1988; Shapiro et al., 1999). The results of such conflicting actions are difficult to predict, and their clinical significance in cases of steroid abusers with myocardial infarction is impossible to interpret.

Anabolic steroid abuse (as opposed to therapeutic replacement) causes plasma high-density lipoprotein concentrations to decrease and concentrations of low-density lipoprotein levels to increase (Glazer, 1991; Sader et al., 2001). The limited research available suggests that atherogenic lipid profiles are more likely to be associated with the use of 17-α-alkylated anabolic steroids but not with 17-β-esterified agents such as nandrolone (Glazer and Suchman, 1994). Whether those changes actually make steroid abusers more susceptible to coronary artery disease is not known (Kabakci et al., 1999).

Another potential mechanism for testosterone cardiotoxicity, apoptosis, has only recently been recognized. In early animal studies, treatment with methandrostenolone was found to result in myocyte necrosis, cellular edema, and mitochondrial swelling (Behrendt and Boffin, 1977; Appell et al., 1983). More recent histochemical studies have shown that myocyte damage in experimental animals is secondary to anabolic androgen-induced apoptosis (Abu-Shakra et al., 1997; Zaugg et al., 2001). The histologic appearance of apoptosis, characterized by the absence of myocyte swelling, plasma membrane bleb formation, rapid disappearance of the nucleolus, and absence of hemorrhage, is easily distinguished from the appearance of ischemia. The histologic features of apoptosis were only first recognized as a distinct entity in the mid-1990s (Panizo-Santos et al., 2000; Saraste and Pulkki, 2000). Because apoptotic myocytes are eventually replaced by fibrous scar tissue, another possible source for re-entrant arrhythmias is created.

7.6.3 *Neurological disorders*

Episodes of cerebral, coronary artery, intracardiac, and peripheral thrombosis have been linked to steroid abuse (Frankle et al., 1988; Akhter et al., 1994; Fisher et al., 1996; Nieminen et al., 1996; Falkenberg et al., 1997; McCarthy et al., 2000), but reports are still rare. Psychiatric disturbances are, on the other hand, relatively common. There is some evidence that in susceptible individuals, suicidal behavior is more common in steroid abuses (Thiblin et al., 1999), and case reports have described men with no previous psychiatric histories who committed violent crimes, including murder, while they were taking steroids. All reverted to their normal personalities once steroids were discontinued (Pope and Katz, 1990; Schulte et al., 1993).

Claims of steroid-related psychosis ("roid rage") have been used unsuccessfully in some murder trials (Moss, 1988), and the occurrence of clinically proven effects on behavior remains controversial. In a double-blind controlled clinical trial where supraphysiological doses of testosterone (600 mg/wk) were administered to volunteers, aggressive behavior was not increased (Tricker et al., 1996). However, steroid abusers routinely take doses of anabolic agents well in excess of those that any physician would ever administer, and it is certainly possible that if enough testosterone is taken violent behavioral changes could occur, especially if a pre-existing psychiatric disorder is present. One study of 41 self-admitted steroid abusers found that 22% of those interviewed had affective disorders and 12% had episodes of frank psychosis (Pope and Katz, 1988).

In a controlled laboratory study of normal volunteers, methyltestosterone in high doses (240 mg/day), but not in low doses (40 mg/day), was found to cause behavioral changes including euphoria and sexual arousal, irritability, mood swings, and confusion (Su et al., 1993). In a related, more recent study, the 240-mg/day dose of testosterone given to healthy volunteers increased spinal fluid concentrations of 5HIAA. The increase was accompanied by reports of increased energy, increased sexual arousal, and diminished sleep (psychiatrists refer to these as "activation" symptoms); the greater the increase in cerebrospinal fluid (CSF) concentrations of HIAA, the more intense the "activation" symptoms (Daly et al., 2001).

7.6.4 *Musculoskeletal disease*

Despite an explosive increase in the number of publications dealing with testosterone supplementation in the aging population and in patients with HIV infections, surprisingly little is known about the effects of steroid abuse on the musculoskeletal system of young athletes — the group most likely to be abusing testosterone. Compared to controls, tendons from mice chronically treated with anabolic steroids are stiffer, absorb less energy, and rupture with lesser degrees of elongation, although maximal tendon strength is unaffected (Inhofe et al., 1995). Initial suggestions that these mechanical changes were accompanied by recognizable histologic abnormalities have not been confirmed (Michna, 1986a,b; Evans et al., 1998). Still, these alterations may explain the occasional report of steroid-related tendon rupture (Hill et al., 1983; Kramhoft and Solgaard, 1986; Laseter and Russell, 1991; Freeman and Rooker, 1995; Liow and Tavares, 1995).

Avascular necrosis of the femoral heads similar to that seen with long-term glucocorticoid therapy has also been reported, but it is not clear that the phenomenon is due to anabolic steroid abuse. It could just as easily be an idiosyncratic reaction (Pettine, 1991; Frankle, 1992). Exercise-conditioned animals given anabolic steroids have reduced numbers of capillaries, not just in the heart, but also in skeletal muscle fibers. At the same

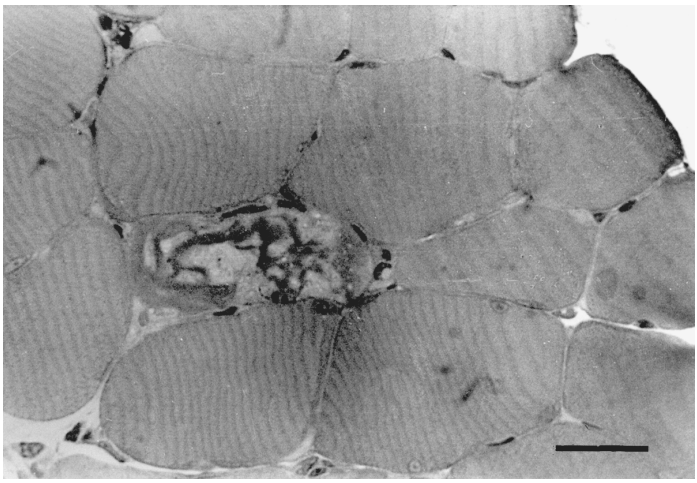


Figure 7.6.4.1 **Degenerating muscle in steroid-treated rat.** The peripheral muscle of rat treated with nandrolone decanoate and forced to exercise. Focal necrosis occurs, with degenerating fibers intermingled with normal appearing fibers (scale bar = 50 mm). Morphometric analysis of these same fibers shows decreased numbers of capillaries when compared to controls. (Courtesy of Dr. J.M. Soares, Faculty of Sport Sciences, University of Porto, Porto, Portugal.)

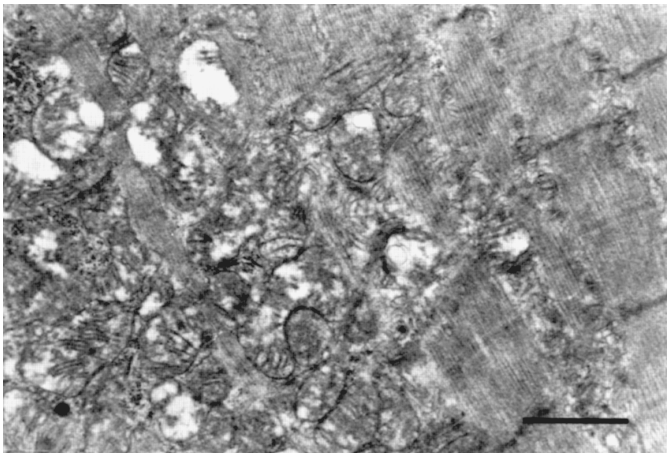


Figure 7.6.4.2 **Steroid-induced mitochondrial damage in rat.** Electron micrographs of rats chronically treated with nandrolone show mitochondrial swelling and disruption very similar to what is seen in the hearts of animals exposed to high levels of catecholamines (scale bar = 2 mm). (Courtesy of Dr. J.M. Soares, Faculty of Sport Sciences, University of Porto, Porto, Portugal.)

time, the amount of fatty and connective tissue in their muscles increases (Soares and Duarte, 1991). The relative decrease in the number of capillaries per fiber suggests an inefficient exchange of respiratory gases and substrates in the hypertrophied muscles. The typical histologic picture in these animals is patchy fiber necrosis. Degenerating fibers are surrounded by fibers that have normal morphology (Figures 7.6.4.1 and 7.6.4.2). Control studies in humans are lacking.

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7.7 Detecting steroid abuse

A clinical profile of typical steroid abusers can be drawn, and reference to it is often helpful when the history is unclear. Typical findings are shown in Table 7.7.1. Testosterone blood concentrations remain poorly characterized and cannot be used to detect abuse. Testosterone concentrations in conditioned athletes have been measured both before and after exercising. Resting levels were 16 to 17 nmol/dL. After an intense period of strength training, levels increased by 27%. Testosterone levels increased even more after endurance training (37%) but after both types of training, levels returned to normal within a few hours (Jensen et al., 1991). In addition to being affected by exercise, measurements are also dependent on time of day, age, and body mass index (BMI). Aging affects both testosterone and the free T index (= testosterone divided by concentrations of SHBG), and so does the use of other drugs, including prescription medications such as beta blockers (Harman et al., 2001). Postmortem blood testosterone concentrations have not been studied.

Testosterone and nandrolone-like drugs can reliably be detected in hair, and the evidence suggests that this approach is much more likely to detect abusers than urine testing. In one study, the effectiveness of urine and hair testing was compared in samples obtained simultaneously from a group of professional bicyclists; 12% of the hair tests, but none of the urine tests, disclosed the presence of anabolic agents (Gaillard et al., 2000).

Table 7.7.1 Profile of a Steroid Abuser

Social
Recent changes in friends, acquaintances
Obsession with health, exercise, weight lifting
Spends most of time in gyms or health clubs
Takes large amounts of vitamins and food supplements
Very high calorie intake
Does not abuse other drugs because of concern with leading a "healthy life style"
Physical
Rapid weight gain and muscle development
Increased body hair, deepening of voice
Acne (both sexes)
Hair loss (both sexes)
Breast enlargement (males)
Testicular atrophy
Difficulty urinating
Elevated blood pressure
Complaints of stomach upset
Jaundice
Edema of extremities
Mental changes
Increased aggression
Hyperactivity, irritability
Auditory hallucinations
Paranoid delusions
Manic episodes
Depression and anxiety
Panic disorders
Suicidal thoughts
Laboratory findings
Decreased HDL cholesterol
Decreased luteinizing hormone
Decreased follicle stimulating hormone
Decreased thyroid stimulating hormone
Decreased thyroid hormones
Elevated liver enzymes
Increased hematocrit
Increased LDL cholesterol
Increased triglycerides
Increased glucose

Source: Adapted from Narducci, W. A. et al., *J. Toxicol. Clin. Toxicol.,* 28(3), 287–310, 1990.

Even though hair drug concentrations are low (in the picogram range), currently available analytic techniques allow for reliable detection (Segura et al., 1998; Deng et al., 1999; Gaillard et al., 1999; Kintz et al., 1999; Cirimele et al., 2000). Hair testing for anabolic steroids is not yet recognized by the IOC, partly because questions still exist about the

influence of hair color and the possibility of racial bias (Kintz et al., 2000). Consequently, the IOC and its component organizations still rely on urine testing for the detection of steroid abuse.

Until the late 1990s, athletes rarely tested positive for oral anabolic agents. Oral anabolic steroids such as nandrolone may remain detectable in the blood and urine for many weeks after ingestion, and so cannot be taken by those who know they are subject to "in-competition" testing. But in 1999, a loophole in IOC regulations allowed a number of prominent athletes to self-administer nandrolone in the form of the precursors 19-norandrostenedione and 19-norandrostenenediol and not be disqualified. The rules of the IOC and the International Amateur Athletic Foundation (IAAF) specify that nandrolone and "related substances" are prohibited, but precursor-containing compounds sold as dietary supplements are not. Once the IOC became aware of these products, they moved to ban their use; 19-norandrostenedione and 19-norandrostenenediol were added to the IOC forbidden list on January 31, 1999. Concentrations measured in the urine of some of these individuals were extraordinary high, and could not have been the result of contamination of androstenedione with 19-norandrostenedione.

Until recently, testosterone had to be administered parenterally, which may have somewhat limited the number of potential abusers. However, now that testosterone-containing skin gels and patches are available by prescription, they now have appeared on the black market, and testosterone abuse is likely to become even more widespread, and the detection of abusers is an increasingly important issue. The detection algorithm used by the IOC relies upon the ratio of testosterone to epitestosterone (17-α-hydroxy-4-androsten-3-one) present in the urine. The exact role of epitestosterone is not clear. Results of *in vitro* studies suggest that epitestosterone has androgen-counteracting activity and may be involved in the prostatic hypertrophy associated with advancing age and possibly with body hair distribution (Starka, 1993). Epitestosterone is secreted by human adrenals, testes, and ovaries, but it is not produced from testosterone. It is poorly metabolized by humans, and at least 50% of injected epitestosterone can be recovered unchanged in the urine (Wilson and Lipsett, 1966).

In adults, but not necessarily during prepuberal development (Raynaud et al., 1993a,b), approximately equal concentrations of testosterone and epitestosterone are excreted in the urine of both women and men. Under normal conditions, the production of epitestosterone remains constant and independent of testosterone production. Thus, abnormally high ratios of testosterone to epitestosterone are considered by the IOC and other sports federations and organizations as proof of exogenous testosterone administration. The difficulty comes with attempting to define "abnormal" ratio.

In normal young men, the testosterone-to-epitestosterone ratio is less than 3:1 and is probably closer to 1:1 (Dehennin, 1993). However, the IOC and other official sports bodies accept any ratio of less than 6:1 as normal. In practice, that means that an athlete who wants to take steroids can do so with relative impunity, as modest doses of testosterone will not alter the ratio sufficiently to lead to disqualification (Dehennin, 1993). When users stop taking testosterone, the testosterone-to-epitestosterone ratio reverts to baseline (typically approximately 1.0) (Catlin et al., 1997). One way to lower the ratio is to take epitestosterone and testosterone at the same time. The difficulty with this approach is that the absolute amount of epitestosterone in the urine will also be abnormally increased. The IOC has banned epitestosterone use and ruled that specimens found to contain more than 150 ng/mL of epitestosterone are proof of misuse. The IOC is also experimenting with other ways of detecting testosterone abuse, the most promising of which involves the

measurement of carbon isotope ratios to determine whether steroids found in the urine are exogenously or endogenously produced (Aguilera et al., 2001).

Until a more reliable test becomes available, false positives remain a possibility. When biological false positives do occur, it is probably a result of abnormal testicular epitestosterone secretion or the abnormal breakdown of epitestosterone once it is produced (Dehennin and Scholler, 1990; Raynaud et al., 1992). Many approaches have been suggested for separating abusers from biological false positives. One way is to administer ketoconazole. This antifungal drug inhibits testosterone production by inhibiting 17-α-hydroxylase and 17,20-lyase activity. If testosterone concentrations are high because testosterone has been injected, ketoconazole will not cause concentrations to drop. On the other hand, if an innocent athlete with a testosterone-to-epitestosterone ratio greater than 6 is given ketoconazole, one would expect a steep drop in testosterone production and a concomitant decrease in the ratio. This has proven to be the case when ketoconazole is given to athletes with high ratios (Kicman et al., 1993; Oftebro et al., 1994).

British 800-meter runner Diane Modahl, who was banned for four years after testing positive for testosterone in 1994, was later cleared after it was revealed that her urine sample had been left unrefrigerated in the official IOC testing laboratory for at least two days before it was analyzed (Bilton, 1995). Modahl's attorneys successfully argued that the resulting bacterial growth caused the positive result. Laboratory studies have partly confirmed these claims. While bacterial contamination does not result in production of testosterone or epitestosterone, a few organisms can synthesize 5-α-androstanedione, 5-β-androstanedione, and androstenedione using endogenous steroids as a substrate. Other organisms are capable of cleaving steroid glucuronides and sulfate conjugates, converting them to measurable free testosterone (de la Torre et al., 2001).

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chapter eight

Solvents

8.1 Incidence

The number of new inhalant abusers has more than doubled in the last decade. It is estimated that 708,000 first-time users experimented with solvents in 1997, compared to only 332,000 in 1989 (Greene et al., 2000).

8.2 Epidemiology

The percentage of young people reporting regular use of inhalants decreased by nearly 50% from 1997 to 1998 (2.0 to 1.1%), but the reported rate of first use among youths ages 12 to 17 rose significantly during that same period. From 1988 to 1996, the number of young adults ages 18 to 25 who abused solvents for the first time increased threefold (from 3.7 to 10.7 per 1000 potential new users). The Medical Examiner component of the 1998 Drug Abuse Warning Network (DAWN) report lists a total of 105 deaths related to "solvents/aerosols." Most decedents (70%) were male. Deaths from solvent abuse accounted for 1% of all reported drug-related deaths (Kissin and Ball, 2000).

8.3 General considerations

Hundreds, perhaps thousands, of commercial and household products contain solvents that can be abused, but the medical complications of acute solvent toxicity remain poorly characterized. The frequency of medical complications in solvent abusers is not really known. Solvent abuse is not a new problem. Recreational solvent abuse was recognized before World War I, and the abuse of ether was popular in England during the 1890s. Deaths from recreational chloroform abuse were first reported at an even earlier date.

Solvent abuse was uncommon in the U.S. until the late 1950s, but the practice was common in both Japan and Europe earlier (Anon., 1988). In the late 1970s, national surveys of American high school seniors found that solvent abuse had been tried on at least one occasion by 10 to 13% of the respondents. The same surveys also disclosed that in addition to glues and solvents, abuse of amyl and butyl nitrates had become relatively common (Smart, 1986).

Solvent abusers are most likely to be males between the ages of 13 and 15, but the prevalence of abuse and the age of the abusers vary from location to location. Some adults, especially those living in rural communities and in locations where there is ready access to the appropriate chemicals, are also abusers (Flanagan and Ives, 1994). For unexplained reasons, solvent abuse is much more common in England than in the U.S. In 1991, 122

solvent-related deaths were reported in England. During that same period, only 56 deaths were reported in the U.S., making the death rate in the U.K. more than 20 times higher than that in the U.S.!

Solvents are highly soluble in lipids and they rapidly enter the central nervous system, where they act as depressants. Solvents share some characteristics with other depressants such as barbiturates, benzodiazepines, and alcohol (Evans and Balster, 1991). Chemicals such as toluene, 1,1,1-trichloroethane (TCE), and trichloroethylene (TCY) affect ligand-gated ion channel activity. *In vitro* studies have shown that solvents may cause reversible enhancement of γ-aminobutyric acid A ($GABA_A$) receptor-mediated synaptic currents in hippocampal brain slices, and increase expression of α-1-glycine receptors (Beckstead et al., 2000). These are essentially the same effects produced by sedative hypnotic drugs such as barbiturates and benzodiazepines. The ability of solvents to produce a state of true dependence remains a matter of some dispute (Miller and Gold, 1991), but the results of animal studies certainly suggest that solvent abusers can become physically dependent (Evans and Balster, 1991).

Psychiatric, neurologic, renal, and hepatic disorders have been reported as complications of solvent abuse, but the primary risk has always been sudden death. A U.K. study analyzed the patterns and mechanisms of death in a series of 1237 solvent abusers over a 20-year period. Deaths were divided into four different groups according to the type of solvent involved: (1) aerosol propellants, (2) gas fuels, (3) chlorinated and other types of solvents, and (4) solvents from adhesives. The proportion of deaths due to direct toxicity, aspiration, and asphyxia was remarkably similar in all the groups except for adhesive solvents (containing mostly toluene). Among individuals abusing adhesives, trauma was the most frequent cause of death, suggesting that impairment of judgment is somewhat more likely with the use of adhesives than with the use of other types of solvents.

8.4 Absorption and tissue disposition

Not all solvents are abused. In order to have abuse potential, a compound must be sufficiently volatile to be inhaled. This explains the generally low abuse potential of petroleum distillates, such as kerosene and ethylene glycol. Industrial workers exposed to ethylene glycol fumes can develop an assortment of chronic disorders, including testicular degeneration (Lee and Kinney, 1989), but reports of toxicity in chronic abusers are rare. Toluene, the solvent most often used in contact adhesives, is highly volatile and frequently abused. Table 8.4.1 lists some of the more commonly abused agents.

The way in which a particular product is abused depends on the boiling range of the solvent. For toluene-containing contact adhesives, the preferred method of self-administration is to pour the solvent into a plastic bag, gather the ends of the bag together, and hold the top of the bag over the mouth and nose. The practice is called "huffing." Plastic bags can also be used to collect propellants from aerosol cans. Volatile agents such as gasoline are simply sniffed from soaked rags (Flanagan and Ives, 1994). When toluene is inhaled, it is rapidly taken up by the brain and by fat stores elsewhere in the body, then slowly released over the course of many hours. Once released back into the circulation, hepatic conjugation is followed by renal excretion as hippuric acid. The co-ingestion of ethanol increases plasma concentrations of most solvents; resultant concentrations of toluene may be nearly double those seen when the solvent is inhaled by itself (Baelum, 1999).

Table 8.4.1 Commonly Abused Solvents[a]

A. *Aerosol propellants* (air fresheners, deodorant spray, hair spray)
   - Dimethyl ether
   - Butane
   - Halogenated fluorocarbons
     - Bromochlorodifluoromethane (from fire extinguishers)
     - Carbon tetrachloride
     - Ethyl chloride
     - Perchloroethylene
     - Trichloroethylene

B. *Gas fuels* (disposable cigarette lighters)
   - Propane
   - Butane
   - Liquid petroleum gas

C. *Chlorinated solvents* (commercial dry cleaning/degreasing agents)
   - Carbon tetrachloride
   - Dichloremethane
   - Methanol
   - Tetrachloroethylene
   - Toluene

D. *Solvents from adhesives* (also paints, nail polish, varnish remover)
   - Acetone
   - Butane
   - Cyclohexanone
   - Toluene
   - Xylene

[a] Partial list of agents that may be responsible for inhalant abuse toxicity, grouped by pattern of toxicity. Agents from group A are more likely to be associated with traumatic injuries and death. Agents from the other three groups are more likely to manifest direct toxicity.

8.5 Clinical syndromes

8.5.1 Neurologic disorders

An acute syndrome of toluene-induced nausea, abdominal pain, impaired judgment, altered consciousness, and seizures is well recognized (Watson, 1982). Transient neurologic symptoms can also occur after the use of amyl nitrite and related compounds, but neurologic sequelae have not been associated with the practice.

The first reports describing a toluene-related neurologic disorder were published more than 40 years ago (Grabski, 1961; Kelly and Sammon, 1975). Cerebellar signs predominate, and patients present with ataxia, tremor, and nystagmus (Rosenberg et al., 1988). A variety of other neurologic disorders may occur, ranging from relatively minor degrees of cognitive dysfunction and poor performance in school (Fornazzari et al., 1983; Hormes et al., 1986) to much more serious disorders with evidence of pyramidal tract damage. Cerebral and cerebellar atrophy have been described (Hormes et al., 1986), and cranial nerve injury has also been reported. Some users, particularly adults, may present with a disorder mimicking Guillian–Barré syndrome (Streicher et al., 1981).

Most of the time symptoms disappear, or at least improve, when exposure to solvent ceases. In some cases, however, symptoms persist. Seizure disorders and evidence of cognitive impairment may be permanent (Byrne et al., 1991). Chronic toluene abuse also causes paranoid psychosis with schizophrenic symptoms that may be atypical, including visual (rather than auditory) hallucinations. Only a limited number of neuropathologic studies have been published (Escobar and Aruffo, 1980; Rosenberg et al., 1988), but the available evidence suggests that when symptoms persist, it is usually because widespread demylination has occurred.

In the three cases described by Kornfeld et al. (1994), the essential features of the disorder were severe but spotty loss of myelin with only relatively mild axonal loss and gliosis. Macrophages filled with PAS-positive granules are a constant feature (Figures 8.5.1.1 to 8.5.1.3). The histologic appearance is not that different from the picture seen in adrenoleukodystrophy. Biochemically, the lesions are characterized by an increase of very long chain fatty acids in the white matter cholesterol esters (Kornfeld et al., 1994). Magnetic resonance imaging (MRI) scanning confirms the loss of white matter, with cerebral atrophy most evident in the corpus callosum and cerebellar vermis (Kamran and Bakshi, 1998). Bilateral abnormalities of the basal ganglia, red nucleus, and thalamus have also been described. (Yamanouchi et al., 1995; Caldemeyer et al., 1996; Miyagi et al., 1999). MRI studies of relatively naïve users are likely to appear normal, even though decreased perfusion of the thalamus and basal ganglia can be demonstrated with single photon emission computed tomography (SPECT) scanning (Ryu et al., 1998).

8.5.2 Renal disease

Hematuria is common (Crowe et al., 2000), and glomerulonephritis has been documented (Streicher et al., 1981), but the actual incidence of these complications is low. Disorders of the renal tubules are more frequent than disease of the glomerulous (Taher et al., 1974; Fischman and Oster, 1979; Moss et al., 1980; Voigts and Kaufman, 1983). The mechanism by which toluene damages the renal parenchyma is not known.

8.5.3 Gastrointestinal disease

Histologic evidence of gastrointestinal disease is uncommon, but symptoms are frequent. Solvent-related centrolobular necrosis was first reported more than 30 years ago (Baerg and Kimberg, 1970), but only one case of fulminant hepatic failure has been linked to solvent abuse (McIntyre and Long, 1992). Surveillance studies of workers with long-term solvent exposure have found no evidence for subclinical alterations in liver or kidney function (Rasmussen et al., 1993). In animal experiments, the simultaneous administration of methamphetamine enhances carbon tetrachloride hepatotoxicity (Roberts et al., 1994). In theory, a solvent abuser taking amphetamines might be at increased risk. In practice, except for ethanol, solvent abusers hardly ever abuse other drugs at the same time.

8.5.4 Cardiovascular disease

Sudden cardiac death is the most common cause of solvent abuse-related deaths. Solvents, like halothane, sensitize the myocardium to catecholamine stimulation. Once sensitized, arrhythmias may be initiated by any event causing the release of catecholamines. Exercise, sexual activity, or even the act of fleeing the police could provide a surge of epinephrine sufficient to precipitate an arrhythmia (Bass, 1970; Reinhardt et al., 1973; Carlton, 1976;

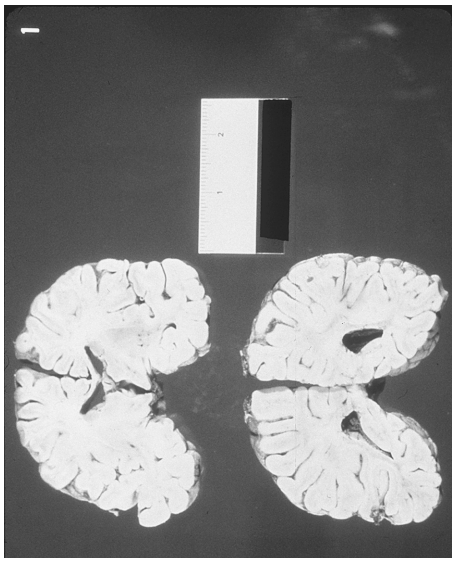

Figure 8.5.1.1 **Discoloration of white matter and atrophy of corpus collosum.** Lesions are confined almost entirely to the white matter, helping to distinguish solvent-related myelinopathy from the pattern seen in hypoxic injury. (Courtesy of A. Morrison; reproduced with permission from the College of American Pathologists.)

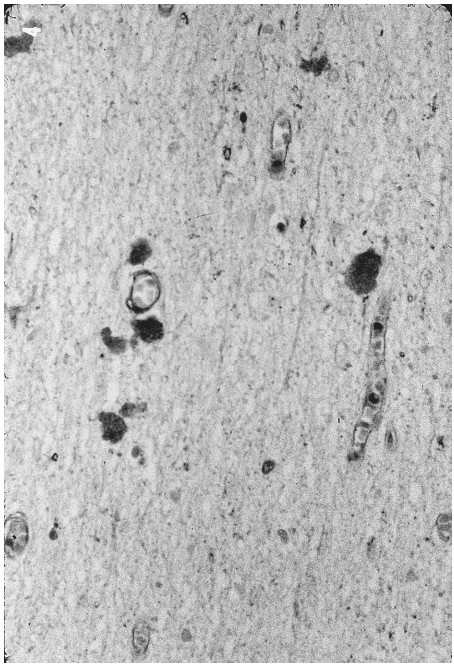

Figure 8.5.1.2 **Macrophages filled with PAS-positive granules, most often with a perivascular distribution, are almost always identified in the brains of solvent abusers.** The histologic appearance is not that different from the picture seen in adrenoleukodystrophy. (Luxor fast blue, PAS stain.) (Courtesy of A. Morrison; reproduced with permission from the College of American Pathologists.)

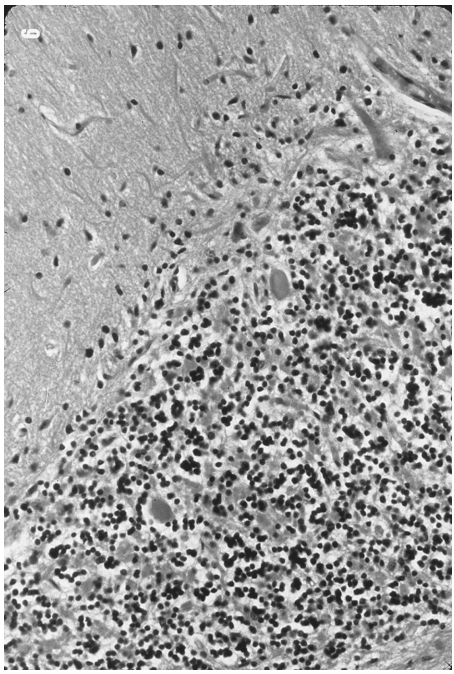

Figure 8.5.1.3 **Cerebellar injury.** Solvent abusers often have prominent cerebellar symptoms. As illustrated by this H & E section, loss of Purkinje cells is accompanied by Bergmann gliosis. (Courtesy of A. Morrison; reproduced with permission from the College of American Pathologists.)

Kobayashi et al., 1982). Exposure to these agents also sensitizes coronary artery receptors, which may explain why cases of myocardial infarction in solvent abusers have been described (Cunningham et al., 1987).

Another possible mechanism may involve decreased concentrations of intracytosolic calcium. Trichloroethylene (and probably other halogenated solvents as well) reduces calcium levels within cardiomyocytes (Hoffmann et al., 1992). The force of myocyte contraction depends on intracytosolic calcium. In order to initiate a contraction, intracytosolic calcium must increase to a certain critical setpoint. Decreased availability of calcium within the cardiac myocytes translates into decreased force of contraction. Whether or not solvent abuse results in myocardial depression sufficient to decrease coronary artery perfusion, causing ischemia and sudden death, has never been established.

Amyl nitrate inhalation causes methemoglobin to form, and fatal amounts of methemoglobin may be produced (Guss et al., 1985; Hoffmann et al., 1992; Sarvesvaran et al., 1992). Alternatively, amyl-nitrate-induced vasodilation and intense vagal stimulation could also lead to arrhythmias and sudden death. Another possible, though unproven, mechanism is fatal respiratory depression; if solvent concentrations in the brain reach sufficiently high levels, fatal respiratory depression could also occur. Proving such a sequence at autopsy would be a difficult if not impossible undertaking, especially given the complete absence of reports describing solvent concentrations in the brains of intoxicated individuals. A much more common cause of asphyxial death is vomiting with aspiration. Flanagan and Ives (1994) reported that aspiration was the cause of death in 20 to 30% of all solvent-related sudden deaths.

8.5.5 Reproductive organs

In animal studies, chronic exposure to high concentrations of toluene (6000 ppm 2 hr/day for 5 weeks) caused no significant changes in hormonal regulation but did damage sperm in the epididymis, and disrupted sperm maturation. Epididymal sperm counts, sperm motility, sperm quality, and *in vitro* penetrating ability to zona-free hamster eggs are all significantly reduced after toluene exposure, although no evidence of testicular atrophy has been observed (Ono et al., 1995, 1999). Female rats exposed to even lower toluene concentrations (2000 ppm) for 6 hours per day, from Day 7 to Day 17 of pregnancy, manifested many signs of toxicity including decreased body weight of both dams and offspring, high fetal mortality, and embryonic growth retardation. In humans, slightly more than one-third of all toluene-exposed infants are born prematurely, with a mortality rate of nearly 10% during the perinatal period (Ono et al., 1999).

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appendix one

Conversion formulas

Toxicology reports are not standardized. Depending on the units of measure used, what looks like a very large number may in fact be a very small one. Forensic toxicology laboratories report results in μg/mL.

Converting units of measure

A blood cocaine concentration of 1200 ng/mL (approximately the plasma concentration after smoking one rock of cocaine), might be reported as:

1200 ng/mL = 1.2 μg/mL = 1200 μg/L = 1.2 mg/L

The concentrations of hormones such as epinephrine are much lower than the concentrations of exogenous drugs, and are usually expressed in picograms (pg). If the concentration of cocaine in the above example was expressed in picograms (which, as a practical matter, it never is), 1200 ng/mL would be equal to 1,200,000 pg/mL.

Converting moles into grams

Clinical laboratories express results in millimoles (mmol) or Standard International Units (SI). To convert to standard concentration measurements, divide 1000 by the molecular weight and then divide that number into the concentration value expressed as μmol/L.

Example: In a research study of morphine pharmacokinetics, the maximum blood concentration after giving a 10-mg subcutaneous injection of morphine to a 70-kg man was reported as 262 ± 49 nmol/L. To convert that concentration into ng/mL,

1. Divide 1000 by the molecular weight of morphine:

   1000/285.34 (the molecular weight of morphine) = 3.50

2. Convert nanomoles (nmol) into micromoles (μmol):

   262 nmol/L = 0.262 μmol/L

3. Divide the number of μmol/L by 3.50:

   0.262/3.50 = 0.0748 μg/mL = 74.8 ng/mL

appendix two

Blood alcohol concentrations

Individuals who take abused drugs often ingest alcohol at the same time. Widmark's formula is the standard method used by forensic toxicologists to calculate blood alcohol concentrations, and is universally recognized by the legal system. However, an approach first suggested by Charles Winek, from Duquesene University, works equally well and is easier to remember (*Forensic Sciences*, C.W. Wecht, Ed., Matthew Binder Press, New York, chap. 31B, 1984). Winek's formula is based on the observation that a 150-lb man will have a blood alcohol concentration of 0.025% after drinking one ounce of 100-proof (50%) alcohol. Given that assumption (which is accurate under almost all circumstances), then the formula for calculating the blood alcohol concentration (BAC) is

$$\text{BAC} = (150/\text{body weight})(\%\ \text{ethanol}/50)(\text{ounces consumed})(0.025)$$

Example: A 200-lb man drinks five 12-ounce cans of beer. The beer contained 4% ethanol. The BAC would be given by the equation:

$$\text{BAC} = (150/200)(4/50)(60)(0.025)$$

$$\text{BAC} = (.75)(.08)(60)(0.025)$$

$$\text{BAC} = 0.090\%$$

Remember when using this calculation that it assumes all the ethanol was ingested at one time.

appendix three

Volume of distribution calculations

Some drugs, such as morphine, rapidly leave the blood and distribute widely throughout the body. Other drugs, such as morphine metabolites, stay mostly in the blood. The tendency for a molecule to remain in the blood or distribute into tissue can only be determined by actual measurement. The volume of distribution is the apparent volume needed to contain all of the drug injected in the body at the same concentration as observed in the blood. If, for example, 10 g of food coloring were dissolved in a 10-L aquarium, the resultant concentration would be 1 g/L, and the volume of distribution, abbreviated as V_d, would be 10 L. The V_d for drugs that remain mostly in the bloodstream, such as the morphine glucuronides, will be much less than 1. The V_d for drugs that penetrate widely into tissue, such as cocaine (V_d = approximately 3), will be much greater than 1. V_d calculations can be used to estimate the amount of drug administered:

Dose = (body weight [kg]) × (volume of distribution [L/kg]) × (blood concentration [mg/L])

V_d calculations apply *only to the living*. Postmortem redistribution and other postmortem changes make V_d calculations in the deceased extremely unreliable.

An example taken from an actual court case appears below. An individual was charged with accidentally administering a lethal dose of diphenhydramine (Benadryl®). Witnesses observed that the accused administered one injection with a 10-cc syringe. The decedent weighed 72.6 kg and at autopsy had a blood diphenhydramine concentration of 5.1 mg/L. Thus, the accused would have to have injected:

$$\text{Dose} = 72.6 \text{ kg} \times 4.5 \text{ } V_d \times 5.1 \text{ mg/L} = 1666.2 \text{ mg}$$

The average 30-mL multidose vial of diphenhydramine contains only 500 mg. The accused had only a 10-cc syringe. If the V_d calculation is to believed, the accused would have to have injected the victim with more than three vials of diphenhydramine, a process that would have required at least 10 separate injections!

The main utility of V_d calculations in postmortem investigations is as a quality assurance check of reported blood concentrations. If the V_d calculation suggests that an implausible amount of drug has been ingested, an error in laboratory or sampling methods may be indicated (the blood analyzed may, for example, have been scooped from the chest cavity).

appendix four

Normal heart weights

Predicted Normal Heart Weight (g) as a Function of Body Height in 392 Women and 373 Men

Body height		Women[a]			Men[a]		
(cm)	(in)	L95	P	U95	L95	P	U95
130	51	133	204	314	164	232	327
132	52	135	207	319	167	236	333
134	53	137	210	324	170	240	338
136	54	139	214	329	173	243	344
138	54	141	217	334	175	247	349
140	55	143	220	338	178	251	355
142	56	145	223	343	181	255	361
144	57	147	226	348	184	259	366
146	57	149	229	353	187	263	372
148	58	151	232	358	189	267	378
150	59	153	236	363	192	271	383
152	60	155	239	368	195	275	389
154	61	157	242	372	198	280	395
156	61	159	245	377	201	284	400
158	62	161	248	382	204	288	406
160	63	163	251	387	207	292	412
162	64	165	254	392	209	296	417
164	65	167	258	397	212	300	423
166	65	169	261	401	215	304	429
168	66	171	264	406	218	308	435
170	67	173	267	411	221	312	440
172	68	176	270	416	224	316	446
174	69	178	273	421	227	320	452
176	69	180	277	426	230	324	458
178	70	182	280	431	233	328	463
180	71	184	283	435	235	332	469
182	72	186	286	440	238	336	475
184	72	188	289	445	241	341	481
186	73	190	292	450	244	345	487
188	74	192	295	455	247	349	492
190	75	194	299	460	250	353	498
192	76	196	302	465	253	357	504
194	76	198	305	469	256	361	510
196	77	200	308	474	259	365	516
198	78	202	311	479	262	369	522
200	79	204	314	484	265	374	527
202	80	206	318	489	268	378	533
204	80	208	321	494	271	382	539
206	81	210	324	499	274	386	545
208	82	212	327	508	276	394	557
210	83	214	330	508	279	394	557

[a] L95 = lower 95% confidence limit; P = predicted normal heart weight; U95 = upper 95% confidence limit.

Note: Observed heart weight should be compared to predicted heart weight in all cases, not just those where drug abuse is suspected. Variations of more than 10% are very likely to be clinically significant but not apparent if only wall thickness is determined. Percentage-based formulas (e.g., 0.4% of body weight for men and 0.45% for women) are approximations only and not nearly so accurate or reliable.

Source: From Kitzman, D. et al., Age-related changes in normal human hearts during the first 10 decades of life. Part II (Maturity). A quantitative anatomic study of 765 specimens from subjects 20 to 99 years old, *Mayo Clin. Proc.*, 63, 1237–1246, 1988. With permission.

Predicted Normal Heart Weight (g) as a Function of Body Weight in 392 Women and 373 Men

Body weight		Women[a]			Men[a]		
(kg)	(lb)	L95	P	U95	L95	P	U95
30	66	133	196	287	162	213	282
32	71	137	201	295	167	220	291
34	75	141	206	302	172	227	300
36	79	144	211	310	177	234	309
38	84	148	216	317	182	240	317
40	88	151	221	324	187	247	325
42	93	154	226	331	191	253	334
44	97	157	230	337	196	259	341
46	101	160	234	344	200	265	349
48	106	163	239	350	205	270	357
50	110	166	243	356	209	276	364
52	115	169	247	362	213	281	371
54	119	171	251	368	217	287	379
56	123	174	255	374	221	292	386
58	128	177	259	379	225	297	392
60	132	179	262	385	229	302	399
62	137	182	266	390	233	307	406
64	141	184	270	395	237	312	412
66	146	187	273	401	240	317	419
68	150	189	277	406	244	322	425
70	154	191	280	411	248	327	431
72	159	194	284	416	251	331	437
74	163	196	287	420	255	336	444
76	168	198	290	425	258	341	450
78	172	200	293	430	261	345	455
80	176	202	297	435	265	349	461
82	181	205	300	439	268	354	467
84	185	207	303	444	271	358	473
86	190	209	306	448	275	362	478
88	194	211	309	453	278	367	484
90	198	213	312	457	281	371	489
92	203	215	315	461	284	375	495
94	207	217	318	465	287	379	500
96	212	219	320	470	290	383	506
98	216	221	323	474	293	387	511
100	220	222	326	478	296	391	516
102	225	224	329	482	299	395	521
104	229	226	331	486	302	399	526
106	234	228	334	490	305	403	531
108	238	230	337	494	308	406	536
110	243	232	339	497	311	410	541
112	247	233	342	501	314	414	546
114	251	235	345	505	316	418	551
116	256	237	347	509	319	421	556
118	260	239	350	513	322	425	561
120	265	240	352	516	325	429	566
122	269	242	355	520	327	432	570
124	273	244	357	523	330	436	575

Predicted Normal Heart Weight (g) as a Function of Body Weight in 392 Women and 373 Men (cont.)

Body weight		Women[a]			Men[a]		
(kg)	(lb)	L95	P	U95	L95	P	U95
126	278	245	360	527	333	439	580
128	282	247	362	531	335	443	584
130	287	249	364	534	338	446	589
132	291	250	367	537	341	450	593
134	295	252	369	541	343	453	598
136	300	253	371	544	346	456	602
138	304	255	374	548	348	460	607
140	309	257	376	551	351	463	611
142	313	258	378	554	353	466	616
144	317	260	381	558	356	470	620
146	322	261	383	561	358	473	624
148	326	263	385	564	361	476	629
150	331	264	387	567	363	479	633

[a] L95 = lower 95% confidence limit; P = predicted normal heart weight; U95 = upper 95% confidence limit.

Source: From Kitzman, D. et al., Age-related changes in normal human hearts during the first 10 decades of life. Part II (Maturity). A quantitative anatomic study of 765 specimens from subjects 20 to 99 years old, *Mayo Clin. Proc.*, 63, 1237–1246, 1988. With permission.