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Book Reviews: Technical Books Section

...A CLASSIC ON FORENSIC AND MEDICOLEGAL ASPECTS OF DRUG ABUSE ...A storehouse of latest information of pathology and forensic aspects of drug abuse. Every forensic pathologist and forensic toxicologist's dream...

Karch's Pathology of Drug Abuse, 4th Edition, by Steven B. Karch MD FFFLM. Hard Bound, 10" x 7" x 1.4".
CRC Press LLC, 2000 Corporate Blvd., N.W., Boca Raton, Florida 33431, , . Publication Date December 15, 2008. 736 pages, ISBN-10: 084937880X; ISBN-13: 978-0849378805 (alk. paper). Price: $139.95

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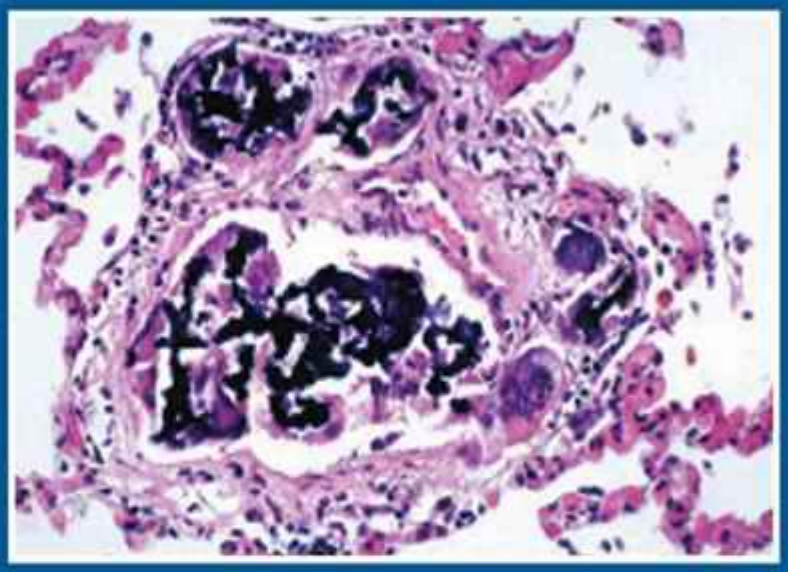
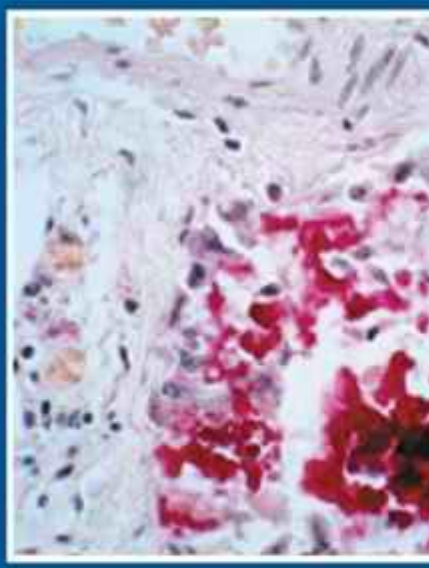
KARCH'S

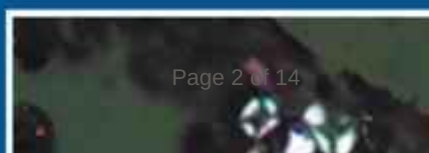




PATHOLOG
DRUG ABU

FOURTH EDIT





We are all aware of ***The Pathology of Drug Abuse*** by Karch for more than 15 years now, when its first edition came out. The book turned out to be an instant success, with its 2nd edition coming out in 1996 and the 3rd in 2001. Now CRC Press have come out with a brand new 4th edition, which gives all the latest developments that have occurred in this field in the last decade.

Karch has divided his book in nine major sections, each section dealing with either a major drug of abuse or a major class of drugs. The major drugs dealt with in this book are Cocaine, Natural Stimulants, Synthetic Stimulants, Hallucinogens, Opiates and Opioids, Dissociative Anesthetics, Anabolic Steroids, Solvents and Marijuana.

This edition is significant in the sense that it adds to the knowledge of drug abuse which has come to us as a result of our mastering of DNA technology and molecular biology. For instance, till some years back, we all fondly believed that stimulant abuse caused myocardial remodeling and that most deaths were a consequence of persistent neurochemical and anatomic alterations within the heart and brain. At that time, we were all sure that these changes were a consequence of chronic catecholamine toxicity, but as this book shows us, we were mistaken. The real explanation is activation of the Calmodulin Kinase II gene; increased levels of this enzyme produce myocardial hypertrophy. Similarly, we presumed that sudden death in methadone users was a consequence of respiratory depression. But the real explanation is vastly more complicated, having to do with genetic polymorphism, the inability of some individuals to properly metabolize the I-form of methadone, and the I-form's ability to bind the hERG channel.

Steven B. Karch, M.D., FFFLM, author of Karch's Pathology of Drug Abuse (Please Click to enlarge)



Cocaine is Karch's favorite topic (he has written an entire book on the history of cocaine!), so it is not surprising that he starts his book with a chapter on cocaine (and spends the most space to it). Among the Natural Stimulants dealt with by Karch are Absinthe, Caffeine, Ephedrine and Khat. Two drugs - Amphetamines and Methylphenidate (Ritalin®) are dealt with in the chapter on Synthetic Stimulants. In the chapter on hallucinogens, Karch deals with a range of compounds such as

Mescaline, Substituted Amphetamines [TMA, DOM, PMA, DOB, 4-Bromo-2,5-Dimethoxyphenethylamine, Nutmeg, 4-Chloro-2-5-Dimethoxyamphetamine (DOC) and 2,5-Dimethoxy-4-Iodophenethylamine], Piperazines, Hallucinogenic Amphetamines, Phenylalkylamines, Psilocybin, a-Ethyltryptamine and Ergolines.

This book should be very useful to forensic toxicologists, forensic pathologists, medical examiners and law enforcement officers.

View this book on Amazon

The detailed list of contents of this book is as follows:

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Excerpts from the book:

This book has become a classic over the years, and no forensic toxicologist worth his salt can claim not to have read this book. Although the entire book is informative, we at the journal office decided to excerpt portions from chapter 4 (Hallucinogens), simply because much of the information given here is not available elsewhere. This chapter also includes many upgradations from the last edition. Here is what Karch has to say on Tryptamine Derivatives (page 315 onwards).

4.3 Tryptamine Derivatives

The most popular hallucinogens are mescaline derivatives, and MDMA is by far the most widely used mescaline analog. Evidence suggests that these compounds may be more toxic than had previously been appreciated, and increasing numbers of deaths attributable to MDMA and MDEA are being reported. But in the absence of an effective, worldwide database it is impossible to tell how much more popular these drugs have become. Experimental studies are difficult because different experimental animals respond differently from other animal models and from humans.

4.3.1 Mescaline

Synonyms: **Lophophora williamsii** is the name of the plant that produces mescaline

Chemical name: 3,4,5-trimethoxybenzeneethanamine or 3,4,5-trimethoxyphenethylamine

Formula: $C_{11}H_{17}NO_3$

Molecular weight: 211.26 daltons

Metabolism: CYP2D6

Bioavailability: unknown

C_{max}: 3.88 mg/L after hallucinogenic dose

T_{max}: hallucinogenic effects after 2 hours

$T_{½}$: not known; approximately 6 hours

V_{ss}: not known

Interactions: potential interaction with other CYP2D6 dependent drugs

4.3.1.1 History

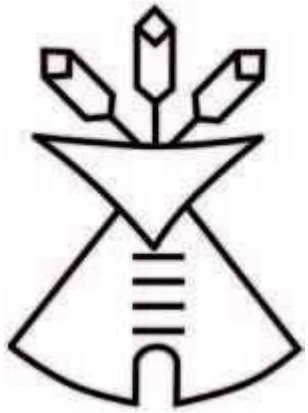
Louis Lewin was one of the first to systematically study mescaline. Mescaline comes from the cactus referred to as either Lophophora williamsii or Anhalonium lewinii. This small cactus can be found growing in dry places and on rocky slopes throughout the southwestern U.S. It grows singly or in clusters. It is an inconspicuous plant that can be difficult to find. Unless it is in flower, it tends to look like a small rock. Indian shamans have used the dried tops of the plants, known as peyote buttons, for centuries. In the early 1800s, the Apaches, Kiowas, and Comanche 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 known as the Native American Church and has more than 200,000 members (Barron et al., 1964). The emblem of this church is shown in Figure 4.3.1.1.2. Mescaline, or 3,4,5-trimethoxy- b-phenethylamine, is the active principle found in peyote cactus. The average mescaline content is 6%. No mescaline-related deaths or emergency room visits have ever been reported in any DAWN survey, either in the "new" or original versions.

Figure 4.3.1.1.1 Peyote buttons. Even though it grows wild throughout the American Southwest, the cactus can be very difficult to find. Except when it is in bloom, it tends to resemble a small rock. (This figure appears on page 316 of this book. Please Click to enlarge)



Lewin and Henning reported the first systematic chemical and pharmacologic studies in 1888. Lewin's work attracted the attention of the famous American neurologist S. Weir Mitchell (Lewin and Henning, 1888). 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. He then went on publish an account of his experiences in the British Medical Journal (Metzer, 1989). 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 now being made for MDMA have considerably more substance.

Figure 4.3.1.1.2 The emblem of the Native American Church.(This figure appears on page 316 of this book. Please Click to enlarge)



4.3.1.2 Production

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

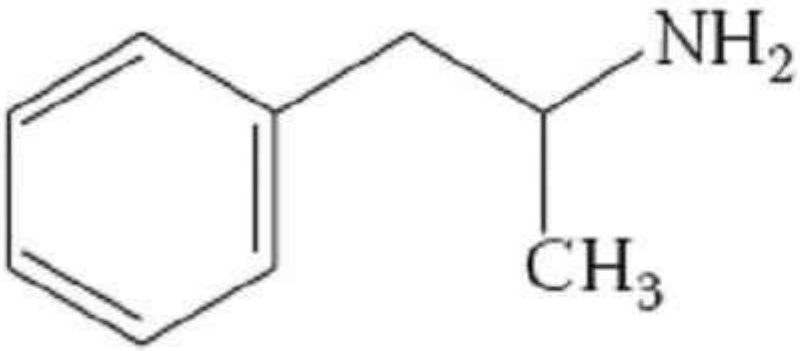
the tarry material in gelatin capsules with the hope of reducing the nausea induced by mescaline use.

4.3.1.3 Mechanism of Action

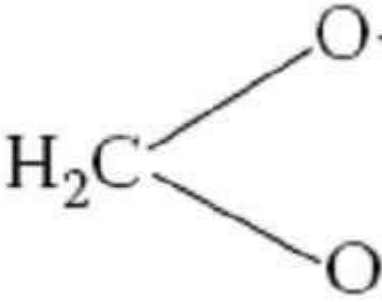
Very little has been written about mescaline's mode of action. It has been proposed that the two major classes of psychedelic hallucinogens, the indoleamines (e.g., LSD) and the phenethylamines (e.g., mescaline), have a common site of action in the central nervous system and act as partial agonists at 5-HT2A and other 5-HT2 receptors, but this view appears overly simplistic. It is true that all of these drugs are 5-HT (serotonin) agonists, but the results of in vitro studies and of animal studies all suggest that phenylisopropylamines and their phenethylamine counterparts can actually be distinguished by their activity at the 5-HT(2A) receptor; most hallucinogenic compounds behave as partial agonists. However, at 5-HT(2C) receptors, all phenylisopropylamines are more effective than their phenethylamine counterparts. The differentiation is the result of differing abilities of the two compounds to activate the enzyme phospholipase (Moya, 2007). The noradrenergic neurons of the locus caeruleus and others located in the cerebral cortex are among the regions where hallucinogens exert their most prominent effects via their actions upon 5-HT2A receptors (Aghajanian and Marek, 1999).

Figure 4.3.1.3.1 Mescaline and the "designer" amphetamines. Whether small recreational doses of the
appears on page 317 of this book. Please Click to enlarge)

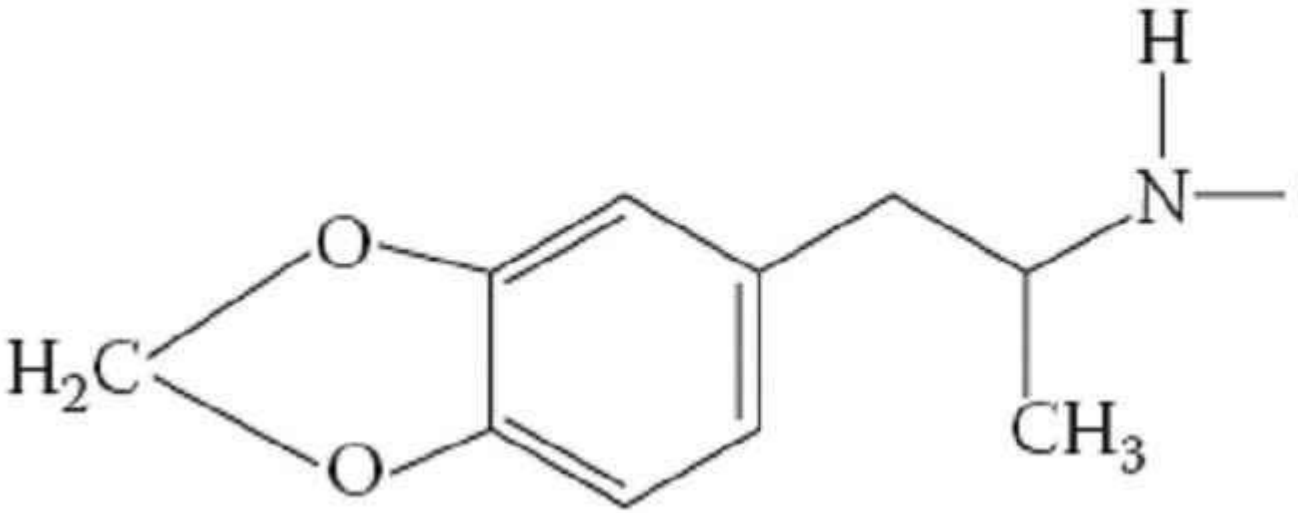
Amphetamine



3, 4-Methylen



3, 4-Methylenedioxymethamphetamine



4.3.1.4 Metabolism and Tissue Levels

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). Animals metabolize mescaline differently than humans, and it may be that the resultant tissue concentrations vary as well. Human tissue levels have been measured in a handful of cases: one mescaline user, who died of a head injury, was found to have had a blood concentration of 9.7 mg/L, a concentration eight times higher than that in the liver (Reynolds and Jindrich, 1985). In 2003, a report described blood and tissue levels in another mescaline user who had been shot. Concentrations of the drug were 2.95 mg/L, 2.36 mg/L, 8.2 mg/kg, and 2.2 mg/kg in blood, vitreous, liver, and brain, respectively (Henry et al., 2003).

4.3.1.5 Clinical Syndromes

Healthy volunteers given a 0.5-mg dose of mescaline exhibited symptoms of psychosis indistinguishable from those normally associated with acute schizophrenia. Neuropsychological measurements made during mescaline intoxication have suggested that the observed behavioral changes result from 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 mescalineinduced psychosis showed increased regional flow in the frontal lobes bilaterally (Hermle et al., 1998). Otherwise the symptoms 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 with this drug.

4.3.1.6 Pathologic Findings

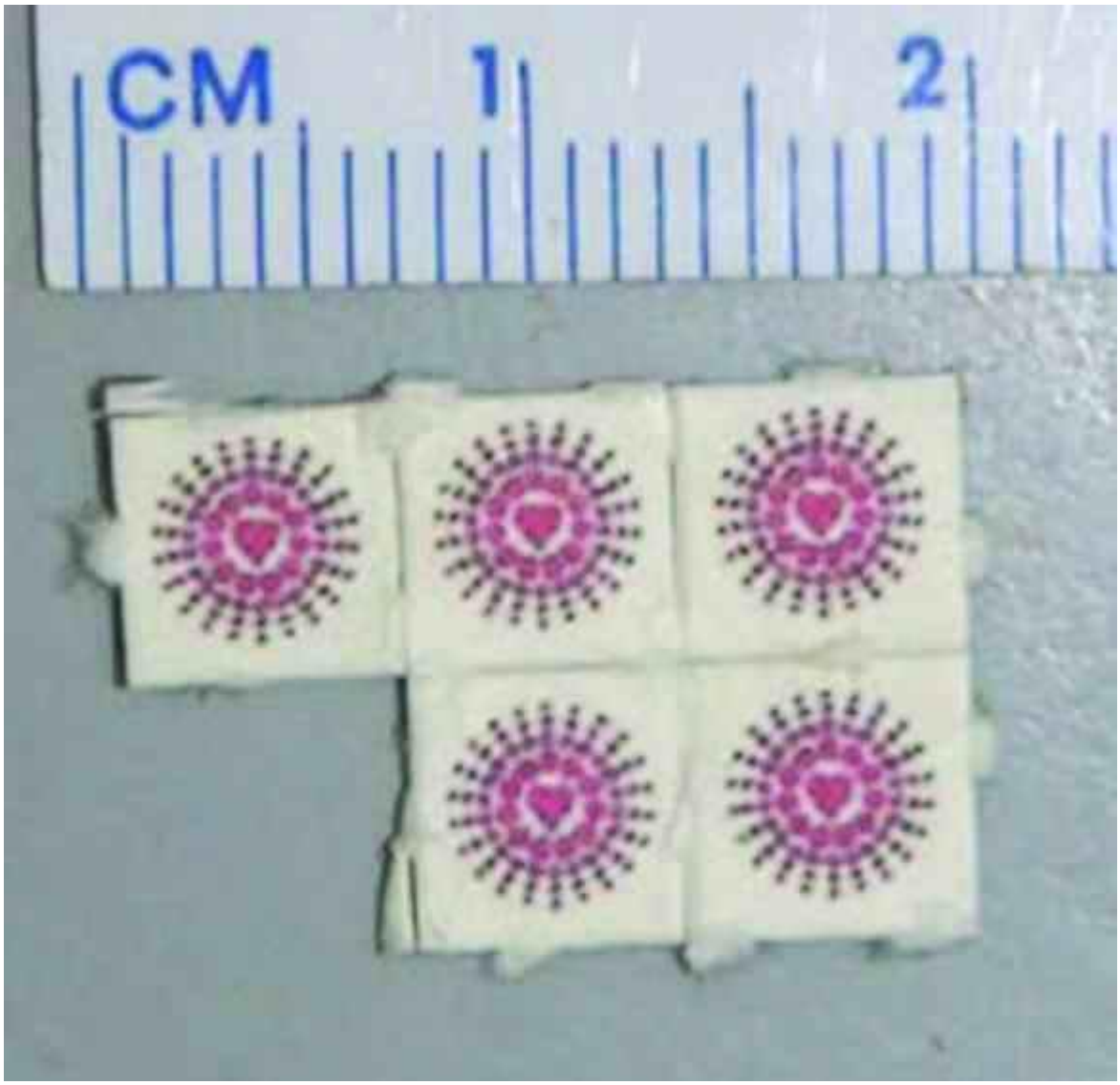
Lethal overdoses of mescaline have never been reported, nor have there been any reports of medical complications associated with its use. Reported deaths have been accidental, usually occurring as a result of drug-induced confusion (Reynolds and Jindrich, 1985).

And here is what Karch has to say about Substituted Amphetamines...

4.3.2 Substituted Amphetamines

4.3.2.4 DOB

Figure 4.3.2.4.2 DOB impregnated in a blotter. This dosage form is only occasionally reported. (This figure appears on page 321 of this book. Please Click to enlarge)



4-Bromo-2,5-dimethoxyamphetamine (DOB, also called bromo-DMA) is another potent hallucinogenic sympathomimetic, though one that is not nearly so often associated with death as PMA. Compared to MDMA (and most of the other mescaline derivatives), the effects are longer lasting. Reports of DOB abuse are becoming more frequent, though use still seems largely confined to Australia (Buhrich et al., 1983). It is occasionally sold as MDMA or found as an adulterant in MDMA tablets, but it is also sold and used under its own name. Occasionally it is sold as blotter acid (Figure 4.3.2.4.2), both in the U.S. and Caribbean. Because it is so potent, DOB can be absorbed into blotter paper and misrepresented as LSD (Shulgin, 1981). The problem with distributing DOB in the form of postage stamps is that DOB is considerably more toxic than LSD. During manufacture, the drug may migrate to the corners or bottom of the sheet of stamps. 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).

In 1991 Shulgin wrote that the d- isomer of this drug is much more potent than the lisomer, but pharmacokinetic and pathology studies are lacking, and chiral separation has never been performed in any forensic setting.

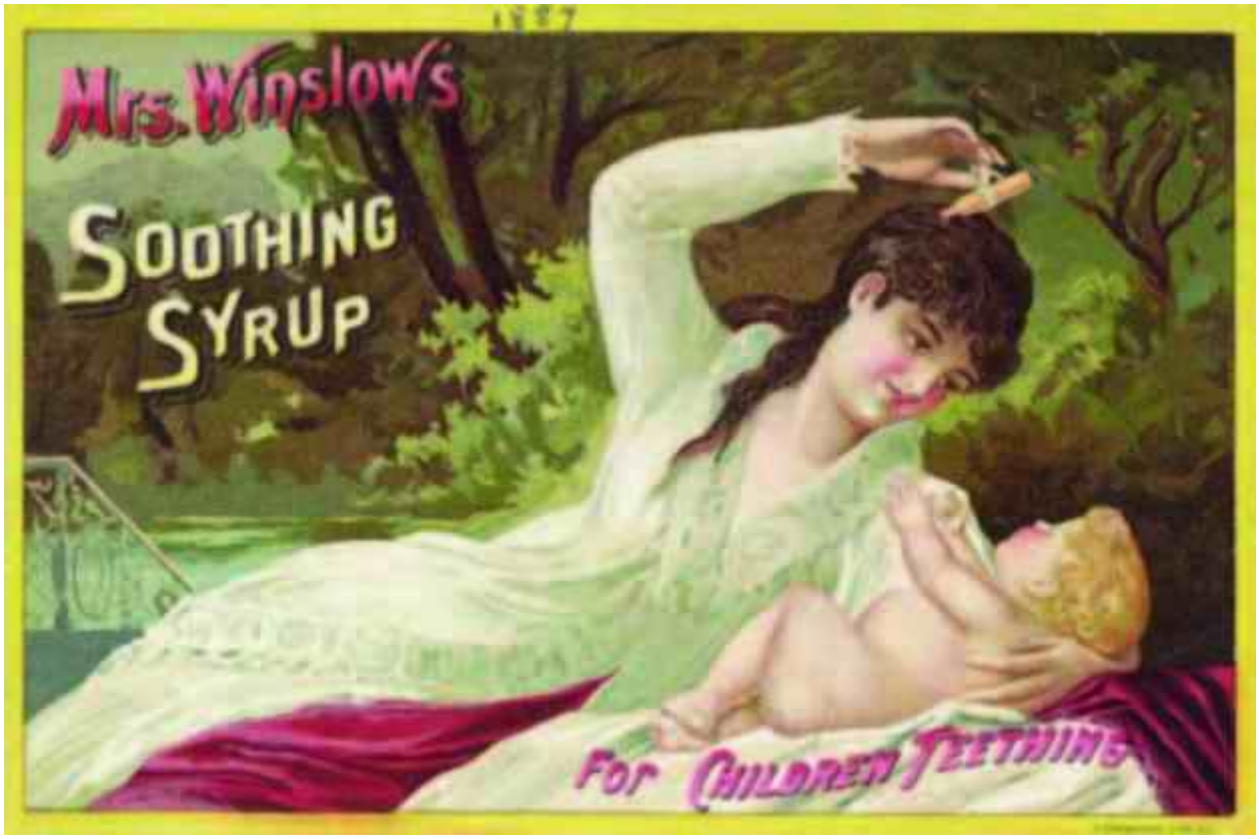
Symptoms of intoxication occur three to four hours after ingestion and may take 24 hours to resolve. Pupillary dilatation, increased pulse and blood pressure, and increased temperature may

be present. 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 for this particular case are shown in Table 4.3.2.4.1. Another case reported from Germany described two men who took what they thought was LSD; it was not, and in one the serum DOB concentration was 13 ng/mL, while the other, who died, had a concentration of 19 ng/mL (Balíková, 2005).

Karch then goes on to describe DOB in more detail. Information in Chapter 5 (Opiates and Opioids) is quite interesting. Here is what Karch has to say on Heroin (page 376 onwards)...

5.4.4 Synthesis of Heroin

Figure 5.4.4.1 "Mrs. Winslows Soothing Syrup for Children Teething." This product was popular before the passage of the Food and Drug Act of 1906. Infants cutting teeth generally are irritable, but not after a dose of morphine. It was also said to be very good for treating colic. (This figure appears on page 376 of this book. Please Click to enlarge)



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 quickly became obvious. 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 5.3.1.1).

Bayer had been in the business of making pharmaceuticals since 1889, but not exactly making great sums of money. The situation changed almost overnight when they began to supply the really profitable market for alkaloids (morphine, quinine, cocaine). Previously this market been dominated by other, larger 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 (in fact, codeine only has any activity as a pain reliever because it is metabolized to morphine, a heroin breakdown product). Based mainly on Strube's observations, Bayer began production, marketing heroin as a safer, more potent, cough suppressant (Figure 5.4.4.1) (deRidder, 1994).

Further down in this chapter, Karch goes on to explain medical consequences of opiate about beautifully (page 499 onwards)...

5.10.1.2 Atrophic Scarring

Figure 5.10.1.2.1 "Skin popping." When an addict has thrombosed all accessible veins they often resort to injecting under the skin. This may introduce infectious agents and form an indolent ulcer. (This figure appears on page 499 of this book. Please Click to enlarge)



Subcutaneous injection is a fairly common practice, especially among novice users, or chronic users with difficult venous access. The flexor aspect of the arm is the preferred site for injection, followed by the anterior thigh. Absorption of heroin is good by this route, but the deposition of excipients in the subcutaneous tissue eventually leads to the development of oval or irregularly shaped lesions measuring 1-3 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. Alternatively, they may become confluent (see Figure 5.10.1.2.1).

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 the lesions were 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 with the aid of nothing more complex than a polarizing filter (Hirsch, 1972).

5.10.1.4 "Track" Marks

This lesion was first described in 1929. It occurred in a heroin addict who had contracted malaria from intravenous injections (Biggam, 1929). Lesions were said to resemble railroad tracks because they were linear, indurated, and hyperpigmented. What the lesions actually look like, and how rapidly they form depends on the substances being injected. The excipients found in illicit cocaine and methamphetamine are usually water soluble, so "track" marks are a less common finding in this group of abusers (Wetli et al., 1972). Paregoric, which is also injected by desperate heroin users, causes an intense sclerotic reaction. When paregoric injecting was popular in the 1960s, addicts quickly ran out of peripheral veins and were forced to inject themselves in the neck and groin (Lerner and Oerther, 1966). Heroin, even in its adulterated form, is less toxic to veins than paregoric, but prolonged use will eventually cause thickening and sclerosis of the subcutaneous veins, if only because impure heroin is being injected.

Figure 5.10.1.4.1 "Track" marks are the result of repeated injection with heroin that is contaminated with substances that irritate the veins. Microscopic examination will show birefringent crystals of the diluent and localized inflammation. (This figure appears on page 501 of this book. Please Click to enlarge)



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. Injection drug users 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, 1992).

The histology of sclerotic veins is variable (Schoster and Lewis, 1968). Only fibrous thickening of the vein wall may be evident, suggesting a low-grade, chronic inflammatory process. In other instances, thrombophlebitis, sterile or septic, may occur. The results are difficult to predict, and Halpern 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" (Halpern, 1972).

The book gives a host of similar information on virtually all known drugs of abuse. We are sure our readers would enjoy the book as much as we at the journal office did.

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