

National Institute on Drug Abuse

RESEARCH

MONOGRAPH SERIES

Methamphetamine

Abuse:

Epidemiologic

Issues and

Implications

115



Methamphetamine Abuse: Epidemiologic Issues and Implications

Editors:

Marissa A. Miller, D.V.M., M.P.H.

Nicholas J. Kozel, M.S.

Research Monograph 115
1991

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

National Institute on Drug Abuse
5600 Fishers Lane
Rockville, MD 20857

ACKNOWLEDGMENT

This monograph is based on the papers and discussion from a technical review on "Methamphetamine Abuse: Epidemiologic Issues and Implications" held on August 28-29, 1990, in Bethesda, MD. The review meeting was sponsored by the National Institute on Drug Abuse.

COPYRIGHT STATUS

The National Institute on Drug Abuse has obtained permission from the copyright holders to reproduce certain previously published material as noted in the text. Further reproduction of this copyrighted material is permitted only as part of a reprinting of the entire publication or chapter. For any other use, the copyright holder's permission is required. All other material in this volume except quoted passages from copyrighted sources is in the public domain and may be used or reproduced without permission from the Institute or the authors. Citation of the source is appreciated.

Opinions expressed in this volume are those of the authors and do not necessarily reflect the opinions or official policy of the National Institute on Drug Abuse or any other part of the U.S. Department of Health and Human Services.

The U.S. Government does not endorse or favor any specific commercial product or company. Trade, proprietary, or company names appearing in this publication are used only because they are considered essential in the context of the studies reported herein,

NIDA Research Monographs are indexed in the *Index Medicus*. They are selectively included in the coverage of *American Statistics Index*, *BioSciences Information Service*, *Chemical Abstracts*, *Current Contents*, *Psychological Abstracts*, and *Psychopharmacology Abstracts*.

DHHS publication number (ADM)91-1836
Printed 1991

Contents

	Page
Introduction and Overview	1
<i>Marissa A. Miller and Nicholas J. Kozel</i>	
Pyrolytic Characteristics, Pharmacokinetics, and Bioavailability of Smoked Heroin, Cocaine, Phencyclidine, and Methamphetamine	6
<i>C. Edgar Cook</i>	
Neurotoxicity of Methamphetamine: Mechanisms of Action and Issues Related to Aging	24
<i>Lewis S. Seiden</i>	
The Environmental Impact and Adverse Health Effects of the Clandestine Manufacture of Methamphetamine	33
<i>Gary D. Irvine and Ling Chin</i>	
Heavy Metal and Organic Contaminants Associated With Illicit Methamphetamine Production	47
<i>Brent T. Burton</i>	
Methamphetamine Abuse in California	60
<i>Bruce Heischober and Marissa A. Miller</i>	
Trends and Patterns of Methamphetamine Smoking in Hawaii	72
<i>Marissa A. Miller</i>	

Methamphetamine Abuse in Japan 84
Hiroshi Suwaki

Trends and Patterns of Methamphetamine Abuse in the
Republic of Korea 99
Byung In Cho

Community Networks for Response to Abuse Outbreaks
of Methamphetamine and Its Analogs 109
James N. Hall and Pauline M. Broderick

List of NIDA Research Monographs 121

Introduction and Overview

Marissa A. Miller and Nicholas J. Kozel

The category of drugs known as stimulants has been used and abused for centuries. Within this general category, abuse of amphetamine and methamphetamine can be traced to the time that they first appeared on the licit market during the 1930s. The international nature of abuse of these substances was chronicled during the Second World War. There is evidence that shows epidemic patterns of methamphetamine abuse in several Asian countries. A resurgence in methamphetamine abuse in the United States also has been documented during the 1980s. The National Institute on Drug Abuse (NIDA) has been monitoring this resurgence of methamphetamine abuse through its surveillance mechanisms and systems.

A convergence of information from the Drug Abuse Warning Network, a drug abuse morbidity and mortality surveillance system reflecting an increasing trend in deaths and nonfatal emergency department episodes related to methamphetamine use, and from the Community Epidemiology Work Group (CEWG) members, a network of State and local drug abuse experts representing 20 cities and metropolitan areas across the United States, indicated that methamphetamine use was on the rise during the 1980s in several U.S. cities. This information prompted NIDA to sponsor a field study in 1988 that added further evidence that methamphetamine abuse was becoming increasingly problematic. In December 1988 methamphetamine smoking was identified as an emerging problem in Hawaii, and NIDA was requested to assist the State of Hawaii Department of Health in investigating and characterizing the nature and extent of the problem.

While these studies were being initiated, it also became apparent that little was known about methamphetamine as a drug of abuse or the implications and consequences from the relatively new route of administration by smoking. To understand more fully the contributing factors to the reemergence of methamphetamine, a technical review was held by NIDA on August 28 and 29, 1990. Trends of drug abuse are influenced by many factors, including physical and biochemical properties of the drug and its neuropharmacologic effects, characteristics of the abusing population and other epidemiologic influences,

and broader factors related to drug manufacturing, marketing, and distribution throughout the world. This monograph attempts to address many of these issues, to describe patterns and trends of the recent resurgence of methamphetamine abuse, and to provide an overview of contributing factors and consequences of that abuse.

C. Edgar Cook's chapter discusses the bioavailability and pharmacokinetics of smoked drugs, revealing that smoking methamphetamine is a highly efficient route of administration. Methamphetamine hydrochloride is readily volatilized and recovered at temperatures compatible with the common methods of smoking. The method of smoking "ice" in a glass pipe was shown to be an efficient smoking delivery system. Smoking results in rapid onset of effect, similar to intravenous use, with large amounts of drug delivered to the brain. The rapid and intense psychoactive effect is desirable to users and serves to reinforce use. This, combined with a long plateau effect and relatively lengthy half-life, suggests serious health consequences, including addiction, to repetitive smoking of methamphetamine.

Lewis S. Seiden's chapter presents evidence that methamphetamine causes damage to dopamine- and serotonin-containing neurons in the brain. This damage occurs in several species of animals, is long-lasting, and is probably irreversible. These methamphetamine-related effects may have implications related to loss of dopamine neurons during the human aging process. Methamphetamine abuse, especially at high levels, may accelerate this aging with subsequent physiologic and pathologic consequences. Seiden points out that more research is needed to explain further the neurotoxicity and delayed consequences of methamphetamine abuse.

Violence as a consequence of methamphetamine abuse was discussed at the technical review by Everett H. Ellinwood. Chronic, moderate- to high-dose methamphetamine abuse often results in assaultive behavior and other forms of violent action. The interaction of methamphetamine's behavioral and psychological effects, including hyperactivity, agitation, lability of emotion, and paranoid delusional thinking, combined with personality factors and the social context, contribute to the occurrence of violence.

Factors contributing to drug abuse related to drug manufacture, distribution, and marketing were discussed at the technical review by Joan Zolac of the Drug Enforcement Administration. In the unique case of ice, production was traced to Korea, Taiwan, and the Philippines, and importation and marketing was traced to organized criminal groups. These factors have combined with others to result in a sharp increase in availability and use in Hawaii during the late 1980s.

Domestic laboratories have replicated the process for synthesizing ice, although only a limited number of ice laboratory seizures have occurred. An indicator of methamphetamine abuse domestically is the number of methamphetamine laboratory seizures that have increased dramatically throughout the 1980s most of them in California, Texas, and Oregon,

Gary D. Irvine and Ling Chin's chapter discusses the environmental impact and adverse health effects related to the sharp increase in domestic methamphetamine laboratories. The illicit manufacture of methamphetamine is a relatively simple chemical process. However, illicit producers may not possess the knowledge or the skill to carry out the synthesis properly. Many of the precursor chemicals are corrosive, irritating, and flammable; the process can result in explosions and toxic fumes; and the final product can be contaminated with metals, unreacted precursors, and unintended by-products—all presenting medical and public health concerns. Special consideration must be given to the environmental cleanup of the methamphetamine laboratory sites and to the protection of exposed populations during this process.

Brent T. Burton's chapter discusses health consequences resulting from illicitly produced methamphetamine contaminated with reagents, solvents, and unintended reaction by-products. Two case reports of human toxicity due to lead contamination of methamphetamine are presented from the scientific literature, as are the problems involved in documenting the extent of contaminant-induced illness from methamphetamine.

The trends, patterns, and characteristics of current methamphetamine abuse in California are discussed by Bruce Heischober and Marissa A. Miller in their chapter. Methamphetamine abuse on the U.S. mainland is primarily a west coast phenomenon, and methamphetamine abuse in California is influenced geographically and is location specific, occurring predominantly in the San Diego and San Francisco areas. Increases in methamphetamine abuse have been reported in adolescent, minority, and gay populations, with increasing numbers of abusers entering treatment and experiencing traumatic consequences.

Findings from the NIDA outbreak investigation and followup field study into ice smoking in Hawaii are presented in the chapter by Marissa A. Miller. The retrospective analysis of treatment records revealed ice smoking to have a lengthy history among certain ethnic groups; however, the widespread smoking of ice is a recent trend cutting across racial and ethnic lines. The study revealed a peak of first use in 1988, resulting in clients entering treatment 1 to 2 years later. These data suggest a decreasing trend in 1990 of users entering treatment, and more current information obtained from Hawaiian treatment

facilities confirms this trend. Adverse health and social consequences and risk factors related to the smoking of ice also are presented.

A perspective on the international character of methamphetamine abuse is provided by two chapters, Hiroshi Suwaki's chapter describes Japan's second epidemic of methamphetamine abuse, which differs significantly from the first. The first occurred during the post-World War II (1945-1956) era largely as a result of wartime use and the postwar release of large pharmaceutical stockpiles of methamphetamine to the general public. With the passage of the Stimulants Control Law (1951) and a vigorous enforcement policy combined with information and education campaigns, the abuse of methamphetamine abated. However, a different situation exists today. Control efforts have been unable to significantly decrease methamphetamine abuse, which has plateaued at a high level.

The chapter by Byung In Cho chronicles Korean association with the methamphetamine trade and market since the Second World War and factors influencing the growth of that association, including changes in laws and regulations such as the stiffening of drug control policies in Japan. Indicators of methamphetamine abuse in the Republic of Korea showed increases throughout the 1980s but appeared to be decreasing in 1989. This decrease appeared to be the result of a nationwide drug control strategy, including increased law enforcement activities directed at abusers and suppliers and increased seizures of raw materials and final product, in Korea methamphetamine is abused primarily by males through multiple daily intravenous injections. Abuse has been noted throughout Korea but is localized primarily in and around the city of Pusan.

The final chapter by James N. Hall and Pauline M. Broderick presents community networks as a response to outbreaks of methamphetamine abuse and abuse of related analog drugs. Due to the localized nature of the methamphetamine problem in the United States, community-based strategies are appropriate and effective in assessing and addressing this type of drug problem. Community networks utilize a multidisciplinary approach and facilitate and enhance cooperation and coordination of strategy among participating organizations. Networks are essential as a method to gather drug abuse data, to monitor existing data systems, and to identify specific needs such as treatment, prevention, or public policy redirection. Community networks frequently are sensitive to changes in drug usage and may detect the emergence of a new drug or drug abuse trend. This drug surveillance function of networks is demonstrated by the CEWG, which detected the reemergence of methamphetamine as cited at the beginning of this chapter.

We are grateful to the participants and authors for their valuable contribution to the technical review meeting and to this monograph. It is our hope that this monograph will serve to inform public health officials, clinicians, epidemiologists, and researchers concerning some of the basic issues of methamphetamine abuse. We anticipate that this monograph will stimulate further directed research into the mechanism, consequences, and patterns of methamphetamine use and abuse.

AUTHORS

Marissa A. Miller, D.V.M., M.P.H.
Epidemiologist

Nicholas J. Kozel, M.S.
Chief

Epidemiology Studies and Surveillance Branch
Division of Epidemiology and Prevention Research
National Institute on Drug Abuse
Rockwall II, Room 815
5600 Fishers Lane
Rockville, MD 20857

Pyrolytic Characteristics, Pharmacokinetics, and Bioavailability of Smoked Heroin, Cocaine, Phencyclidine, and Methamphetamine

C. Edgar Cook

INTRODUCTION

Smoke from plant material containing psychoactive drugs has long been used as a means of self-administration. This route of administration is simple (one merely burns the plant material). It is also highly effective; the major route of blood circulation through the lungs and heart to the brain results in rapid delivery of inhaled substances to the central nervous system. The volatilization of the material can be assisted by codistillation or steam distillation as air is drawn through the burning plant material.

In 450 B.C., Herodotus (translated 1942) described the inhalation of smoke from marijuana by the Scythians. Tobacco was being smoked by the American Indians well before the arrival of the Europeans (Corti 1932), and opium has been smoked for centuries in the Middle and Far East (Masood 1979; Meyers et al. 1972). Δ^9 -Tetrahydrocannabinol (Δ^9 -THC) from marijuana, nicotine from tobacco, and morphine—the major psychoactive component of opium—have volatility properties that facilitate the smoking method of administration. In view of these precedents, it is not surprising that as newer psychoactive drugs were found, attempts were made to smoke these drugs also, either alone or in a mixture with such plant material as tobacco, marijuana, and herbs.

Smoking drugs presents added hazards to the drug user. Since the rate of chemical reactions generally increases with temperature, a variety of new compounds can be produced as a result of smoking. The drug can undergo unimolecular fragmentations. It can react with itself or with other constituents of the smoked mixture in a bimolecular fashion. The combination of oxygen and heat can be expected to lead to oxidized products. The chemical reactivity of the compound, the temperature of smoking and of volatilization, and the

presence of coreactants all can have a significant influence on the product mixture that is inhaled. Thus, there is considerable potential for formation and inhalation of toxic substances. Smoking gives a rapid onset of effect of the drug, comparable in many ways to that from intravenous (IV) administration. The rapid reinforcement also enhances the addicting power of the drug. In combination with the now well-advertised health hazards of IV injection of drugs (particularly human immunodeficiency virus infection), these factors are likely to lead to a further increase in smoking as a route of administration.

Within the past few years, considerable information has been accumulated regarding pyrolysis and smoking of various drugs of abuse (Cook and Jeffcoat 1990). This chapter summarizes work with four of these drugs-heroin, cocaine, phencyclidine, and methamphetamine-and attempts to compare and contrast their pyrolytic properties and the factors that affect their bioavailability.

HEROIN

Around the beginning of this century, heroin was introduced into China and began to replace opium as a narcotic. Since opium generally was smoked, it was natural that heroin was used in the same way (Huizer 1987). The earliest scientific study of the bioavailability of heroin by this route was reported in 1937 (Ito 1937). Mo and Way (1968) found that 14 percent of the dose of heroin smoked on cigarettes could be recovered in urine as morphine (conjugated and free), whereas a 25-percent morphine recovery was achieved in urine for "dragon chasing" (inhaling the vapors of heroin heated on foil). Compared with the recovery of 68 percent of an IV dose of heroin as morphine, this would give bioavailabilities of 21 percent for smoking on cigarettes and 37 percent for dragon chasing.

Significant amounts of the drug are decomposed on heating. Cook and Brine (1985) studied the pyrolysis products of both heroin and heroin hydrochloride by a combination of proton and 13-carbon nuclear magnetic resonance, mass spectrometry, and comparison with authentic materials. They identified heroin and three major pyrolysis products in the 250°C pyrolysate of heroin hydrochloride. The products were 6-O-acetylmorphine, N,6-O-diacetylnormorphine, and N,3-O,6-O-triacetylnormorphine. In addition, a minor component was suggested to be 3,4-diacetoxypheanthrene on the basis of high-resolution mass spectrometric analysis. Formation of this compound illustrates the extensive breakdown that can occur under pyrolytic conditions. HPLC analysis showed many other ultraviolet-absorbing peaks present in minor amounts, some of which were tentatively identified (figure 1) (Cook and Jeffcoat 1990). Similar pyrolysis products were apparently present upon pyrolysis of heroin.

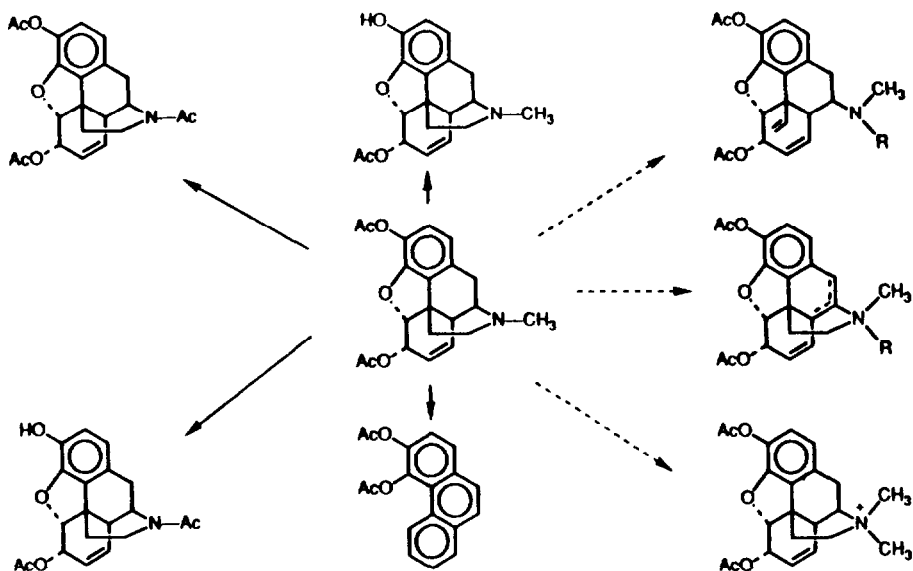


FIGURE 1. *Pyrolytic products of heroin*

NOTE: Solid arrows lead to identified products; broken arrows lead to other tentative products.

Huizer (1987) followed this work by studying the volatilization of heroin under a variety of conditions, particularly in the presence of various diluents often used in the smoking process. A common means of smoking heroin is by dragon chasing. Heroin for smoking often is diluted with a barbiturate or caffeine and sometimes small amounts of strychnine.

When heroin hydrochloride was heated on aluminum foil (Huizer 1987) the aforementioned major products reported by Cook and Brine (1985) were found in the residue. The amounts of these products increased with increasing temperature. Heroin base gave smaller amounts of pyrolysis products, with 6-O-acetylmorphine predominating. Caffeine enhanced the volatilization and changed the ratio of products to favor 6-O-acetylmorphine. Thus, caffeine has a very strong positive effect on the volatilization of heroin hydrochloride, as does barbital (Mo and Way 1966), whereas ascorbic acid markedly reduced the amount of the drug in the smoke. Recoveries of heroin in the fumes from heating on aluminum foil ranged from nearly 80 percent for the freebase mixed with caffeine to about 1 percent when ascorbic acid was used as the diluent (Huizer 1987). Thus, the amount of heroin inhaled by smoking is strongly

dependent on the presence of diluents, and these also may influence the ratio of pyrolysis products obtained.

COCAINE

In the case of basic compounds that are heated as their acid salts, pyrolytic degradation may be facilitated by hydrogen ion catalysis. Furthermore, the generally higher melting point and lower volatility of the hydrochloride salts also favor pyrolytic breakdown and reduce the amount of drug available for inhalation. Both these factors are probably operative in the case of cocaine. The freebase melts at 98°C is volatile above 90°C, and boils at 187-188°C and 0.1 mm pressure. In contrast, cocaine hydrochloride melts at around 195°C (Windholz et al. 1983). Studies in the author's laboratory have shown that only 1 percent of the cocaine can be recovered after heating cocaine hydrochloride to 800°C, whereas 16 percent of the freebase is recovered at that high temperature. When cocaine freebase was heated in a glass pipe at 265°C under simulated smoking conditions, about 44 percent of the drug was recovered in the smoke (Perez-Reyes et al. 1982; Jeffcoat et al. 1989).

When the freebase was smoked in a tobacco cigarette, only 6 percent of the cocaine could be recovered in the smoke. It appears that the cocaine interacts with constituents in the plant material to reduce the amount that can be obtained on smoking. The concentration of cocaine in coca leaves is relatively low as well—Rivier (1981) indicates less than 1 percent of dry weight in cocaine. Thus, in contrast to marijuana and Δ^9 -THC, smoking coca leaves has not been used as a method of cocaine administration (Carroll 1982). It was not until drug users and suppliers began to convert cocaine hydrochloride to the neutral form (either freebase or, more recently, "crack" cocaine) that the popularity of smoked cocaine began to grow.

A variety of reaction pathways are available to cocaine upon pyrolysis (figure 2), and the products obtained appear to depend strongly on the precise conditions used. In experiments in which cocaine was pyrolyzed in the presence of a stream of air that swept the volatile pyrolysis products into a collection trap, the formation of methyl ecgonidine and two isomers was observed. These compounds could be separated by capillary gas chromatography but had essentially identical mass spectra. These products could result from benzoic acid elimination followed by isomerization of the double bond to the β - δ position as well as internal ring opening (Cook et al. 1985; Cook and Jeffcoat 1990). Four other components with similar retention times and mass spectra appeared to be double-bond isomers of methyl cycloheptatrienecarboxylate. The presence of these materials can be explained by further internal eliminations leading eventually to loss of methylamine from the tropane structure. Benzoic

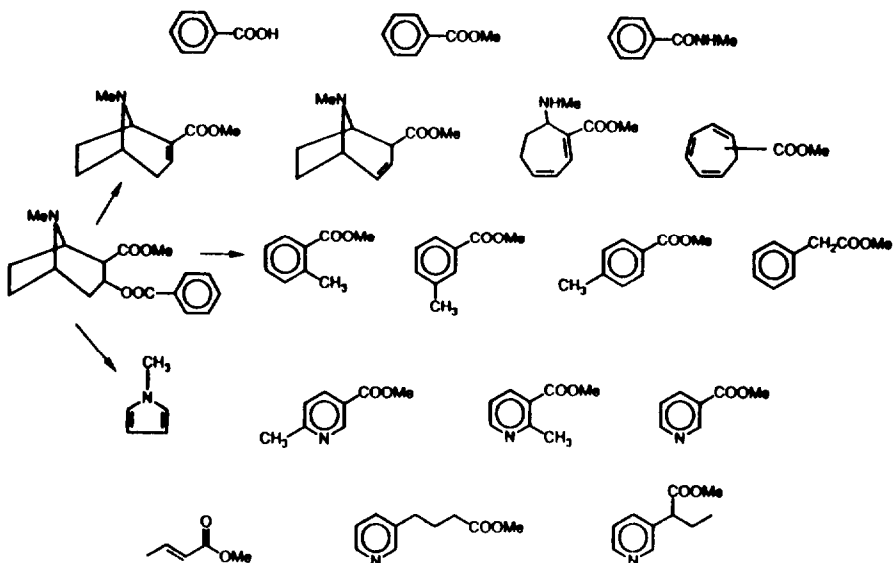


FIGURE 2. *Reported pyrolysis products of cocaine*

acid also was observed as well as methyl benzoate and N-methylbenzamide. All these products are chemically reasonable, and straightforward mechanisms can be drawn to explain their occurrence.

Novak and Salemink (1989) heated cocaine at 600°C in a nitrogen atmosphere and identified 15 products. They found only a trace of amethylcycloheptatriene-carboxylate but identified three isomeric methyl toluate compounds as well as methyl phenyl acetate, all of which were suggested to arise via a methyl cycloheptatrienecarboxylate intermediate. Under these conditions, a major pyrolysis product (7 percent of total) was methyl-4-(3-pyridyl)butanoate. This compound and an isomer were suggested to be derived by a combination of elimination, rearrangement, and aromatization. Methyl nicotinate and its 2- and 6-methyl homologs also were observed and were presumably the result of a combination of elimination, N-demethylation, and aromatization. At 400°C under these conditions, cocaine essentially was unchanged, with only methyl ecgonidine identified as a pyrolytic product.

Sisti and Fowler (1989) subjected cocaine to flash vacuum thermolysis in an oven at 500 to 550°C. The conditions used were such as to favor unimolecular reactions. They observed the formation of N-methylpyrrole and

methyl 3-butenolate in addition to benzoic acid. Martin and colleagues (1989) vaporized cocaine in a glass pipe heated in a furnace at 260°C in a stream of air and recovered benzoic acid and methyl ecgonidine as the major decomposition products.

For studies in which pure cocaine is delivered by inhalation, Hatsukami and colleagues (1990) have reported the use of a device in which the drug is deposited on a wire (Nichrome). The wire is heated electrically, and the heating mechanism is activated when the subject begins to inhale. Excellent reproducibility of delivery is reported by use of this device.

A smoked drug may be delivered to the lungs as a true vapor or as an aerosol. In the case of an aerosol, particle size is important for efficient delivery to the alveolar region, with 3 µm particles having the greatest alveolar deposition from mouth breathing (Hinds 1982). Recently, Snyder and colleagues (1988) reported that smoking crack cocaine in a pipe resulted in only 6 percent vapor, with 94 percent of the drug being delivered as particles with an average size of 2.3 µm.

All the factors involved make the bioavailability of smoked cocaine quite variable. In a study in which cocaine was smoked by human subjects, the calculated bioavailability based only on the amount of material inhaled (which was about 80 percent of the amount of drug placed in the pipe) ranged from 32 to 77 percent, with an average of 57 percent. Since simulated smoking studies indicated that an average of 56 percent of the drug was decomposed under these conditions, the true bioavailability of the cocaine that reached the body is probably nearly 100 percent. Smoked cocaine results in rapidly attained peak plasma levels (average 6 minutes after beginning smoking). Apparent terminal elimination rates of cocaine after smoking (58 minutes) were similar to those after IV (78 minutes) or intranasal (80 minutes) administration (Jeffcoat et al. 1989).

PHENCYCLIDINE

The thermal elimination of an amine to yield an olefin appears to be a particularly facile reaction in the case of phencyclidine (PCP), yielding as initial products (figure 3) 1-phenylcyclohexene (Freeman and Martin 1981; Cook et al. 1961) and piperidine (Cook et al. 1981). The hydrochloride of PCP is 95 percent decomposed on heating at 300°C for 5 minutes (Cook et al. 1981). However, simulated smoking studies with the hydrochloride on parsley cigarettes in conjunction with human smoking studies showed that, on a molar basis, 39 percent of the PCP was in the mainstream smoke together with 30 percent of phenylcyclohexene. Fifteen percent of the material remained in the butt, and 16 percent was lost in sidestream smoke (Cook et al. 1983).

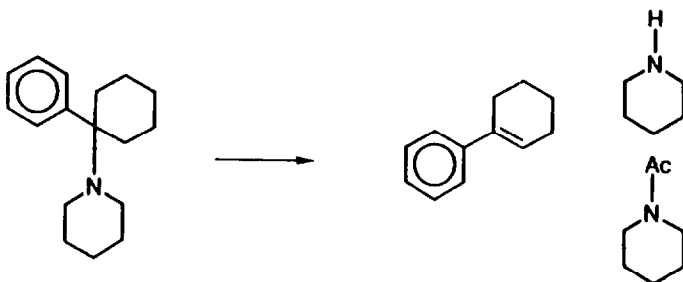


FIGURE 3. *Products of phencyclidine from pyrolysis and smoking on marijuana cigarettes*

In another simulated smoking study involving PCP on marijuana cigarettes, 1-phenylcyclohexene (47 percent), PCP (40 percent), piperidine (15 percent), and N-acetylpiperidine (9 percent) were found in trapped mainstream smoke (Lue et al. 1986). Thus, the piperidine formed undergoes reaction with other constituents of the plant material. Under stringent pyrolysis conditions, PCP can yield a variety of aromatic and polynuclear aromatic compounds (Beaver and Jones 1984), but these were not found in the simulated smoking studies.

As with cocaine, the bioavailability of smoked PCP is not easy to determine precisely but has been estimated by Cook and colleagues (1982a) to be about 100 percent, if based on the PCP inhaled. The terminal elimination rate for PCP when it was smoked (24 hr) was similar to that observed when it was taken orally (27 hr) or intravenously (16 hr) (Cook et al. 1982b).

METHAMPHETAMINE

One would expect, based on their relative molecular weights, the volatility of methamphetamine to be similar to that of nicotine and considerably greater than that of PCP. Also, as a secondary amine, methamphetamine should be less likely than PCP to undergo thermal elimination to an olefin. It is not surprising then to find that, when methamphetamine is placed in a pyrolysis tube that then is put into a heated furnace, the methamphetamine volatilizes, and at temperatures of 200 to 400°C more than 98 percent of it can be recovered intact. Recovery falls to 88 percent at 600°C and 62 percent at 800°C. At these temperatures, small amounts of amphetamine (0.7 and 1.5 percent) are formed (K.H. Davis, personal communication, July 1990).

Hydrochloride salts of simple amines are also volatile, and 91 percent of methamphetamine hydrochloride is recovered unchanged after volatilization at

300°C in a tube furnace (compared with 5 percent of PCP hydrochloride). Recovery from the hydrochloride drops to 81 percent at 400°C, 62 percent at 600°C, and 38 percent at 800°C. The salt form is more subject to N-dealkylation due to the presence of a protonated nitrogen and a chloride nucleophile, so that even at 400°, 5 percent of amphetamine is formed by N-demethylation (10 percent at 600°C and 9 percent at 800°C) (K.H. Davis, personal communication, July 1990). Significant amounts of at least four other pyrolysis products were observed but not identified.

The availability of methamphetamine is much reduced by smoking it in a mixture with tobacco. Thus, Sekine and Nakahara (1987) found that from 6 to 17 percent (depending on amount and smoking conditions) of the methamphetamine hydrochloride added to tobacco was recovered from the mainstream smoke of cigarettes. This was confirmed by Davis and colleagues (personal communication, July 1990) who recovered 4.7 ± 1.1 (SD) percent of added methamphetamine hydrochloride in mainstream smoke when cigarettes were smoked in the puff mode and 12.7 ± 2.9 percent when a constant draft mode of smoking was used. Results were essentially the same in the latter study when the freebase was used (4.8 ± 0.6 percent/puff mode and 15.6 ± 1.3 percent/draft mode), again in confirmation of the report of Sekine and Nakahara (1987).

Seven significant pyrolysis products (figure 4) were rigorously identified in the tar from methamphetamine/tobacco cigarettes—amphetamine, phenylacetone, dimethylamphetamine, and N-formyl, N-acetyl, N-propionyl, and N-cyanomethyl methamphetamine (Sekine and Nakahara 1987), with the N-cyanomethyl compound predominating. In a later study, phenylacetone was the predominant product, and trans- β -methylstyrene also was found. It was shown that formation of the N-cyanomethyl compound required both heat and air and that other amines formed N-cyanomethyl products when smoked with tobacco (Sekine and Nakahara 1990).

The hydrochloride salt of S-(+)-methamphetamine is the form that is smoked as “ice” (Cho 1990). Reports from Hawaii indicate a common method of administration of “ice” is to smoke it in a glass pipe. Interest in studying this phenomenon led to the initiation of human studies using this material smoked in a glass pipe (Cook et al. 1991; Perez-Reyes et al. 1991).

Six informed, healthy, male, paid volunteers familiar with the use of amphetamines were the subjects. Cardiovascular effects of the drug were monitored during the experiment. Heart rate and blood pressure were measured. Other cardiovascular parameters were measured by computer-averaged impedance cardiogram. The subjects gave a subjective rating of drug

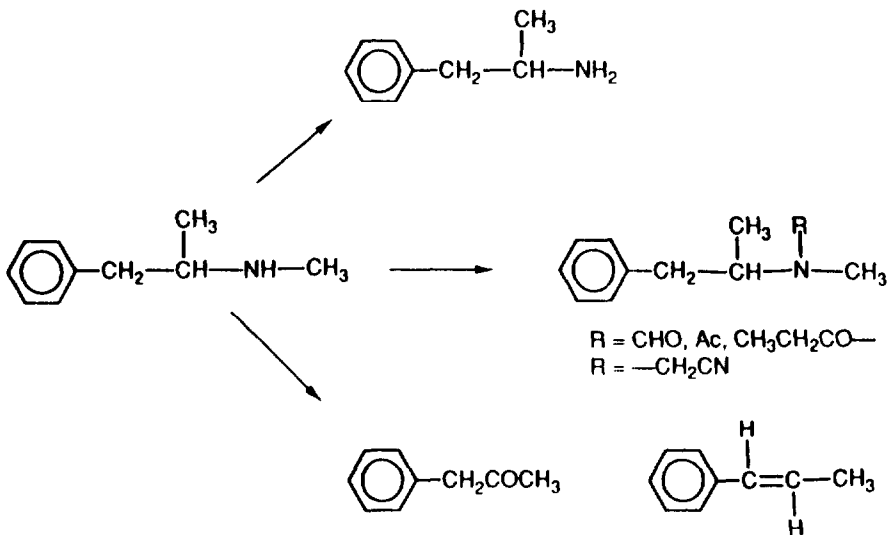


FIGURE 4. *Products of methamphetamine hydrochloride from pyrolysis and smoking on tobacco cigarettes*

effect during the study on a scale of 0-100, with 100 representing the most affected they had ever been after taking amphetamines (Perez-Reyes et al. 1991).

Smethamphetamine hydrochloride was placed in a glass pipe. The pipe was inserted in a heated aluminum block, and the subjects inhaled the vapor at 1-minute intervals for approximately 4 minutes (Perez-Reyes et al. 1991), Plasma samples were collected at intervals and analyzed for methamphetamine and amphetamine by the procedure shown in figure 5.

Preliminary experiments with the glass pipe were carried out by partially immersing it in a silicone oil bath, making use of a large-volume syringe to simulate the smoker's lungs and pulling the vapors through a series of acid traps. When methamphetamine hydrochloride was placed in the pipe and the pipe was lowered into an oil bath at 268°C, roughly 9 to 11 mg of the methamphetamine hydrochloride was recovered from the pipe, with the balance being drawn into the traps. The residue remaining in the pipe appeared to be more a function of the area of cooler surface on which it can condense than of the absolute amount placed in the pipe and remained relatively constant with increasing doses placed in the pipe.

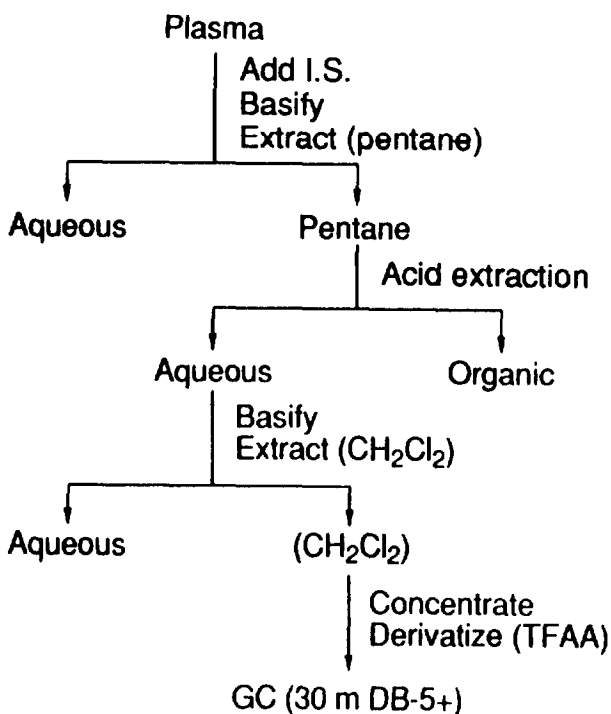


FIGURE 5. Analytical procedure for methamphetamine and amphetamine in plasma

For human experiments, the pipe was inserted into an aluminum block heated to 302-308°C on a hot plate. Approximately 30-mg doses of methamphetamine hydrochloride were placed in the pipe. Analysis of pipe residue showed that an average of 7.8±1.0 (SD) mg of methamphetamine hydrochloride remained in the pipe and pipe stem after the experiments with the volunteers were complete. Thus, the apparent dose of the methamphetamine hydrochloride was approximately 20 to 21 mg, assuming that, as in the *in vitro* studies, little decomposition occurred during the smoking process.

In the analytical procedure (figure 5), methamphetamine recoveries through the extraction process were monitored by use of radiolabeled compounds and averaged 69 to 73 percent. The trifluoroacetamide derivatives were chromatographed on a DB-5 gas chromatography column. The standard curve was linear over a range of 1 to 225 ng of methamphetamine. Similar standard curves were obtained for 1 to 15 ng for amphetamine. Control samples showed

an average difference from nominal values of 3.5 to 6.4 percent, with a relative standard deviation of 1.9 to 4.5 percent at values from 5.4 to 8 ng/mL for methamphetamine. At 2 ng/mL, the values were 15 percent and 10 percent for methamphetamine and 10 percent and 4 percent for amphetamine.

Analysis of plasma samples from the subjects who smoked the methamphetamine hydrochloride gave the results shown in figure 6. Although the initial plasma concentrations of methamphetamine rose rapidly after the start of smoking, they did not decline rapidly. In fact, there was essentially a plateau over the first 3 to 4 hours of the experiment, after which plasma levels began to decline. It was therefore not possible to fit a standard one- or two-compartment pharmacokinetic model with an absorption phase to these data. However, by use of a noncompartmental approach, it was possible to determine an elimination half-life with an average value of 11.7 ± 3.3 (SD) hours and a range of 8 to 17 hours.

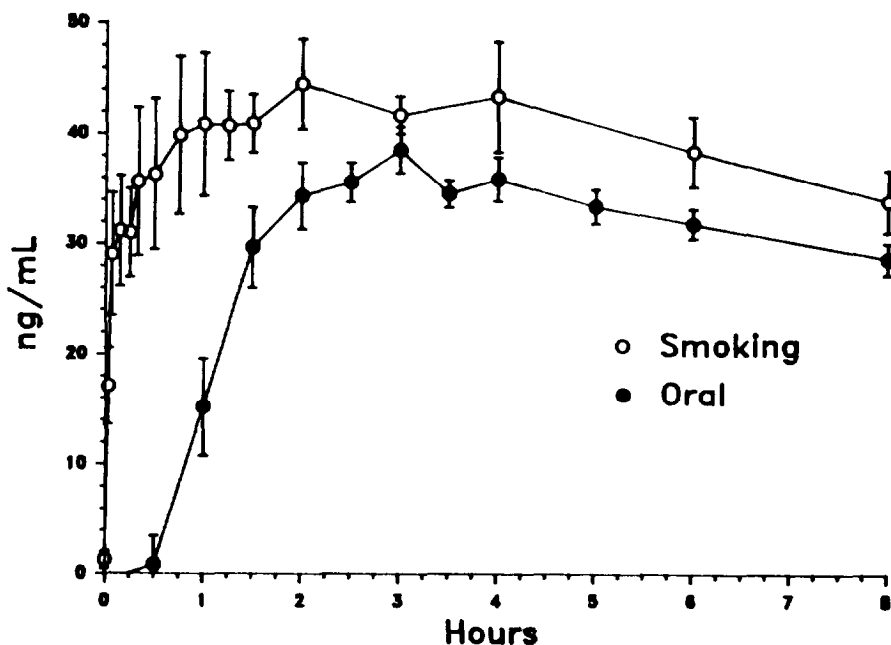


FIGURE 6. Comparison of plasma concentrations of methamphetamine after oral administration (●) and smoking (○). Only the time points through 8 hours are shown. The oral dose was 0.250 mg/kg, and the smoking dose was slightly higher (about 21 mg/subject). Means of six subjects \pm SEM are shown.

In another study (Cook et al. 1990), a 10-mg daily oral dose of a slow-release form of S-(+)-methamphetamine hydrochloride (Gradumet) was administered to volunteers over a 13-day period. On the day preceding and the day after this continuous dosage, oral S-(+)-d₃-methamphetamine hydrochloride was administered at doses of 0.125 mg/kg or 0.250 mg/kg. The deuterium label was present on the terminal methyl group of the compound, a position that does not appear to be involved with the primary metabolism of methamphetamine. The subjects again were monitored medically and psychologically. Urine, blood, and saliva were collected. Urine and saliva pH were measured but not controlled. Plasma, urine, and saliva were analyzed for the quantities of d₃- and d₀-methamphetamine and amphetamine present. Analysis was by gas chromatography and mass spectrometry of the pentafluorobenzoylchloride derivative, and internal standards were penta-deuteromethamphetamine and hexadeuteroamphetamine. Chromatography was carried out on a 30 m DB-1 column, and analysis was positive methane CI [M+H]⁺.

A one-compartment pharmacokinetic model with a first-order absorption phase could be fit to plasma concentrations of each subject at the high dose and five out of six subjects at the low dose by means of a computer curve-fitting program (SAS NLIN) (Cook et al. 1990). A better fit for all subjects was achieved by introducing a lag time into the model. Area under the plasma concentration time curve also was determined by a model independent method (trapezoidal rule). Maximum concentration and time to achieve it were determined from the model and from individual data points. Statistical comparisons were made to determine whether there were any significant differences before and after the 13-day daily treatment with methamphetamine hydrochloride or whether there was any evidence of differences between the two doses.

There was no evidence of dose-dependent pharmacokinetics when the 0.125 mg/kg and 0.250 mg/kg doses were compared for the various parameters. Comparisons between day 1 and day 15 indicated that the maximum concentration was slightly (about 14 percent) but significantly (paired t-test) greater on day 15 than on day 1. None of the other parameters measured showed any statistically significant differences. In view of this, the values of various parameters were averaged. Analysis of the data showed a lag time of approximately 30 minutes, an absorption half-life thereafter of 38 minutes, and a terminal elimination half-life of 10 hours (figure 7). The maximum concentration was reached at approximately 3 hours. The maximum plasma concentration averaged about 35 to 38 ng/mL after an oral dose of approximately 18 mg (0.250 mg/kg) (figure 6). This does not differ markedly from the plateau plasma concentrations of methamphetamine (40 to 44 ng/mL) after a 30-mg dose was smoked. In spite of this, the maximum subjective effects were quite modest (10 to 16 percent) when compared with the subjective effects of 38 percent for smoked methamphetamine (Perez-Reyes et al. 1991).

Parameter	Mean
Lag time	0.524 h
Absorption $t_{1/2}$	0.640 h
Elimination $t_{1/2}$	10.2 h
t_{max}	3.1 h
Cl_{ap}	496.0 mL/min
$C_{max}(0.125 \text{ mg/kg})$	20.2 ng/mL
$C_{max}(0.250 \text{ mg/kg})$	39.8 ng/mL

$$C = C_1 \cdot (e^{-k_{el}(t-lag)} - e^{-k_a(t-lag)})$$

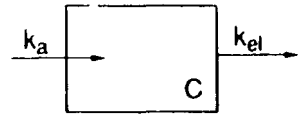


FIGURE 7. Average pharmacokinetic parameters for oral 1,1,1-trideuteromethyl-S-methamphetamine hydrochloride

NOTE: These average values do not show trends with dose or time. Cl_{ap} is the apparent clearance, assuming complete absorption of the dose.

Since the dose of methamphetamine inhaled was approximately 20 to 21 mg (analogous to the oral dose) and the maximum plasma concentrations were similar, the difference in subjective effects between the oral dose and the smoked dose may have to be explained on the basis of the rate of change in concentration (figure 8).

Figure 8 shows a comparison of plasma levels of cocaine after smoking cocaine freebase with those of methamphetamine after smoking methamphetamine hydrochloride. There is a strong contrast between the two drugs. Cocaine levels after smoking cocaine freebase rapidly peak and, with some minor deviations, also rapidly decline with a terminal half-life of about 56 minutes. As pointed out previously, the methamphetamine levels, although they rapidly approach peak concentrations, remain high for a considerable period before declining with a half-life of about 11 to 12 hours. A somewhat similar phenomenon, with a secondary maximum, also was observed in the inhalation of smoked PCP (Cook et al. 1982a).

One possible explanation for these differences is that the vaporization of methamphetamine hydrochloride physically presents a much different picture than that of cocaine freebase. In the case of cocaine freebase, relatively little visible condensation appears on the pipe, although a considerable amount of

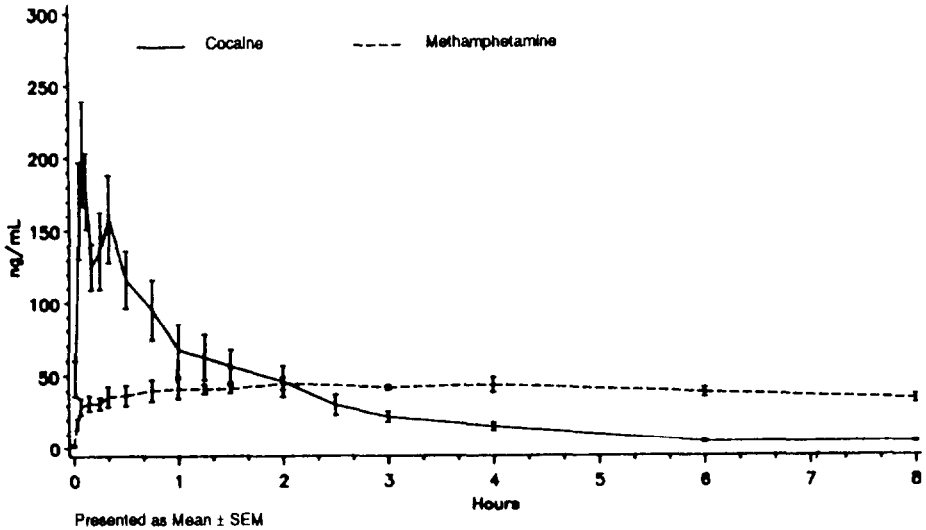


FIGURE 8. Comparison of plasma levels of methamphetamine and cocaine after smoking S-methamphetamine HCl or cocaine

NOTE: Data points from 8 to 48 hr are not shown.

the cocaine is lost by pyrolysis. On the other hand, although the methamphetamine hydrochloride was volatilized at temperatures only slightly above those for cocaine, it condensed readily to a crystalline solid on the cooler portions of the pipe. Similar condensation may be occurring in the mouth and throat of the subject who subsequently swallows or absorbs the methamphetamine through mucous membranes. Thus, some of the methamphetamine presumably reaches the lung, but another portion of it may undergo oral or buccal absorption resulting in an apparent sustained release of the drug to the systemic circulation. Another explanation for this finding is based on the observation that several lipophilic amines are known to accumulate and persist in rat and rabbit lungs (Wilson et al. 1979).

Regardless of the explanation for this phenomenon, this long plateau effect and the much longer half-life of methamphetamine vs. cocaine suggests considerable dangers in repeated smoking of methamphetamine since markedly higher plasma concentrations could be expected to occur if the dose is repeated, even at fairly long intervals.

CONCLUSIONS

Smoking of psychoactive drugs in plant material has a long history, and this technique has been transferred to newer drugs. The volatility and stability of the drug have great bearing on the efficiency of the smoking process, as does the presence of other substances that can codistill, enhance stability, or react with the drug being smoked. Of the four drugs discussed—heroin, PCP, cocaine, and S-methamphetamine hydrochloride (ice)—the last one is most efficiently delivered when the substances are heated in a glass pipe. This factor, combined with the addictive properties of the compound and with the justifiable fears about use of IV injection, is likely to lead to an increase in this mode of administration unless educational efforts on the hazards of ice and research efforts to find the bases of drug addiction and treatment methods are successful.

REFERENCES

- Beaver, R.W., and Jones, L.A. Pyrolysis products of 1-(1-phenylcyclohexyl)-piperidine (PCP). *Can J Chem* 62:1022-1027, 1984.
- Carroll, E. COCA: The plant and its use. In: Petersen, R.C., and Stillman, R.C., eds. *Cocaine: 1977*. National Institute on Drug Abuse Research Monograph 13. DHHS Pub. No. (ADM)82-471. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1982. p. 43.
- Cho, A.K. ice: A new dosage form of an old drug. *Science* 249:631-634, 1990.
- Cook, C.E., and Brine, D.R. Pyrolysis products of heroin. *J Forensic Sci* 30(1):251-261, 1985.
- Cook, C.E.; Brine, D.R.; Jeffcoat, A.R.; Hill, J.M.; Wall, M.E.; Perez-Reyes, M.; and Di Guiseppi, S.R. Phencyclidine disposition after intravenous and oral doses. *Clin Pharmacol Ther* 31(5):625-634, 1982b.
- Cook, C.E.; Brine, D.R.; Quin, G.D.; Perez-Reyes, M.; and Di Guiseppi, S.R. Phencyclidine and phenylcyclohexene disposition after smoking phencyclidine. *Clin Pharmacol Ther* 31(5):635-641, 1982a.
- Cook, C.E.; Brine, D.R.; Quin, G.D.; Wall, M.E.; Perez-Reyes, M.; and Di Guiseppi, S.R. Smoking of phencyclidine: Disposition in man and stability to pyrolytic conditions. *Life Sci* 29:1967-1972, 1981.
- Cook, C.E., and Jeffcoat, A.R. Pyrolytic degradation of heroin, phencyclidine, and cocaine: Identification of products and some observations on their metabolism. In: Chiang, C.N., and Hawks, R.L., eds. *Research Findings on Smoking of Abused Substances*. National Institute on Drug Abuse Research Monograph 99. DHHS Pub. No. (ADM)90-1690. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1990. pp. 97-120.
- Cook, C.E.; Jeffcoat, A.R.; and Perez-Reyes, M. Pharmacokinetic studies of cocaine and phencyclidine. In: Barnett, G., and Chiang, C.N., eds.

- Pharmacokinetics and Pharmacodynamics of Psychoactive Drugs. Foster City, CA: Biomedical Publications, 1985. pp. 48-74.
- Cook, C.E.; Jeffcoat, A.R.; Perez-Reyes, M.; Sadler, B.M.; Hill, J.M.; White, W.R.; and McDonald, S. Plasma levels of methamphetamine after smoking of methamphetamine hydrochloride. In: Harris, L.S., ed. *Problems of Drug Dependence 1990: Proceedings of the 52nd Annual Scientific Meeting, The Committee on Problems of Drug Dependence, Inc.* National Institute on Drug Abuse Research Monograph 105. DHHS Pub. No. (ADM)91-1753. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1991. pp. 578-579.
- Cook, C.E.; Jeffcoat, A.R.; Perez-Reyes, M.; Sadler, B.M.; Voyksner, R.D.; Hill, J.A.; White, W.R.; and McDonald, S. Pharmacokinetics of oral d₃-S-methamphetamine in humans before and after 13 days of oral dosing with S-methamphetamine hydrochloride. *Eur J Pharmacol* 183:456-457, 1990.
- Cook, C.E.; Perez-Reyes, M.; Jeffcoat, A.R.; and Brine, D.R. Phencyclidine disposition in humans after small doses of radiolabeled drug. *Federations Proc* 42(9):2566-2569, 1983.
- Corti, C. *A History of Smoking*. New York: Harcourt Brace, 1932.
- Freeman, A.S., and Martin, B.R. Quantification of PCP in mainstream smoke and identification of phenyl-cyclohex-1-ene as pyrolysis product. *J Pharm Sci* 70:1002-1004, 1981.
- Hatsukami, D.; Keenan, R.; Carroll, M.; Colon, E.; Geiske, D.; Wilson, B.; and Huber, M. A method for delivery of precise doses of smoked cocaine base to humans. *Pharmacol Biochem Behav* 36(1):1-7, 1990.
- Herodotus. *Historae IV. The Persian Wars*. Trans. by G. Rawlison. New York: Modern Library, 1942. p. 75. (Quoted in Paris, M., and Nahas, G.G. Botany: The unstabilized species in marijuana. In: Nahas, G.G., ed. *Science and Medicine*. New York: Raven Press, 1984. p. 9.)
- Hinds, W.C. *Aerosol Technology: Properties, Behavior and Measurement of Airborne Particles*. New York: John Wiley & Sons, 1982. pp. 211-221.
- Huizer, H. Analytical studies on illicit heroin. V. Efficacy of volatilization during heroin smoking. *Pharm Weekbl [Sci]* 9:203-211, 1987.
- Ito, R. Amount of effective component which passes into smoke when heroin is smoked. *JPN J Med Sci IV Pharmacol*. Trans. 9, 1977 (*Chem Abstr* 31: 8022-8026, 1937).
- Jeffcoat, A.R.; Perez-Reyes, M.; Hill, J.M.; Sadler, B.M.; and Cook, C.E. Cocaine disposition in humans after intravenous injection, nasal insufflation (snorting), or smoking. *Drug Metab Dispos* 17(2):153-159, 1989.
- Lue, L.P.; Scimeca, A.; Thomas, B.F.; and Martin, B.R. Identification and quantification of phencyclidine pyrolysis products formed during smoking. *J Anal Toxicol* 10:81-86, 1986.
- Martin, B.R.; Lue, L.P.; and Boni, J.P. Pyrolysis and volatilization of cocaine. *J Anal Toxicol* 13:158-162, 1989.

- Masood, A. Opium smoking in the frontier province of Pakistan. *Bull Narc* 31(1):59-66, 1979.
- Meyers, S.A.; Craves, F.B.; Caldwell, D.F.; and Loh, H.H. Inhalation induced tolerance and physical dependence: The hazard of opiate suffused marihuana. *Milit Med* 137(12):431-433, 1972.
- Mo, B.P., and Way, E.L. An assessment of inhalation as a mode of administration of heroin by addicts. *J Pharmacol Exp Ther* 154(1):142-151, 1988.
- Novak, M., and Salemink, C.A. Novel rearrangement during pyrolysis of cocaine. *Tetrahedron* 45(13):4287-4292, 1989.
- Perez-Reyes, M.; Di Guiseppi, S.; Ondrusek, G.; Jeffcoat, A.R.; and Cook, C.E. Free-base cocaine smoking. *Clin Pharmacol Ther* 32:459-465, 1982.
- Perez-Reyes, M.; White, R.; McDonald, S.; Hill, J.; Jeffcoat, R.; and Cook, C.E. Pharmacologic effects of methamphetamine vapor inhalation (smoking) in man. In: Harris, L.S., ed. *Problems of Drug Dependence 1990: Proceedings of the 52nd Annual Scientific Meeting, The Committee on Problems of Drug Dependence, Inc.* National Institute on Drug Abuse Research Monograph 105. DHHS Pub. No. (ADM)91-1753. Washington, DC: Supt. of Docs., US. Govt. Print. Off., 1991. pp. 575-577.
- Rivier, L. Analysis of alkaloids in leaves of cultivated *Erythroxylum* and characterization of alkaline substances used during coca chewing. *J Ethnopharmacol* 3:313-335, 1981.
- Sekine, H., and Nakahara, Y. Abuse of smoking methamphetamine mixed with tobacco: I. Inhalation efficiency and pyrolysis products of methamphetamine. *J Forensic Sci* 32(5):1271-1280, 1987.
- Sekine, H., and Nakahara, Y. Abuse of smoking methamphetamine mixed with tobacco: II. The formation mechanism of pyrolysis products. *J Forensic Sci* 35(3):580-590, 1990.
- Sisti, N.J., and Fowler, F.W. The flash vacuum thermolysis of (-)-cocaine. *Tetrahedron Lett* 30(44):5977-5980, 1989.
- Snyder, C.A.; Wood, R.W.; Graefe, J.F.; Bowers, A.; and Magar, K. "Crack smoke" is a respirable aerosol of cocaine base. *Pharmacol Biochem Behav* 29:93-95, 1988.
- Wilson, A.G.E.; Pickett, R.D.; Eling, T.; and Anderson, M.W. Studies on the persistence of basic amines in the rabbit lung. *Drug Metab Dispos* 7:420-424, 1979.
- Windholz, M.; Budavari, S.; Blumetti, R.F.; and Otterbein, E.S., eds. *Merck Index*. 10th ed. Rahway, NJ: Merck & Co., Inc., 1983. p. 348, #2411.

ACKNOWLEDGMENT

Work reviewed here from Research Triangle Institute and the University of North Carolina was supported by National Institute on Drug Abuse contracts

271-87-8128 and 271-80-3705. Dr. Mario Perez-Reyes of the University of North Carolina carried out the clinical portions of our collaborative work. The contributions of my colleagues at Research Triangle Institute are indicated by the various references listed.

AUTHOR

C. Edgar Cook, Ph.D.
Vice President
Chemistry and Life Sciences
Research Triangle Institute
P.O. Box 12194
Research Triangle Park, NC 27709-2194

Neurotoxicity of Methamphetamine: Mechanisms of Action and Issues Related to Aging

Lewis S. Seiden

INTRODUCTION

Historically, the use of mood-altering drugs has increased or decreased in cycles similar to those observed with bacterial or viral epidemics. Increases in the abuse of psychomotor stimulants such as cocaine and methamphetamine have occurred in different countries at different times (Seiden and Ricaurte 1987). Cocaine and methamphetamine are similar in their discriminative stimulus properties, and both cocaine and methamphetamine compounds are self-administered by humans as well as nonhuman animals. The patterns of social problems engendered by cocaine or methamphetamine abuse indicate similarities in behavior, and similarities in their neuropharmacological actions strongly suggest that cocaine and methamphetamine may continue to be problematic drugs in society. In recent years, cocaine has been abused to a far greater extent than methamphetamine, although the converse was true in the 1950s through 1970s in Japan, Great Britain, Sweden, and the United States (Kramer et al. 1967; Inghe 1969; Brill and Hirose 1969). Cocaine continues to be a frequently abused psychomotor stimulant (Wish 1990), but there are some indications that methamphetamine abuse has increased because of marketplace pressures as well as differences in the duration of action between methamphetamine and cocaine, with methamphetamine having about 10-fold longer duration of action in humans. Accurate data on the frequency and prevalence of illicit drug abuse is difficult to obtain, but there are some indications that the prevalence of methamphetamine use in Hawaii and California is sizeable enough to warrant concern (Miller, this volume; Heischober and Miller, this volume). The estimates of prevalence are based on the number of seizures of illicit manufacturers of methamphetamine and the number of hospital admissions that are believed to be related to methamphetamine ingestion.

The crystalline form of methamphetamine hydrochloride, known as “ice,” is volatile at low temperatures, and the pharmacological effects can be achieved by inhaling vapors. The inhaled route of administration delivers a bolus of methamphetamine to the brain. Similar effects can be achieved with intravenous (IV) injection, but smoking omits dangers inherent in IV drug administration such as contracting blood-borne diseases. In this way it is similar to “crack” cocaine, which is smoked and inhaled. Health officials, law enforcement agencies, and the public have perceived cocaine and methamphetamine as damaging to an individual’s ability to serve a useful role in society. Based on animal studies, there is evidence that methamphetamine causes long-lasting changes in the central nervous system (CNS), indicating that methamphetamine is neurotoxic, especially at high doses. Although CNS effects on humans due to methamphetamine or cocaine have not been determined, data from animal studies suggest that caution be exercised.

This chapter presents evidence that methamphetamine causes damage to dopamine and serotonin (5-hydroxytryptamine [5HT])-containing neurons in the brain and that this damage occurs in several species of animals, is long lasting, and probably is irreversible. Data and theory are presented that suggest a mechanism by which methamphetamine may engender toxicity to dopamine and 5HT neurons. Finally, the implications of these data are discussed in terms of changes in humans as a function of age.

METHAMPHETAMINE ENGENDERS NEUROTOXICITY

Early findings revealed that high and repeated doses of methamphetamine in the rhesus monkey and the rat caused long-lasting depletion of dopamine and decreased the activity of tyrosine hydroxylase (TH) in the brain (Seiden et al. 1976; Koda and Gibb 1973). In the Seiden and colleagues study, rhesus monkeys received IV injections eight times per day in escalating doses that reached a final cumulative dose of between 9 and 15 mg/kg/day. Monkeys injected with high doses of methamphetamine for 3 to 6 months were sacrificed 3 or 6 months after the last injection of methamphetamine. The most remarkable finding in this study was a large depletion of caudate dopamine from the monkeys treated with methamphetamine. An indirect replication of this experiment used similar doses of IV methamphetamine for 2 weeks, with a 2-week interval between the last injection and assay for brain catecholamines; this shorter injection regimen also caused large depletions of caudate dopamine. Koda and Gibb (1973) injected rats with five large doses of methamphetamine over a 24-hour period and found that TH was decreased for 7 days after the last injection.

It seemed unlikely that methamphetamine would remain in the brain or other tissues for 3 to 6 months, and since methamphetamine does not inhibit TH, the drug remaining in the system even after the shorter interval would not be likely to affect the enzyme directly. The results of these early experiments suggested that repeated and high doses of methamphetamine lead to long-lasting depletions of dopamine in the caudate and a reduction in the amount of enzyme available for the rate-limiting synthetic step. These results suggested that methamphetamine is neurotoxic to these cells.

Neurotoxicity in a dopamine-containing cell occurs when (1) there is a long-lasting effect on dopamine levels that persist after the withdrawal of the drug, and the total activity of the rate-limiting enzyme is decreased; (2) the number of dopamine high-affinity-uptake sites is reduced; and (3) there is morphological evidence for degeneration.

Methamphetamine has been shown to engender long-lasting transmitter depletion on the dopamine and 5HT systems in rhesus monkeys, rats, mice, guinea pigs, and cats (Seiden et al. 1976; Wagner et al. 1979, 1980, 1983; Levine et al. 1980; Steranka and Sanders-Bush 1980). The generality of this effect is important because it implies that the effects of methamphetamine on dopamine and 5HT levels extends to humans. In all species that have been examined, the methamphetamine dose that causes the neurotoxic effects on dopamine cells is between 20-fold and 30-fold greater than the dose required for engendering behavioral effects such as increased locomotion, decreases in food intake, or stereotypic behavior (Seiden and Dykstra 1977). Humans who use methamphetamine or amphetamine for controlling food intake or counteracting narcolepsy or fatigue take approximately 0.2 to 0.4 mg/kg, whereas humans using the drug for its mood-altering effects use as much as 10 to 20 mg/kg over a 24-hour period (Gilman et al. 1985). Comparing doses in humans used for altering mood with doses that engender toxic responses in other animals suggests that it is reasonable to be concerned that humans using methamphetamine in large doses will be susceptible to the same neurotoxicity observed in other species.

The same doses of methamphetamine that reduce dopamine levels and TH activity in brain also cause prolonged reductions of 5HT levels and the activity of the rate-limiting enzyme in 5HT synthesis, tryptophan hydroxylase (Ricaurte et al. 1980; Bakhit et al. 1981; Hotchkiss and Gibb 1980). These results suggest that high and repeated dosing with methamphetamine can lead to long-lasting reductions of dopamine and 5HT levels as well as the enzymes that are rate limiting in their synthesis, suggesting that methamphetamine produces neurotoxicity to these systems. It is of interest that methamphetamine is not neurotoxic to norepinephrine, gamma-amino-butyric-acid, glutamic acid, or the

acetylcholine system, and increases in levels of peptides have been observed following methamphetamine treatment (Seiden and Ricaurte 1987). The neurotoxicity engendered by methamphetamine is long lasting if not permanent, and depletions of dopamine and 5HT have been observed in rhesus monkeys as long as 3 years after the cessation of methamphetamine administration (Woolverton et al. 1989).

Methamphetamine-induced degeneration of neurons has been detected using silver-staining techniques. It has been possible to demonstrate that about 24 hours after methamphetamine there are cells in the caudate that are argyrophillic (Ricaurte et al. 1982, 1984). These silver-stained cells are apparent in the caudate nucleus, where there are dopamine and 5HT cells. It is not possible, however, to use silver techniques to determine the transmitter in the damaged cell. Therefore, one must infer that the same damaged cells contain the transmitter that is measured with the chemical assays. The main factor that favors this interpretation is that the pattern of positive argyrophillic cells is similar to terminal field loss for dopamine and 5HT.

In summary, three factors indicate that methamphetamine is neurotoxic to dopamine and 5HT cells. First, methamphetamine produces a long-lasting change in the levels of dopamine and 5HT as well as the quantity of enzyme catalyzing the rate-limiting step in their synthesis. Second, the number of high-affinity-uptake sites is reduced, indicating that a fraction of nerve endings are destroyed. Third, neuronal degeneration is indicated by the number of cells that take up silver after methamphetamine administration.

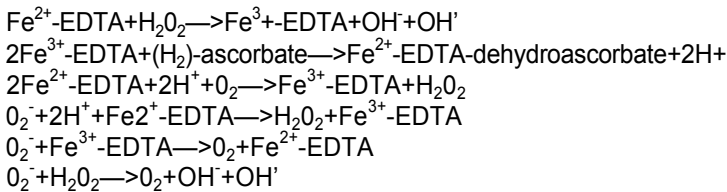
MECHANISM OF ACTION IS RELATED TO OXIDATIVE STRESS

The molecular mechanism by which methamphetamine produces long-lasting and irreversible damage to dopamine-containing and 5HT-containing neurons in the CNS is not completely understood, but some interesting data and theory exist.

A number of observations are consistent with a mechanism by which methamphetamine engenders the release and conversion of dopamine to a toxic metabolite, 6-hydroxydopamine (6-OHDA). First, it was shown that inhibition of dopamine synthesis by alpha-methyl-tyrosine protects against the toxic effects of methamphetamine (Wagner et al. 1983). Blockade of synthesis suggests that dopamine is important in mediating methamphetamine-engendered neurotoxicity. Furthermore, pretreatment of rats with reserpine potentiates methamphetamine neurotoxicity. At first, it would seem that the protection from the neurotoxicity by alpha-methyl-tyrosine is inconsistent with the potentiation of neurotoxicity caused by reserpine, but alpha-methyl-tyrosine

depletes dopamine from the newly synthesized dopamine pool that is bound to the cytoplasm, while reserpine depletes dopamine from the vesicular bound pool and therefore causes a shift in the equilibrium between cytoplasmic and vesicular pools that increases the cytoplasmically bound pool. Amphetamine and probably methamphetamine engender dopamine release from the cytoplasmically bound pool (Ralteri et al. 1979); therefore, methamphetamine-induced release of dopamine is retarded under conditions in which the cytoplasmically bound pool decreases and can be enhanced when the pool is increased. Alpha-methyl-tyrosine decreases and reserpine increases the cytoplasmically bound pool, thus diminishing or enhancing methamphetamine-induced toxicity, respectively.

The formation of an endogenous neurotoxin is based on the observation that the catecholamine neurotoxin 6-OHDA has been found in the urine of humans and that dopamine can be metabolized to 6-OHDA through a Fenton-type reaction in which a hydroxy radical is formed from hydrogen peroxide in the presence of ferrous iron according to the reaction system below:



Ferrous iron, hydrogen peroxide, and ascorbic acid are all present in the brain, and although ethylenediaminetetraacetic acid (EDTA) is an important factor of the in vivo Fenton reaction, there are other electrophilic molecules in brain that could serve as intermediates in place of EDTA. Furthermore, Slivka and Cohen (1985) have found that dopamine reacts in a Fenton-type system to yield trihydroxyphenethylamine derivatives, of which 6-OHDA is one, and therefore it seemed possible that the dopamine released by methamphetamine into the synapse could be converted to 6-OHDA; once formed, 6-OHDA could be actively transferred into the dopamine terminal by the high-affinity-uptake pump, and once inside the dopamine cell, 6-OHDA is toxic. Seiden and Vosmer (1984) detected small amounts of 6-OHDA in the caudate nucleus after a large single injection of methamphetamine that is sufficient to cause long-lasting dopamine depletions. Furthermore, the formation of 6-OHDA engendered by treatment with methamphetamine can be blocked by pretreating rats with *alpha*-methyl-*p*-tyrosine (AMPT) (Axt et al. 1990). Pretreatment with AMPT attenuates many of the behavioral and physiological consequences of methamphetamine

and further indicates that methamphetamine-induced release is from the cytoplasmically bound pool rather than a vesicular bound pool. Similar experimental procedures have revealed methamphetamine-induced formation of 5,6-dihydroxytryptamine (5,6-DHT, a neurotoxin to the 5HT system) after a neurotoxic dose of methamphetamine (Commins et al. 1987). It is possible that the formation of neurotoxins from endogenous amines that are released by methamphetamine may mediate methamphetamine neurotoxicity.

Aside from observation of 6-OHDA and 5,6-DHT, there are also indirect observations that support these data and theory. Ascorbic acid attenuates methamphetamine neurotoxicity (Wagner et al. 1985). According to a Fenton type of reaction system, an excess of ascorbate should protect against 6-OHDA formation. Conversely, if one deprives guinea pigs of ascorbic acid in the diet, then one can make them more susceptible to methamphetamine-induced neurotoxicity (Matsuda et al. 1987). Inhibition of catalase leads to increased hydrogen peroxide and increases neurotoxicity in rats (Axt 1988). In summary, there is direct and indirect evidence that the formation of neurotoxic substances from dopamine and 5HT are responsible for the toxicity of methamphetamine to dopamine and 5HT nerve endings.

There are findings, however, that are either inconsistent with the data and theory or findings that apparently do not reinforce the data. Rollema and coworkers (1986) have not been able to detect 6-OHDA after methamphetamine administration using the technique of *in vivo* dialysis. Other investigators who have attempted direct replication of these results have seen either variable results or not seen the 6-OHDA at all (J.W. Gibb and G. Cohen, personal communication, 1990). Seiden and Vosmer (1984) reported the number of rats in which the endogenous formation of the toxin was observed as well as the number of rats examined. The formation of neurotoxins was not detected in every animal. Attempts to replicate the experiment also have been variable. In some experiments, no 6-OHDA in tissue was observed, but in other experiments six of eight rats were seen to form 6-OHDA. Formation of 6-OHDA was seen in hooded rats and in guinea pigs.

Sonsalla and colleagues (1989) have found that the N-methyl-D-aspartate (NMDA) receptor antagonist MK801 can antagonize the neurotoxic effects of methamphetamine on the dopamine and 5HT systems. This finding suggests that the release of glutamate may be an important factor in the mediation of methamphetamine-induced neurotoxicity. Although these data are not inconsistent with the idea that methamphetamine exerts its toxicity because of an oxidative stress response, it is not clear how the glutamate and the oxidative stress are related to one another. NMDA receptors are localized in part on

dopamine cell bodies, but the damage engendered by methamphetamine occurs at the nerve ending.

Oxidative stress reactions seem to occur more frequently in older mammals, and the hypothesis has been advanced that the progressive loss of dopamine neurons in humans as a result of aging may be a result of oxidation reactions, and this finding has implications for Parkinson's disease. Humans lose dopamine neurons with advancing age (Hornykiewicz 1989), and insofar as Parkinson's disease is related to dopamine and aging, this dopamine loss might account for the onset of the symptoms. It is possible that this process could be accelerated in humans taking large amounts of methamphetamine. Both dopamine and 5HT have been related to feeding and affective disorders, and 5HT has been related to depression, transmission of pain, sleep, and sexuality. Since both 5HT and dopamine are depleted by a high dose of methamphetamine, systematic work to determine the relationship between methamphetamine abuse and subsequent symptoms is needed. One of the chief difficulties is that the effects of a large dose of methamphetamine may deplete dopamine and 5HT enough to cause minimal or no effects shortly after drug ingestion, but as the amine loss with aging occurs, the loss may become more apparent; however, it may be difficult to obtain accurate drug histories at the time such symptoms begin to occur. One of the challenges in this area is to be able to track toxic changes in the brain with consequences only apparent a decade or two later.

REFERENCES

- Axt, K.J. "Characterization of the Formation of Endogenous Neurotoxins in the Rat Brain Following Administration of Neurotoxic Amphetamines." Ph.D. dissertation, University of Chicago, 1988.
- Axt, K.J.; Commins, D.L.; Vosmer, G.; and Seiden, L.S. A-methyl-p-tyrosine pretreatment partially prevents methamphetamine-induced endogenous neurotoxin formation. *Brain Res* 515:269-276, 1990.
- Bakhit, C.; Morgan, M.A.; Peat, M.A.; and Gibb, J.W. Long-term effects of methamphetamine on the synthesis and metabolism of 5-hydroxytryptamine in various regions of the rat brain. *Neuropharmacology* 20:1135-1140, 1981.
- Brill, H., and Hirose, T. The rise and fall of a methamphetamine epidemic: Japan 1945-55. *Semin Psychiatry* 1:179-194, 1969.
- Commins, D.L.; Axt, K.J.; Vosmer, G.; and Seiden, L.S. 5,6-Dihydroxytryptamine, a serotonergic neurotoxin is formed endogenously in the rat brain. *Brain Res* 403:7-14, 1987.
- Gilman, A.G.; Goodman, L.S.; Rall, T.W.; and Murad, F. *The Pharmacological Basis of Therapeutics*. 7th ed. New York: MacMillan, 1985.

- Hornykiewicz, O. Ageing and neurotoxins are causative factors in idiopathic Parkinson's disease: A critical analysis of the neurochemical evidence. *Prog Neuropsychopharmacol Biol Psychiatry* 13:319-328, 1989.
- Hotchkiss, A.J., and Gibb, J.W. Blockade of methamphetamine-induced depression of tyrosine hydroxylase by GABA transaminase inhibitors. *Eur J Pharmacol* 66:204-205, 1980.
- Inghe, G. The present state of abuse and addiction to stimulant drugs in Sweden. In: Sjoqvist, F., and Tottie, M., eds. *Abuse of Central Stimulants*. Stockholm: Almqvist and Wiksell, 1969. pp. 187-219.
- Koda, L.Y., and Gibb, J.W. Adrenal and striatal tyrosine hydroxylase activity after methamphetamine. *J Pharmacol Exp Ther* 185:42-48, 1973.
- Kramer, J.C.; Fischman, V.S.; and Littlefield, D.C. Amphetamine abuse. Pattern and effects of high doses taken intravenously. *JAMA* 201:305-309, 1967.
- Levine, M.S.; Hull, C.D.; Garcia-Rill, E.; Erinoff, L.; Buchwald, A.; and Heller, A. Long-term decreases in spontaneous firing of caudate neurons induced by methamphetamine in cats. *Brain Res* 194:263-268, 1980.
- Matsuda, L.A.; Schmidt, C.J.; Gibb, J.W.; and Hanson, G.R. Ascorbic acid-deficient condition alters central effects of methamphetamine. *Brain Res* 400:176-180, 1987.
- Raiteri, M.; Cerrito, F.; Cervoni, A.M.; and Levi, G. Dopamine can be released by two mechanisms differentially affected by the dopamine transport inhibitor nomifensine. *J Pharmacol Exp Ther* 208:195-202, 1979.
- Ricarte, G.A.; Guillery, R.W.; Seiden, L.S.; and Schuster, C.R. Selective neurodegenerative changes in the somatosensory cortex following treatment with methylamphetamine, p-chloroamphetamine but not 6-HDA. *Soc Neurosci* 6(259.7):764, 1980.
- Ricarte, G.A.; Guillery, R.W.; Seiden, L.S.; and Schuster, C.R. Nerve terminal degeneration after a single injection of d-amphetamine in iprindole-treated rats: Relation to selective long-lasting dopamine depletion. *Brain Res* 291:378-382, 1984.
- Ricarte, G.A.; Guillery, R.W.; Seiden, L.S.; Schuster, C.R.; and Moore, R.Y. Dopamine nerve terminal degeneration produced by high doses of methylamphetamine in the rat brain. *Brain Res* 235:93-103, 1982.
- Rollema, H.; DeVries, J.B.; Westerink, B.H.C.; VanPutten, F.M.S.; and Horn, A.S. Failure to detect 6-hydroxydopamine in rat striatum after the dopamine releasing drugs dexamphetamine, methylamphetamine and MPTP. *Eur J Pharmacol* 132:65-69, 1986.
- Seiden, L.S., and Dykstra, L.A. *Psychopharmacology: A Biochemical and Behavioral Approach*. New York: Van Nostrand Reinhold Company, 1977.
- Seiden, L.S.; Fischman, M.W.; and Schuster, C.R. Long-term methamphetamine-induced changes in brain catecholamines in tolerant rhesus monkeys. *Drug Alcohol Depend* 3:215-219, 1976.

- Seiden, L.S., and Ricaurte, G.A. Neurotoxicity of methamphetamine and related drugs. In: Meltzer, H., ed. *Psychopharmacology: The Third Generation of Progress*. New York: Raven Press, 1987. pp. 359-366.
- Seiden, L.S., and Vosmer, G. Formation of 6-hydroxydopamine in caudate nucleus of the rat brain after a single large dose of methylamphetamine. *Pharmacol Biochem Behav* 21:29-31, 1984.
- Slivka, A., and Cohen, G. Hydroxyl radical attack on dopamine. *J Biol Chem* 260:15466-15472, 1985.
- Sonsalla, P.K.; Nicklas, W.J.; and Heikkila, R.A. Role for excitatory amino acids in methamphetamine-induced nigrostriatal dopaminergic toxicity. *Science* 243:398-400, 1989.
- Steranka, L.R., and Sanders-Bush, E. Long-term effects of continuous exposure to amphetamine in brain dopamine concentration and synaptosomal uptake in mice. *Eur J Pharmacol* 65:439-443, 1980.
- Wagner, G.C.; Carelli, R.M.; and Jarvis, M.F. Pretreatment with ascorbic acid attenuates the neurotoxic effects of methamphetamine in rats. *Res Commun Chem Pathol Pharmacol* 47:221-228, 1985.
- Wagner, G.C.; Lucot, J.B.; Schuster, C.R.; and Seiden, L.S. Alpha-methyltyrosine attenuates and reserpine increases methamphetamine-induced neuronal changes. *Brain Res* 270:285-288, 1983.
- Wagner, G.C.; Ricaurte, G.A.; Johanson, C.E.; Schuster, C.R.; and Seiden, L.S. Amphetamine induces caudate dopamine depletion. *Neurology* 30:547-550, 1980.
- Wagner, G.C.; Schuster, C.R.; and Seiden, L.S. Methamphetamine induced changes in brain catecholamines in rats and guinea pigs. *Drug Alcohol Depend* 4:435-438, 1979.
- Wish, E.D. U.S. drug policy in the 1990s: Insight from new data from arrestees. *Int J Addict* 25(3A):377-409, 1990.
- Woolverton, W.L.; Ricaurte, G.A.; Forno, L.S.; and Seiden, L.S. Long-term effects of chronic methamphetamine administration in rhesus monkeys, *Brain Res* 486:73-78, 1989.

AUTHOR

Lewis S. Seiden, Ph.D.

Professor

Department of Pharmacology and Physiological Sciences

University of Chicago

947 East 58th Street

Chicago, IL 60637

The Environmental Impact and Adverse Health Effects of the Clandestine Manufacture of Methamphetamine

Gary D. Irvine and Ling Chin

INTRODUCTION

Seizures of clandestine methamphetamine drug laboratories are becoming increasingly common. In the 1980s the number of methamphetamine drug laboratory seizures had risen dramatically, from 88 seizures in 1981 to 652 in 1989, an increase of more than 600 percent (figure 1). Since 1987 more than over 80 percent of all clandestine laboratories seized have been involved with the synthesis of methamphetamine (unpublished data, Office of Intelligence, Drug Enforcement Administration 1990). Although these drug laboratories can be found throughout the United States, three states accounted for 76.5 percent of all laboratories seized in 1988: California (50.1 percent), Texas (13.4 percent), and Oregon (13.0 percent) (U.S. Department of Justice 1989) (figure 2). States with the next highest number of seizures were New Mexico (3.5 percent) and Washington (3.2 percent).

The illicit manufacture of methamphetamine was dominated historically by outlaw biker gangs. These bikers were known to purchase the precursor chemicals in cities and produce the methamphetamine in remote country areas where the telltale fumes were vented more easily. Other groups have now become involved with the illicit manufacture of methamphetamine and are quite versatile in where they place their laboratories, which have been found in private residences, rental homes, motel rooms, garages, campgrounds, moving vans, storage facilities, horse trailers, houseboats, and commercial establishments. These makeshift laboratories have increased the mobility of the individuals involved: it is not uncommon for them to cook up a batch, make a sale, discard the equipment and chemical residues onsite, and move on to continue the process at another location.

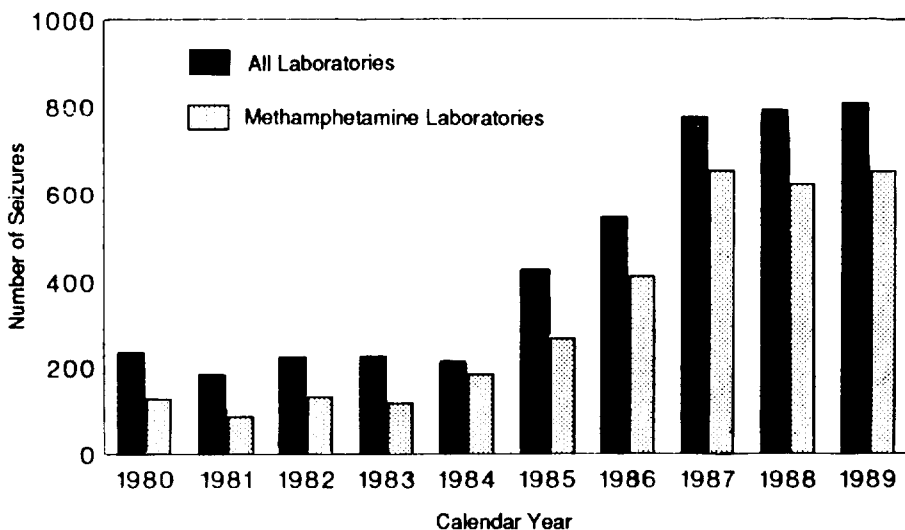


FIGURE 1. *U.S. clandestine laboratory seizures, 1988*

SOURCE: US. Department of Justice 1989

METHAMPHETAMINE SYNTHESIS

The illicit manufacture of methamphetamine is a relatively simple process and can be carried out by individuals without special knowledge or expertise in chemistry. "Cookers" have produced methamphetamine batches by following cookbook-style recipes (which may have been obtained while they were in jail). Therefore, methods of methamphetamine production and the final product can vary from laboratory to laboratory.

The two predominant methods of methamphetamine production are the amalgam and ephedrine methods (Oregon Department of Human Resources 1988).

The amalgam method uses phenyl-2-propanone (P2P) and methylamine as the primary precursors. Hydrochloric acid, mercury, and aluminum-containing reagents also are used. In forensic chemistry reports on 190 methamphetamine laboratories seized by the Drug Enforcement Administration (DEA) during the 45-month period ending in September 1981, three methods of synthesis predominated (Frank 1983). The most common method of synthesis (employed by more than 50 percent of laboratories) uses P2P, methylamine, mercuric chloride, and aluminum metal in alcohol; the second most common

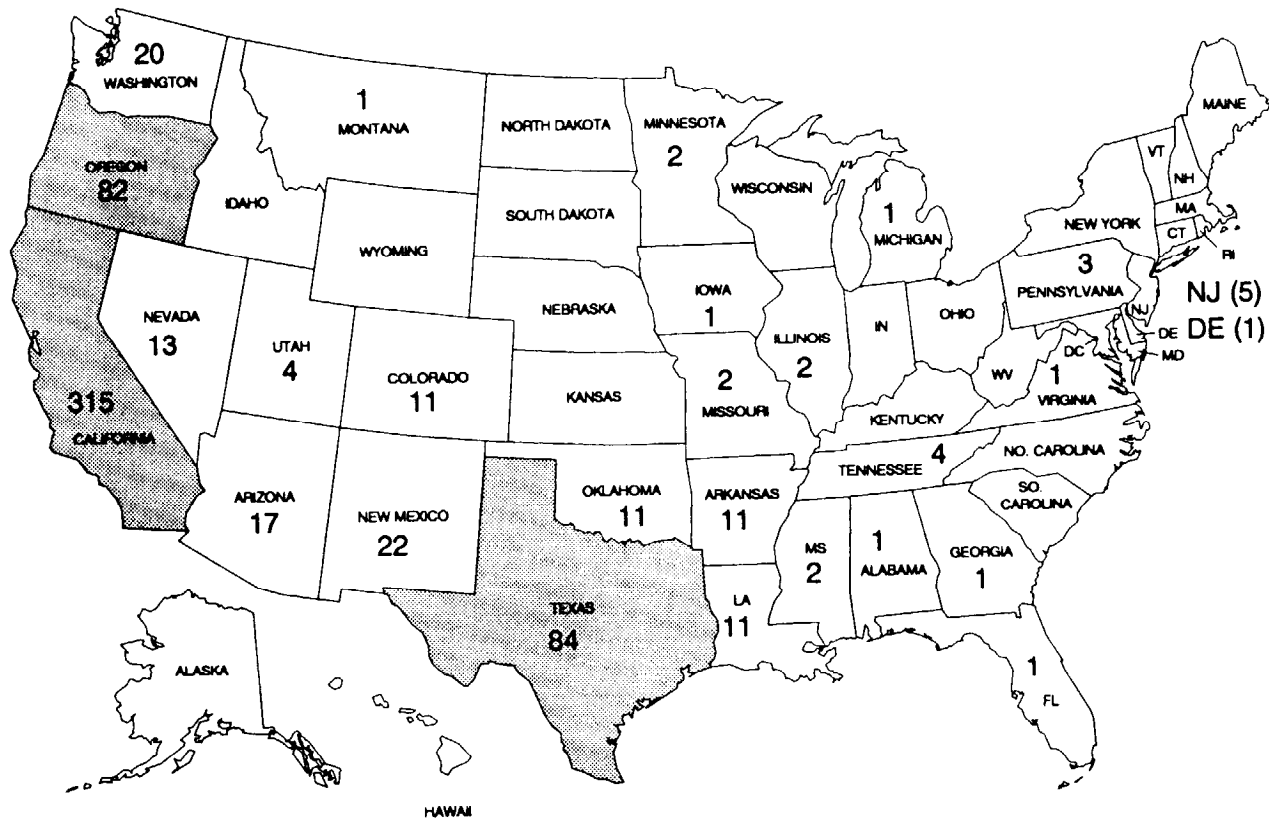


FIGURE 2. *Clandestine methamphetamine laboratory seizures in the United States, 1988*

SOURCE: U.S. Department of Justice 1989

method (<10 percent) uses acetaldehyde, methylamine, and benzylmagnesium chloride. The third (<10 percent) uses a Leuckart reaction, utilizing P2P, methylamine, formic acid or N-methylformamide, and hydrochloric acid.

The ephedrine method is a newer and cleaner method employing ephedrine as the primary precursor. The most common ephedrine process known involves the use of red phosphorus. Whatever the process used to manufacture methamphetamine, the inclusion of by-products and contaminants in the final product is inevitable.

In February 1980, P2P became a Schedule II controlled substance, and the popularity of the P2P method of making methamphetamine waned as a result. Some illicit manufacturers began making their own P2P. The most frequently used method (>75 percent) of making P2P used phenylacetic acid and acetic anhydride, with sodium acetate or pyridine.

The ephedrine method of synthesizing methamphetamines gained popularity after P2P became a controlled substance. The use of ephedrine and pyridine with hydrogen iodide and red phosphorus was observed for the first time in 1981 (Frank 1983). The use of the ephedrine method in clandestine laboratories first began in southern California, spreading north to other California cities, and then to other cities along the west coast.

DEA data from 1989 showed a total of 652 methamphetamine laboratories seized, with a breakdown on method of synthesis used for 416 of these laboratories; 219 (53 percent) laboratories were using the ephedrine method, whereas 197 (47 percent) laboratories were using the P2P method (unpublished data, Office of Intelligence 1990).

ADVERSE EFFECTS

Although the production of methamphetamine is a relatively simple process, it can have dangerous consequences and can place several groups of people at risk of exposure to toxic chemicals and its subsequent effects. Those most likely to be exposed include the drug manufacturers; law enforcement officers: local health, fire, and police personnel: residents near laboratory sites; and future occupants of discarded laboratory sites. The chemicals used in the manufacturing process can be corrosive, explosive, flammable, toxic, and, possibly, radioactive. There is also a potential for infectious disease from exposure to drug paraphernalia such as used needles left onsite by manufacturers who may be users. Exposure can occur via skin absorption, inhalation, ingestion, or injection. Inhalation and/or skin absorption are the most likely routes of exposure for those exposed directly to the laboratory environment.

Environmental Effects

The underlying problem with the illicit production of methamphetamine is that for the most part the producers possess neither the knowledge nor the skill to carry out the synthesis appropriately. They often do not use the correct proportion of precursors, reagents, solvents, or catalysts, and they may not follow instructions for the synthetic process exactly as stated. They may not be able to eliminate undesirable by-products or contaminants; thus, end products are of variable purity and quality. Also, they may operate under suboptimal conditions with poor ventilation and temperature control systems. When the final product is obtained, leftover equipment and chemicals often are neither stored nor disposed of appropriately. All these factors create a highly dangerous environment where the potential for chemical spills, fire, explosion, and environmental contamination could have significant impact on the public's health.

Several of the chemicals used in the production of methamphetamine are highly flammable and/or explosive. Typical chemicals in a clandestine methamphetamine laboratory, such as methylamine, petroleum ether, phosphine, benzene, ethanol, and lithium aluminum hydride, are highly or extremely flammable (Joint Federal Task Force 1990). Other chemicals, such as sodium, magnesium, and potassium metals, are extremely reactive with air and water and can ignite or explode. There is always potential for a fire or explosion at one of these clandestine laboratories. In fact, approximately 30 percent of drug laboratories found by police in Oregon are found secondary to mysterious explosions (VanDyk 1989). The lack of proper ventilation and temperature controls at these laboratories further compound this problem of fire, explosion, and human exposure.

Chemical spills are another potentially serious problem. In a large chemical spill, ambient air concentrations could be great enough to cause symptoms from the inhalation of solvents, corrosives, or cyanide.

Another serious problem with wider public health implications is the indiscriminate contamination of the environment with hazardous chemicals. Residual chemicals and other chemical by-products are usually not stored or disposed of according to regulations governing hazardous wastes. Solvent chemicals may be dumped into the ground or into sewers or septic systems, thus contaminating surface water, ground water, and wells, requiring extensive cleanup efforts.

Traces of chemicals can permeate the walls, drapes, carpets, and furniture of a laboratory site and can leave a lingering odor that is not easily dissipated.

Phenylacetic acid produces a disagreeable odor, characteristically described as “cat urine” smell, which is a giveaway sign of methamphetamine production. Other toxic vapors also can permeate building walls or be vented outside. Clandestine operators are often afraid that these vapors may alert law enforcers to the laboratory and purposely seal all potential outlets to prevent the vapors from escaping. Since these vapors are potentially toxic, the operators may suffer fatal consequences from overexposure.

Methamphetamine producers also are known to install booby traps to prevent entry by unwanted individuals and to destroy the evidence should the facility be discovered. These booby traps are designed to cause serious injury. When chemical booby traps are used, there is significant potential for serious chemical exposure to intruders and/or law enforcement personnel.

Acute Health Effects

The most significant health risk related to the production of methamphetamine is the acute injury secondary to massive chemical exposure. Primary routes of exposure occur via inhalation and contact to the skin and eyes.

Acute health effects from exposure to any combination of corrosive chemicals include irritation to the skin, eyes, nose, throat, and lungs causing symptoms such as burning of the skin and eyes, lacrimation, coughing, chest pain, and shortness of breath. Conjunctivitis and corneal injury may result from the exposure. Pulmonary edema and hemoptysis may occur in severe cases. Other symptoms of inhalation of chemical vapors include nausea, dizziness, headache, anxiety, and lethargy (Oregon Department of Human Resources 1988).

When hydrogen cyanide gas is present, inhalation may result in rapid progression of symptoms to coma, respiratory failure, and death. Freon spilled onto the skin may cause a freezing injury to the skin. Inhalation of solvent vapors at low concentrations causes mild eye, nose, and throat irritation. At higher concentrations, drowsiness and incoordination may occur. High doses of exposure to solvent chemicals also could lead to liver and kidney impairment (Oregon Department of Human Resources 1988).

Other substances that may be present in the laboratories include various metals and salts. These substances are usually stable solids but in the presence of moisture may become extremely corrosive and/or reactive. When heated, some of these substances could be present in the air as dust or fumes and may be inhaled, with subsequent health effects (Oregon Department of Human Resources 1988). (See Appendix 1 for a list of possible chemicals used in the

synthesis of methamphetamine. See Appendix 2 for a list of exposure routes and health effects by type of chemical involved.)

Chronic Health Effects

Little is known about the chronic health effects of exposure to clandestine drug laboratories. There is some data from animal and human toxicology studies that indicate that some of the chemicals used in the manufacture of methamphetamine may cause cancer, brain damage, liver and kidney problems, and birth defects and reproductive problems. There is no current scientific evidence that human health risk continues once the site is properly decontaminated (Oregon Department of Human Resources 1988).

Health Effects Due to Product Contamination

The presence of contaminants in the final product of clandestine methamphetamine synthesis presents other health problems. Illicit methamphetamine is not produced under good manufacturing practices. For example, lead acetate used as a reagent in the manufacture of P2P, a precursor for methamphetamine production using the amalgam method, can result in significant quantities of lead being present in the methamphetamine thus produced. In 1987 two cases of acute lead poisoning were reported in intravenous users of illicitly produced methamphetamine in Oregon (Allcott et al. 1987). In 1988, also in Oregon, a cluster of lead poisoning cases was discovered among intravenous methamphetamine drug users (Centers for Disease Control 1990). Patients commonly presented with symptoms such as abdominal pain, nausea, vomiting, body pains, Weakness, weight loss, and anorexia. Testing of a sample of illicitly produced methamphetamine provided by one of these cases revealed the presence of 60 percent lead by weight.

Another potential contaminant found in illicitly produced methamphetamine is mercury. The "mercury method" uses P2P and methylamine, which undergo condensation in the presence of aluminum foil and mercuric chloride. Inadequate purification produces a final product contaminated with mercury, residues of which have been found in varying amounts ranging from zero to 1,300 ppm, in methamphetamine samples from 25 clandestine methamphetamine laboratories Seized by DEA (Davidson 1983). However, a literature search did not reveal any cases of mercury poisoning in methamphetamine users in the United States.

Impurities found in the final product of some of these clandestine drug laboratories have resulted in severe and permanent neurologic disability to the drug user. One dramatic example, although not related to methamphetamine,

is the observance of parkinsonism in drug users exposed to meperidine analogs contaminated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin8e (Ballard et al. 1985; Rutenber et al. 1986).

Economic Effects

A deserted clandestine methamphetamine laboratory poses significant risks to the health of the public in nearby vicinities, and proper decontamination of such sites must be carried out. A typical cleanup of a property that has been used as a methamphetamine drug laboratory may cost more than \$5,000. If it is a rental property, the owner may be burdened with the costs and responsibility of the cleanup. The DEA uses asset forfeiture funds to finance the cleanup of clandestine laboratories and advises the States to develop and implement their own asset forfeiture programs. In some instances, proper decontamination for reuse may not be feasible, and the property may have to be totally destroyed.

The cleanup process may involve all the following:

- Removal of surface material layers
- Use of encapsulants and fixative sealers
- Neutralization of corrosives
- Steam cleaning with light-duty equipment
- Use of industrial steam and pressure washers
- Use of detergent washes
- Use of chemical neutralizers/coverups
- "Bake-out" of a property

CONCLUSION

Use of methamphetamine is endemic in certain parts of the United States, and according to the Drug Abuse Warning Network of the National Institute on Drug Abuse, increases were observed in indicators of methamphetamine use during the 1980s in several west coast cities. In keeping with this trend is the problem of the proliferation of clandestine methamphetamine drug laboratories as evidenced by the greater than 600-percent increase in number of such laboratories seized from 1981 to 1989 (National Institute on Drug Abuse 1990). This proliferation of clandestine drug laboratories poses a serious problem because it places innocent bystanders, public officers, and individuals who are manufacturing the drug at risk of exposure to hazardous chemicals. It also should be of public health concern because the potential for a larger segment of the population to be affected is significant via the inappropriate dumping of hazardous chemicals into the environment, thereby causing contamination of both ground and surface water.

Several significant steps have been taken in recent years to address this emerging problem, including the formation of state clandestine drug laboratories committees, passage of State precursor laws, development of guidelines on how to respond to methamphetamine drug laboratory complaints, and adoption of local regulations that deal with the health and safety hazards associated with methamphetamine drug laboratories.

Precursor control legislation has been passed in the States of California, Oregon, Washington, and Texas during 1987 and 1988 (U.S. Department of Justice 1999). For example, California requires a 21-day waiting period and full identification of the purchaser before dispensing any one of 17 specified chemicals, among which are ephedrine and pseudoephedrine. Oregon requires transactions involving the transfer of precursor substances to be reported to the State Police. Texas requires records to be kept of identifying information on purchasers of chemicals, a copy of which goes to the Department of Public Safety, Narcotics Service.

However, much more needs to be done to curtail the demand for methamphetamine and the production of methamphetamine by illicit drug laboratories. Some recommendations for a future strategy to combat this problem include:

- Establish comprehensive drug programs to decrease the problem of drug abuse.
- Increase public awareness of the clandestine drug laboratory problem.
- Conduct further research on the health effects, especially chronic health effects, of exposure to hazardous chemicals used in the manufacture of methamphetamines.
- Conduct further research to determine the safe levels for reoccupation of a property that had been used as a drug laboratory.
- Consider national strategies to impose stricter controls on the availability of precursor chemicals for methamphetamine production.

REFERENCES

- Allcott, J.V.; Barnhart, R.A.; and Mooney, L.A. Acute lead poisoning in two users of illicit methamphetamine. *JAMA* 258(4):510-511, 1987.
- Ballard, P.A.; Tetrud, J.W.; and Langston, J.W. Permanent parkinsonism in humans due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): A

- report of seven moderate-to-severely affected cases. *Neurology* 35:949-956, 1965.
- Centers for Disease Control. Lead poisoning associated with intravenous-methamphetamine use—Oregon, 1988. *JAMA* 263(6):797-798, 1990.
- Davidson, A. Mercury residues in illicit methamphetamine. *Microgram* 16(9):142-146, 1983.
- Frank, R.S. The clandestine drug laboratory situation in the United States. *J Forensic Sci* 28(1):18-31, 1983.
- Joint Federal Task Force: Drug Enforcement Administration, Environmental Protection Agency, U.S. Coast Guard. *Guidelines for the Cleanup of Clandestine Drug Laboratories*. Washington, DC: U.S. Department of Justice, Drug Enforcement Administration, March 1990.
- National Institute on Drug Abuse. *Semiannual Report*. Data from the Drug Abuse Warning Network. DHHS Pub. No. (ADM)90-1664. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1990.
- Oregon Department of Human Resources. *Hazardous Chemicals: Guidelines for Local Law Enforcement Personnel: (Substances Found in Methamphetamine Menufactories)*. 4th ed. Portland, OR: Department of Human Resources, Health Division, June 1988.
- Ruttenber, A.J.; Garbe, P.L.; Kalter, H.D.; Castro, K.G.; Tetrud, J.W.; Porter, P.; Irwin, I.; and Langston, J.W. Meperidine analog exposure in California narcotics abusers: Initial epidemiologic findings. In: Markey, S.P.; Castagnoli, N.; Trevor, A.J.; Kopin, I.J., eds. *MPTP: A Neurotoxin Producing a Parkinsonian Syndrome*. Orlando, FL: Academic Press, 1986. pp. 339-353.
- U.S. Department of Justice. *Clandestine Laboratory Seizures in the United States: Calendar Year 7988*. Washington, DC: U.S. Department of Justice, Drug Enforcement Administration, Office of Intelligence, August 1989.
- VanDyk, J. Drug labs require special ecology attention, *Baseline* 8(5):4, 1989.

AUTHORS

Gary Irvine, B.S., R.S.
Environmental Health Supervisor
Seattle-King County Department of Public Health
Suite 101
1404 Central Avenue South
Kent, WA 98032

Ling Chin, M.D., M.P.H.
Epidemiologist
Division of Epidemiology and Prevention Research
National Institute on Drug Abuse
Rockwall II, Suite 815
5800 Fishers Lane
Rockville, MD 20857

APPENDIX 1

Chemicals Associated With Illicit Methamphetamine Manufacture

METAL/SALT REAGENTS

Aluminum foil
Iodine
Lead acetate
Lithium aluminum hydride
Magnesium
Mercuric chloride
Palladium
Red phosphorus
Sodium
Sodium cyanide
Thionyl chloride

SOLVENTS

Acetone
Benzene
Chloroform
Ethyl ether
Freon
Hexane
Isopropanol
Methanol
Pyridine

PRECURSORS

Acetaldehyde
Benzyl chloride
Ephedrine
Methamphetamine
Phenylacetic acid
P2P

ACID-BASE REAGENTS

Acetic acid
Acetic anhydride
Ammonia
Hydrochloric acid
Hydrogen peroxide
Hydroiodic acid
Sodium hydroxide
Sulfuric acid

By-Products and Contaminants Associated With the Manufacture of Methamphetamine

P2P AMALGAM METHOD

Dibenzyl ketone
Enol acetate of P2P
Lead oxides
Aluminum oxides
Aluminum hydroxide
Mercury
Acetic acid
 α -benzyl-N-methylphenethylamine

N,N-dimethylamphetamine
Amphetamine
Di-(1-phenylisopropyl) amine
Di-(1-phenylethyl) methylamine
Tri-(1-phenylisopropyl) amine
Benzyl methyl ketone phenylisopropylamine
Benzyl methyl ketone benzylamine
2,4-dihydroxy-1,5-diphenyl-4-methylpentane

EPHEDRINE METHOD

Iodine
Chloropseudoephedrine
Phosphine (produced from overheating)
Yellow phosphorus (produced from overheating)

SOURCE: Oregon Department of Human Resources 1988

APPENDIX 2

Chemical Toxicity and Routes of Exposure (Skin and Respiratory)

CYANIDE

<u>Substance</u>	<u>Form</u>	<u>Exposure</u>
Sodium cyanide	Solid	Skin, eyes
Potassium cyanide	Solid	Skin, eyes
Benzyl cyanide	Liquid	Skin, eyes, inhalation
Hydrogen cyanide	Gas	Inhalation

Health effects: Highly toxic substances. If solid salt forms are mixed with acid, hydrogen cyanide gas will be released. Inhalation of hydrogen cyanide may result in rapid progression of symptoms to coma, respiratory failure, and death.

CORROSIVES AND IRRITANTS

<u>Substance</u>	<u>Form</u>	<u>Exposure</u>
Acetic acid	Liquid	Skin, eyes, inhalation
Acetic anhydride	Liquid	Skin, eyes, inhalation
Benzyl chloride	Liquid	Skin, eyes, inhalation
Hydroiodic acid	Liquid	Skin, eyes, inhalation
Methylamine	Gas, liquid, solid	Skin, eyes, inhalation
Perchloric acid	Liquid	Skin, eyes, inhalation
Phosphine	Gas	Eyes, inhalation
Sodium metal	Solid	Skin, eyes
Sodium hydroxide	Liquid, solid	Skin, eyes
Thionyl chloride	Liquid	Skin, eyes

Health effects: Vapors of volatile corrosives may cause eye irritation, lacrimation, conjunctivitis, and corneal injury. Inhalation may cause irritation of mucous membranes of the nose and throat and lung irritation resulting in cough, chest pain, shortness of breath. Pulmonary edema and hemoptysis may occur in severe cases. High concentrations of vapor may cause skin irritation. Additional symptoms of vapor inhalation may include headache, nausea, dizziness, and anxiety. Direct contact with corrosives may result in severe eye or skin burns.

SOLVENTS

<u>Solvents</u>	<u>Form</u>	<u>Exposure</u>
Acetone	Liquid	Skin, eyes, inhalation
Benzene	Liquid	Skin, eyes, inhalation
Benzylchloride	Liquid	Skin, eyes, inhalation
Chloroform	Liquid	Skin, eyes, inhalation
Ethanol	Liquid	Skin, eyes, inhalation
Ethyl ether	Liquid	Skin, eyes, inhalation
Freon	Liquid	Skin, eyes, inhalation
Hexane	Liquid	Skin, eyes, inhalation
Isopropanol	Liquid	Skin, eyes, inhalation
Methanol	Liquid	Skin, eyes, inhalation
Petroleum ether	Liquid	Skin, eyes, inhalation
Pyridine	Liquid	Skin, eyes, inhalation

Health effects: inhalation of vapors at low concentrations may result in mild eye, nose, and throat irritation. Symptoms of intoxication (drowsiness and incoordination) or loss of consciousness may occur at high concentrations. Liver and kidney impairment also may occur at high doses. Freon spilled onto the skin may result in freezing injury to the skin.

METALS/SALTS

<u>Substance</u>	<u>Form</u>	<u>Exposure</u>
Aluminum	Solid	Skin, eyes
Magnesium	Solid	Skin, eyes
Palladium	Solid	Skin, eyes
Red phosphorous	Solid	Skin, eyes
Iodine	Solid	Skin, eyes
Mercuric chloride	Solid	Skin, eyes
Lead acetate	Solid	Skin, eyes
Lithium aluminum hydride	Solid	Skin, eyes
Sodium acetate	Solid	Skin, eyes
Sodium hydroxide	Solid	Skin, eyes
Sodium metal	Solid in kerosene	Skin, eyes
Potassium metal	Solid in kerosene	Skin, eyes
Thorium	Solid	Skin, eyes

Health effects: Most metals and salts are stable solids with minimal potential for exposure unless ingested or unless the metal is present in the air as dust or fumes, if heated. Sodium and potassium metal and sodium hydroxide are extremely corrosive in the presence of moisture. Lithium aluminum hydride is extremely reactive. Thorium is an alpha-emitting radioactive material.

PRECURSORS

<u>Substance</u>	<u>Form</u>	<u>Exposure</u>
Phenylacetic acid Solid, with characteristic foul odor. Used in fragrances, flavorings. May produce irritation upon direct contact.	Solid	Skin, eyes

P2P Specific toxicity data lacking. Similar compounds used in fragrances and pharmaceuticals.	Liquid	Skin, eyes
Methylamine Ammonia odor present at very low levels. See also irritants, corrosives.	Gas Liquid Solid	Skin, eyes, inhalation Skin, eyes inhalation Skin, eyes

SOURCE: Oregon Department of Human Resources 1988

Heavy Metal and Organic Contaminants Associated With Illicit Methamphetamine Production

Brent T. Burton

INTRODUCTION

Methamphetamine is a powerful stimulant drug commonly known on the street as “crank” or “speed.” It is currently the most popular and widespread amphetamine that is illegally manufactured, distributed, and abused.

Illicit methamphetamine is produced in clandestine laboratories that are widespread in the United States. The profit motive for the clandestine chemist is enormous, with some laboratories producing in excess of \$800,000 per week in street value. Although several other illicit drugs of abuse are occasionally manufactured in clandestine laboratories, methamphetamine accounts for almost 95 percent of all clandestine laboratory seizures. The frequency of laboratory seizures has been increasing nationwide over the past decade (Anon 1988). The States of California, Texas, Oregon, and Washington have shown the greatest increase in clandestine laboratory activity.

Adverse health effects to the abuser are not limited to toxic effects of the drug. Illicit drugs produced in clandestine laboratories by unskilled chemists are likely to contain potentially toxic contaminants due to unintended reaction by-products and reagent residuals. Process errors in the production of clandestine drugs previously have resulted in severe health effects, including acute Parkinson's disease from attempted production of 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP) and acute lead poisoning from injection of methamphetamine (Alicott et al. 1987; Ballard et al. 1985; Norton et al. 1989).

The average concentration of methamphetamine street samples is approximately 40 to 50 percent (Hall et al. 1988). Most contaminants found in illicit drugs are intentionally added by the distributor to dilute or “cut” the product to increase profits. Such substances include lactose, mannitol, lidocaine, procaine, caffeine, quinine, and sodium bicarbonate and may account for as

much as 94 percent of the finished product (Grinspoon and Bakalar 1985). In the case of drugs produced by the clandestine chemist, additional contaminants may be introduced by the production process. One can predict such potential contaminants due to unreacted substances or unintended reaction products from known production methods available to the clandestine chemist. Though unintended contaminants may be introduced into the finished drug by the clandestine chemist, the extent and types of substances as a result of the production process have not yet been adequately studied.

HISTORY

Methamphetamine was developed in 1919 as an amphetamine derivative by A. Ogata, a Japanese pharmacologist. However, it was not until the 1930s that the pharmacologic properties of amphetamines became known. The sympathomimetic properties of amphetamines initially made them useful as vasoconstrictor agents, and they were first introduced into the marketplace in 1932 as Benzedrine, an inhaler designed for relief of nasal congestion. Users of these nonprescription inhalers soon noted that the amphetamine contents were powerful central nervous system stimulants. This property subsequently made amphetamines useful drugs in the treatment of narcolepsy and some forms of depression but also made them desirable as drugs of abuse.

The abuse of amphetamine began almost as soon as it was available as an over-the-counter medication. Shortly after the Benzedrine nasal inhaler became available in 1931, abusers were taking apart the spray bottle to retrieve the paper inside containing 250 mg of amphetamine. These strips of paper then were consumed in chewing gum or stirred into a beverage for its stimulating and euphoric effect (Grinspoon and Hedblom 1975).

By 1962 the legal production of amphetamines was estimated by the Food and Drug Administration to be more than 8 billion tablets per year, with output increasing every year. Much of the amphetamine abuse of the 1950s and 1960s occurred as a result of prescription abuse by individual patients obtaining drugs from their private physician, many of whom knowingly were writing prescriptions for profit.

The drug culture of the 1960s brought a dangerous new route of administration for amphetamines. An injectable form of pharmaceutical methamphetamine rapidly became responsible for the amphetamine abuse lifestyle known as the "speed freak." The dangerously addictive nature of injectable amphetamines became obvious with the advent of the amphetamine-tolerant freak who would inject as much as 15 g of amphetamine during a single day (Grinspoon and Hedblom 1975).

Until the 1970s most amphetamines were obtained from pharmaceutical sources that were diverted into the black market. It has been estimated that as much as 50 percent of legitimate amphetamine production was diverted by shipments to unauthorized persons, thefts, or prescription forgeries (Morgan 1981).

Due to the abuse of amphetamines and other drugs in the United States, the Controlled Substance Act (CSA) was passed in 1970, which designated control schedules for drugs according to their abuse potential. This act dramatically changed the availability of pharmaceutical amphetamines by requiring special procedures for manufacturers to register shipments and provide detailed accounting of transactions involving controlled substances. Predictions that strict controls would result in a shift to clandestine production of methamphetamine did not materialize at that time. However, the increased availability and use of cocaine in the 1970s may have temporarily reduced market demand for methamphetamine.

As amphetamines became more difficult to obtain, purity of street samples began to decline. During the mid-1970s many street samples sold as amphetamine contained little or none of it, and a variety of drugs began to show up that were being sold as amphetamine. Samples of street amphetamines in 1973, after the effect of the CSA was apparent, contained only about 10 percent amphetamine on average (Morgan 1981). Most often, over-the-counter drugs with stimulant properties such as caffeine, ephedrine, and phenylpropanolamine were substituted and sold as amphetamine. This practice eventually led to the drug "look-alike" business, a thriving mail-order enterprise offering these legal over-the-counter drugs packaged and promoted with names, tablet shapes, and colors designed to mimic amphetamines.

Since the mid-1980s there has been a reemergence of the illicit use of methamphetamine. One such indicator is the rapid increases that have been documented in numbers of clandestine laboratories seized by law enforcement agencies. Most recently, media reports have focused on the increasing popularity of "ice," a smokable form of methamphetamine (Lerner 1969). The use of this crystalline form of methamphetamine has been prevalent especially in Hawaii, where it is imported from Pacific rim countries. As this form of methamphetamine becomes more widely available in the United States, it is possible that stimulant users once again will shift to methamphetamine.

CLANDESTINE SYNTHESIS OF METHAMPHETAMINE

Illicit manufacture of methamphetamine is a simple process that does not require special knowledge or expertise in chemistry. Most methamphetamine is

produced by relatively uneducated persons who synthesize the drug from published or handwritten recipes. The drug subculture provides abundant opportunities for the potential clandestine chemist to obtain recipes, or even attend cooking classes, for methamphetamine. Many recipes in circulation are handwritten instructions that describe how to procure the needed chemicals, glassware, and supplies. These instructions often include detailed sketches and descriptions of the procedure so the novice can produce methamphetamine without prior training. Some underground recipes even describe the legal status of various chemicals and methods to avoid detection by law enforcement officials.

Several publications, available in bookstores or by mail order, describe the methods of drug manufacture. One such publication, *Psychedelic Chemistry*, describes detailed recipes for the production of several drugs. In addition, information is provided about how to obtain chemicals and laboratory equipment without prompting the attention of law enforcement officials (Smith 1981).

The clandestine chemist need not resort to handwritten underground recipes or try to locate the proper reference text in a bookstore. Numerous scientific journals provide a wealth of information regarding drug synthesis, including alternate procedures for a variety of processes, that the chemist may select depending on chemical availability. The educational level of persons utilizing such references must be more sophisticated than that of the typical clandestine chemist due to the highly technical nature of the journals. An example of such an article is a description of a currently unused but proposed method of production, authored by chemists of the U.S. Drug Enforcement Administration (DEA) (Cason et al. 1984). These references usually are torn or cut out of library journals, presumably to reduce competition from other would-be clandestine chemists.

Because the clandestine chemist usually lacks skill and training in chemistry, there are multiple opportunities for errors or misunderstanding of proper procedure. Attempts at shortcuts, inadequate filtering, salt washing, or solvent extraction could result in serious contamination with reagents. At least one clandestine chemist apparently completely misunderstood the proper procedure and produced a finished product that contained 60 percent lead with phenyl-2-propanone (P2P) but no methamphetamine (Norton et al. 1989).

Numerous chemicals associated with the illicit production of methamphetamine are listed below. Although only a few chemicals may be required for production, there are multiple reagents and precursors that can be substituted for those that are difficult to obtain legally. Thus, there may be many chemicals that potentially can contaminate the finished product.

SOLVENTS

Acetone
Benzene
Chloroform
Ethyl ether
Ethanol
Freon
Hexane
Isopropanol
Methanol
Pyridine
Toluene

PRECURSORS

Acetaldehyde
Acetic anhydride
Allyl benzene
Benzyl cyanide
Benzylchloride
Diethylmalonate
Dimethylformamide
Ephedrine
Ethanol
Ethyl acetate
Formic acid
Hydrogen gas
Hydrogen peroxide
Methylamine
N-methylformamide
Nitroethane
Phenyl-2-propanone
Phenylacetic acid
Phenylacetylchloride

REAGENTS

Metals

Aluminum
Barium sulfate
Calcium chloride
Copper chloride
Iron
Lead acetate
Lithium aluminum hydride
Magnesium
Magnesium sulfate
Manganese oxide
Mercuric oxide
Mercuric chloride
Palladium
Palladium chloride
Potassium cyanide
Sodium acetate
Sodium ethoxide
Sodium cyanide
Sodium
Cyanotrihydroborate
Sodium
Thorium oxide

Nonmetals

Butylamine
Iodine
Phosphorous
Phosphorouapentachoride
Thionyl chloride

Acids

Acetic acid
Hydrochloric acid
Hydroiodic acid
Perchloric acid
Phosphoric acid
Sulfuric acid

Bases

Ammonia
Sodium hydroxide
Sodium carbonate

PRODUCTION PROCESSES

P2P is the primary precursor most often used by the clandestine chemist. The amalgam and Leukart processes are the most popular (figure 1), accounting for about 90 percent of clandestine methamphetamine production (Frank 1983). Processes involving P2P as the precursor often utilize methylamine to provide the amine group and thus formulate methamphetamine in a simple single-step reaction procedure. The amalgam method utilizes a combination of mercuric chloride and aluminum foil as catalysts (figure 1). These and all reactions require a variety of acids and solvents for extraction and purification of the finished product.

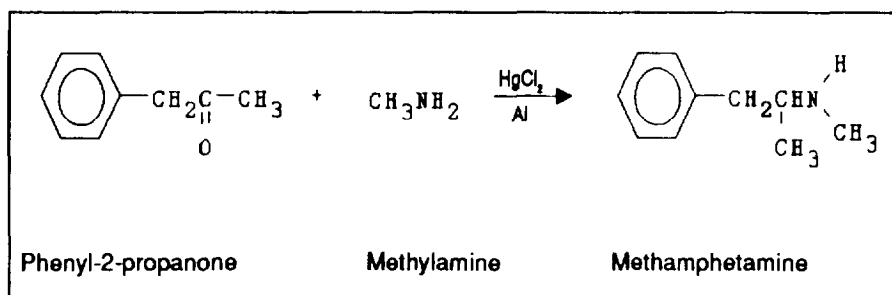


FIGURE 1. *Synthesis of methamphetamine utilizing the amalgam method catalyzed by mercuric chloride and aluminum foil*

The clandestine manufacturing and purification procedure is represented by the following instructions paraphrased from a recipe obtained from a clandestine chemist (Dallosta 1985): The process is initiated by adding mercuric chloride, aluminum foil, isopropanol, and sodium hydroxide to a reaction vessel and heating. When the solution comes to a boil, the P2P and methylamine are added to the mixture and heated for 4 hours. The reaction mixture then is passed through filter paper to remove contaminants. Excess methylamine is removed by the application of heat to the reaction product. The remaining mixture containing "freebase amine" is purified with a salt wash to "kill the poisonous mercuric chloride." The product then is acidified to adjust the pH, crystallized, purified with solvent in a separatory funnel, and then recrystallized and packaged for distribution.

Unavailability of P2P and legal controls of other precursors have resulted in the increasingly popular use of ephedrine as a primary precursor. Ephedrine is a

common over-the-counter decongestant cold remedy that differs in molecular structure from methamphetamine only by the presence of a hydroxyl group at the p-carbon. A single-step hydrogenation reaction of ephedrine, which can be accomplished by several methods, will produce a high yield of methamphetamine. This reaction has the advantage of considerably less noticeable odor than reactions utilizing P2P (the unpleasant, lingering odor of P2P and another precursor, phenylacetic acid, has frequently been a clue to the operation of a clandestine laboratory). To escape detection and also utilize easily available chemicals, clandestine chemists may resort to using hydrogenation methods of ephedrine using red phosphorous as a catalyst with hydroiodic acid. In some cases clandestine chemists are fabricating high-pressure reaction vessels to react ephedrine with hydrogen gas. If ephedrine or P2P are not available, the chemist may resort to industrial chemicals, such as benzyl chloride, as the precursor.

PRECURSOR SYNTHESIS

Clandestine manufacture of methamphetamine became more complicated in 1980 when P2P was classified as a Schedule II controlled substance by DEA. In addition, States with clandestine drug laboratory problems, that is, California, Oregon, and Washington, have passed laws requiring that any person who purchases listed chemicals that may be used in methamphetamine production be reported to the State police. These legal restrictions on P2P, intended to curb the growth of clandestine methamphetamine, spurred the development of clandestine laboratories specializing in the production of P2P from phenylacetic acid. Legitimate P2P sells commercially for less than \$100 per liter, but the same amount will net more than \$4,000 for the clandestine chemist. Synthesis of P2P usually is accomplished by utilizing lead acetate as the primary reagent in a process that requires a distillation procedure (figure 2). In the hands of the unskilled or careless clandestine chemist, these processes may result in the introduction of contamination from lead and other reagents used in the production process.

In the absence of phenylacetic acid there are several alternative reactions the clandestine chemist may choose to produce methamphetamine, utilizing easily available chemicals but requiring more complex and often more dangerous reactions. For example, phenylacetic acid may be synthesized from industrial chemicals such as benzylchloride, toluene, or benzene. In a possible endless source of potential reaction pathways, the chemist may resort to manufacturing many precursors from uncontrolled chemicals. For example, ephedrine may be synthesized from propiophenone, or methylamine may be produced in a reaction with ammonia and methanol. The increasing complexity of the reaction sequence and the substantial numbers of chemicals required in the production

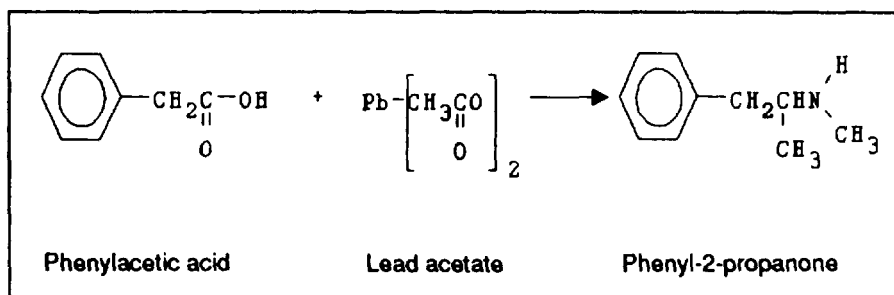


FIGURE 2. *Synthesis of the precursor P2P from phenylacetic acid and lead acetate*

process increase the risk of errors and the probability of toxic contamination in the final product.

TOXICITY OF DRUG CONTAMINANTS

Although drug contamination may result in potentially serious adverse health effects for the drug user, the difficulty in studying such a group of subjects has made it problematic to document the extent of drug Contaminant-induced illness from methamphetamine. For this reason most reports of drug contaminant illness have been anecdotal cases. Epidemiological investigation into this problem has not yet been accomplished.

There have been reports of contaminated drugs produced in clandestine laboratories that have resulted in disastrous health effects in the unsuspecting user. One such major outbreak of serious illness from contaminated drugs occurred in 1982 when an attempt was made by a clandestine chemist to produce the meperidine congener, MPPP. Instead, due to a relatively minor aberration in the reaction process, highly toxic 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) was synthesized and distributed on the street. Drug users unlucky enough to inject MPTP developed severe and permanent Parkinson's disease. Only by a series of coincidences was the cause of the Parkinson's disease traced to the contaminated drug (Ballard et al. 1985). It is not known how many other toxic substances may be created by the clandestine chemist attempting to make other illegal drugs, including methamphetamine.

Two case reports have documented human toxicity due to methamphetamine contamination. In both instances illness was caused by heavy contamination of lead. In 1987 two patients in Oregon were reported to have developed lead toxicity as a result of the injection of methamphetamine. Both patients

developed illnesses consistent with lead intoxication and presented with symptoms of nausea, vomiting, constipation, numbness and tingling, weakness, and headache. Laboratory data revealed elevation of liver enzymes, suggesting a diagnosis of infectious hepatitis. However, in view of the nonspecific clinical presentation, the possibility of lead poisoning apparently was not considered until basophilic stippling was found on the blood smear, which prompted an investigation for lead toxicity. A blood lead level of 204 µg/dL was measured in one of the patients (<40 µg/dL is normal). A blood lead level was not reported for the second patient, although a free erythrocyte protoporphyrin was elevated at 68 µg/L (<50 µg/L is normal). Both patients required chelation therapy with disodium calcium edetate. A sample of methamphetamine obtained later from one of the victims was shown to contain 899 ppm of lead. This would result in the injection of approximately 0.1 mg of lead per dose of drug (Allcott et al. 1987).

The second outbreak of lead poisoning was reported in 1988 and involved 12 methamphetamine abusers in a three-county area in Oregon. All cases came to medical attention between April 18 and September 15, 1988. The mean age of these patients was 27 years (range 24 to 36 years), nine males and three females. The most common complaints were gastrointestinal, that is, nausea, vomiting, abdominal pain, and constipation. Although lead poisoning typically is associated with neurological findings, only one patient complained of paresthesias. The physical examinations were remarkable for abdominal tenderness, but evidence of encephalopathy or neuropathy was not present. Anemia was common with a mean hematocrit of 29.8 percent (range 20 to 44 percent). Basophilic stippling was present in 10 cases. Elevation of liver enzymes was consistent with chemical hepatitis. The most severely poisoned patient also developed a clinical pancreatitis. The mean blood lead level was 146 µg/dL, with a range from 49 µg/dL to 513 µg/dL, the latter being the highest level yet reported in a living person. Seven patients underwent chelation treatment. Although followup was not possible for all patients, it appeared that all improved with treatment. It was presumed that this outbreak resulted from perhaps a single source because of the close proximity of the cases. Although the source or the responsible clandestine chemist could not be identified, one of the victims supplied a sample of the drug he had allegedly injected. Analysis of this drug revealed that the sample contained 80 percent lead (Norton et al. 1989). This concentration of lead would result in a dose of more than 50 mg of lead per injection.

The cases described above involved relatively large doses of lead that resulted in severe acute poisoning. Although smaller doses of lead in methamphetamine may result in illness, the effects may not be readily apparent to the clinician, particularly in view of the nonspecific symptoms frequently seen in lead poisoning. It is not known if methamphetamine abusers, as a group,

may be at risk of unrecognized chronic lead toxicity due to chronic low-level exposure to lead; chronic accumulation may not result in illness until large body burdens of lead have been attained.

It has been suspected, but not yet documented, that drug abusers may be at risk of developing poisoning from other reagents used in the manufacturing process. Although mercury has been considered as a possible contaminant with significant health impact, there have not yet been any confirmed cases of mercury poisoning. However, it must be recognized that this may be due to the lack of case recognition in patients that have complications that are consistent with drug abuse such as hepatitis and nephritis. In an attempt to document excessive mercury exposure, hair samples of 12 methamphetamine abusers were measured for mercury. None of the samples showed a significant increase in mercury concentrations compared with nonuser controls (French 1985). However, this exploratory study could not overcome the difficulty of self-selection of patients and the inherent technical problems associated with collection and interpretation of hair sampling for mercury. Blood or urine levels were not measured, and drug samples were not assayed to determine if the drug users had been exposed to methamphetamine contaminated with mercury. Injection of mercuric chloride probably would produce severe burning pain at the injection site and the development of thrombophlebitis. Hepatitis and nephritis likely would occur following systemic absorption.

In addition to heavy metal contamination from reagents, the clandestine production process also may result in the formation of a variety of possible organic contaminants. One study revealed that contamination by organic products to be as high as 10 to 39 percent of the sample (LeBelle et al. 1973). Of the few studies that have attempted to characterize the contamination of illicit methamphetamine, most have attempted to identify drug contaminants as intermediates or markers of a particular process for evidentiary purposes (Kram et al. 1976; Sottolano 1988). It has been noted by forensic chemists that gas chromatographic analysis of illicit methamphetamine has demonstrated a variety of substances, including several contaminants that, thus far, have not been identified and have unknown toxicity. These contaminants are most often due to incomplete reactions, inadequate purification procedures, or unintended reactions. Attempts to identify some of these substances have required synthesis of expected contaminants to use as standards for confirmation of chemical structure. Noggle and colleagues (1985), utilizing liquid chromatographic procedure, noted that *a*-benzylphenethylamine derivatives were the most common contaminants. These derivatives were shown to have greater potency to induce seizures in mice than methamphetamine. Organic contaminants found in illicit methamphetamine are summarized in table 1.

TABLE 1. *Organic contaminants of illicit methamphetamine*

Substance	Reference
N,N-dimethylamphetamine	Kram et al. 1976
N-formylamphetamine	Kram et al. 1976
N-formylmethamphetamine	LeBelle et al. 1973
Dibenzylketone	Kram et al. 1976
a-benzylphenethylamine	Noggle et al. 1985
a-benzyl-N-methylphenethylamine	Barron et al. 1974
a,a'-dimethyldiphenethylamine	Kram et al. 1976
N-methyldiphenylethylamine	Kram et al. 1976
N,a,a'-trimethyldiphenethylamine	Barron et al. 1974

CONCLUSION

The clandestine production of methamphetamine is performed by unskilled chemists utilizing an array of potentially toxic chemicals. Residual reagents, solvents, and unintended reaction by-products may remain as contaminants in the finished product. Fourteen cases of acute lead poisoning have been reported in the medical literature as result of methamphetamine contamination. It is unknown if lead poisoning from methamphetamine is episodic, due to poor technique, or is more widespread but at a **lower** level of toxicity. Further investigation into the prevalence of lead toxicity is currently under way.

Toxicity due to other reagents and organic by-products remains a distinct possibility, although known cases have not been reported. Further research is needed to examine the extent of contaminants in illicit methamphetamine and to determine their adverse health implications.

REFERENCES

- Allcott, J.V.; Barnhart, R.A.; and Mooney, L.A. Acute lead poisoning in two users of illicit methamphetamine. *JAMA* 258:510-511, 1987.
- Anon. *Clandestine Laboratory Seizures in the United States, 1988 and 1987*. Washington, DC: U.S. Drug Enforcement Administration, 1988.
- Ballard, P.A.; Tetrud, J.W.; and Langston, J.W. Permanent human parkinsonism due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *Neurology* 35:949-956, 1985.
- Barron, R.P.; Kruegel, A.V.; Moore, J.M.; and Kram, T.C. Identification of impurities in illicit methamphetamine samples. *J Assoc Off Anal Chem* 57:1147-1158, 1974.

- Cason, T.A.; Angelos, S.A.; and Raney, J.K. A clandestine approach to the synthesis of phenyl-2-propanone from phenylpropenes. *J Forensic Sci* 29:1187-1208, 1984.
- Dalosta, K.L. *Clandestine Laboratory Manual*, Sacramento, CA: Western States Information Network, 1985.
- Frank, R.S. The clandestine drug laboratory situation in the United States. *J Forensic Sci* 28:18-31, 1983.
- French, J.F. *Methamphetamine and Mercury Ingestion*. New Jersey: Department of Health, Division of Alcohol, Narcotics, and Drug Abuse, 1985.
- Grinspoon, L., and Bakalar, J.B. *Cocaine: A Drug and its Social Evolution*. New York: Basic Books, 1985.
- Grinspoon, L., and Hedblom, P. *The Speed Culture: Amphetamine Use and Abuse in America*. Cambridge, MA: Harvard University Press, 1975.
- Hall, J.N.; Uchman, R.S.; and Dominguez, R. *Trends and Patterns of Methamphetamine Abuse in the United States*. National Institute on Drug Abuse. Miami, FL, 1988.
- Kram, T.C.; Kram, B.S.; and Kruegel, A.V. The identification of impurities in illicit methamphetamine exhibits by gas chromatography/mass spectrometry and nuclear magnetic resonance spectroscopy. *J Forensic Sci* 22:40-52, 1978.
- LeBelle, M.; Sileikam, M.; and Romach, M. Identification of a major impurity in methamphetamine. *J Pharm Sci* 62:862, 1973.
- Lerner, M.A. The fire of ice. *Newsweek*, November 27, 1989. pp. 37-40.
- Morgan, J.P. Amphetamine. In: Lowinson, J.H., and Ruiz, P., eds. *Substance Abuse: Clinical Problems and Perspectives*, Baltimore: Williams & Wilkins, 1981.
- Noggle, F.T.; Clark, C.R.; and Davenport, T.W. Synthesis, identification, and acute toxicity of α -benzylphenethylamine and α -benzyl-N-methylphenethylamine. Contaminants in clandestine preparation of amphetamine and methamphetamine. *J Assoc Off Anal Chem* 88:1213-1222, 1985.
- Norton, R.L.; Kauffman, K.W.; Chandler, D.B.; Burton, B.T.; Gordon, J.; and Foster, L.R. Intravenous lead poisoning associated with methamphetamine use. (Abstract.) *Vet Human Tox* 31:379, 1989.
- Smith, V.S. *Psychedelic Chemistry*. Port Townsend, WA: Loompanics Unlimited, 1981.
- Sottolano, SM. The quantitation of phenyl-2-propanone using high-performance liquid chromatography. *J Forensic Sci* 33:1415-1420, 1988.

AUTHOR

Brent T. Burton, M.D.
Medical Director
Oregon Poison Center
Associate Professor of Emergency Medicine
Oregon Health Sciences University
3181 Southwest Sam Jackson Park Road
Portland, OR 97201

Methamphetamine Abuse in California

Bruce Heischober and Marissa A. Miller

INTRODUCTION

Methamphetamine is a drug that historically has been abused and continues to be abused among Californians. There is no reliable estimate of exact prevalence of methamphetamine abuse in the State of California, and there also is a general paucity of epidemiologic and clinical data in the scientific literature describing the current problem, which developed during the 1980s.

Historical information from previous epidemics of methamphetamine abuse in the United States reveals that during the 1950s and 1980s methamphetamine and amphetamines were diverted pharmaceutical products most commonly taken orally by truck drivers, students, and housewives as insomniac agents and anorectics (Lukas 1985). Later, intravenous (IV) use became popular among white, young adults, particularly in the Haight-Ashbury district of San Francisco (Smith 1972). Over the past several years the demographics of the amphetamine abuser have been changing to include more ethnic minorities, adolescents, and women. Today, alternate methods of administration, such as intranasal, smoking in pipes, inhaling vapors from methamphetamine heated on aluminum foil (known as "chasing the dragon"), and mixing in soft drinks are becoming more common. In addition, there clearly have been major changes in production and distribution patterns in recent years.

NOMENCLATURE

Amphetamines and methamphetamine fall within the phenylethylamine class of stimulants. Methamphetamine typically is referred to and marketed as "speed," "crystal," "crank," "go," and, most recently, "ice." At this time in California virtually all the chemicals offered as amphetamine or by the other terms listed above have been shown by laboratory analysis to contain d-methamphetamine or a mixture of d- and d/l-methamphetamine (Puder et al. 1988). During the early 1980s when other chemicals such as cocaine, phenylpropanolamine hydrochloride (PPA), d-amphetamine, ephedrine, and pseudoephedrine were mixed with or substituted for methamphetamine, street

products being marketed as methamphetamine did not always contain the drug (Heischober and Derlet 1989).

In 1980 the majority of drugs sold on the street as methamphetamine or speed were a combination of ephedrine, PPA, and caffeine (Lake and Quirk 1984). This combination came to be termed “look-alike” speed because the powder or capsules looked identical to the real thing. Research has shown that this combination can mimic the central nervous system (CNS) discriminative cue for amphetamine. However, a major difference is noted in the area of stimulation of alpha and beta receptors vs. cortical stimulation. The PPA and ephedrine molecules are structurally configured to result in decreased potency as central stimulants with retained peripheral activity. Users of look-alike speed attempting to achieve the same level of cortical stimulation may overadminister the drug and risk overstimulation of the cardiovascular system. An increased risk and incidence of stroke has been noted in abusers of PPA (Kase et al. 1987).

The term “ice” most often refers to a pure form of d-methamphetamine HCl that is marketed in a large crystalline form. Ice typically is smoked or ground up and injected or snorted. Public Law 101-647, passed on November 29, 1990, refers to smokable crystal methamphetamine, and the guidelines subsequently released in the *Federal Register* further define ice as a mixture or substance containing d-methamphetamine HCl of at least 80-percent purity (*Federal Register* 1991).

Geographic variations on street drug names exist within California. Crystal commonly refers to methamphetamine in southern California, while in other areas of the State it can mean heroin. The street name in San Diego for the mixture of methamphetamine and cocaine is “croak.” Another example of the variations seen in street terminology is the term “night owl.” In a recent interview with Heischober, a patient described night owl as a marijuana cigarette dipped in phencyclidine and sprinkled with a mixture of crack cocaine and methamphetamine.

PATTERNS OF METHAMPHETAMINE PRODUCTION

Methamphetamine is relatively simple to synthesize in a laboratory from precursor chemicals (Allen and Cantrell 1989). Traditionally, production was controlled by white motorcycle gangs, which continue to produce methamphetamine in clandestine laboratories, but there has been a change toward two other types of production and distribution patterns. First, there has been an increase in the number of individuals who alone or with a few others buy precursors and attempt to produce moderate amounts of

methamphetamine and distribute it independently. It has been suggested that the relative simplicity of production and profit associated with methamphetamine production and sale may underlie this recent development. A second development reported by law enforcement agencies has been the apprehension of illegal aliens hired by organized groups of criminals to produce methamphetamine and initiate distribution. This has suggested interest and involvement on the part of groups involved with sale and distribution of drugs such as heroin, cocaine, and marijuana.

California also has experienced a shift in the method used to produce illicit methamphetamine. The two primary methods for the synthesis of methamphetamine are the amalgam method and the ephedrine reduction method. Historically, methamphetamine in California was produced by the amalgam method using phenyl-2-propanone (P2P) as the primary precursor. In 1980 P2P was reclassified nationally as a Schedule II controlled substance, which reduced the availability of this precursor for illicit methamphetamine synthesis. At least partially as a result of the change in the availability of P2P, in the past several years ephedrine reduction laboratories have become more prevalent, first in southern California, then in areas to the north. The ephedrine reduction process is responsible for more than 90 percent of the methamphetamine currently produced in southern California (Derlet and Heischouer 1990). This is a significant shift because the resulting product is d-methamphetamine rather than the racemic mixture of d/l-methamphetamine resulting from the P2P method. D-methamphetamine is 2 to 10 times as physiologically active as l-methamphetamine (Taylor and Snyder 1970). This increased potency translates into increased CNS stimulation and the potential for increased neurotoxicity.

TRENDS OF METHAMPHETAMINE ABUSE IN CALIFORNIA

Although methamphetamine abuse has increased in the 1980s little has been written on current trends and consequences of abuse. A paper in the *American Journal of Drug and Alcohol Abuse* states, "The previous image of methamphetamine used intravenously by 'speedfreaks' and members of motorcycle gangs has never been entirely accurate" (Puder et al. 1988). National drug use surveillance systems such as the Drug Abuse Warning Network (DAWN), a national system for tracking morbidity and mortality consequences of drug abuse, shows methamphetamine abuse as a regional phenomenon primarily localized in west coast cities such as Seattle, San Francisco, Los Angeles, and San Diego (National Institute on Drug Abuse 1990). Other cities and localities have experienced sporadic outbreaks of methamphetamine abuse (e.g., Phoenix and Dallas) and ice abuse (e.g. Hawaii) (Miller and Tomas 1989).

A National Institute on Drug Abuse (NIDA) publication describing trends and patterns of methamphetamine abuse in the United States noted that the typical methamphetamine abuser in treatment was white, low to middle income, high school educated, and from 20 to 35 years old (National Institute on Drug Abuse 1989). Clients interviewed for this study ranged from 18 to 44 years of age; 89 percent of the clients were white, and 11 percent were black. Average age for first use of methamphetamines was 20.6 years old, and the IV route was preferred by 82 percent of the participants. The NIDA study was limited to small numbers of methamphetamine abusers in selected treatment programs in San Diego, CA, Portland, OR, and Dallas, TX. Although the NIDA study generally describes typical methamphetamine abusers in the United States, some differences are appearing in California since the NIDA study.

Stimulant abuse does not appear to be a major problem throughout the State of California. However, in certain counties and subpopulations methamphetamine abuse is a significant problem. An examination of 1988 and 1990 data from the National Household Survey on Drug Abuse estimates that a total of 2.3 percent of Californians used stimulants in the year before the interview. The highest prevalence of use was seen in the 18- to 25-year-old age group at 8.4 percent, higher than that seen for the same age group in the coterminous United States (4.9 percent) (unpublished data). This reflects use of methamphetamine predominantly but also includes amphetamines and other illicit and licit products (but not cocaine). Although the total numbers are small, the California Drug Abuse Data System (CAL-DADS) shows an increase in methamphetamine use among whites (140 percent), American Indians (342 percent), and Hispanics (185 percent) in publicly supported treatment programs in California between 1982-83 and 1987-88 (figure 1).

The localized nature of methamphetamine abuse is reflected in treatment data from San Diego and San Francisco. In San Diego County, located in the extreme southwestern corner of California, methamphetamine is the most commonly abused drug among the treatment population (Haight 1990). From January 1988 to October 1990 methamphetamine was the most frequent primary drug problem at admission to drug treatment programs. In 1989 methamphetamine accounted for 39 percent of all admissions. From these CAL-DADS statistics the typical profile of a methamphetamine abuser entering treatment was a white (79 percent) female (54 percent), age 21 to 30 (82 percent). The primary route of administration reported was inhalation (88 percent), with 27 percent injecting the drug. In a questionnaire administered through crisis intervention, diversion, and early intervention services, clients listed methamphetamine as the primary drug problem for each program category from January 1988 to October 1990.

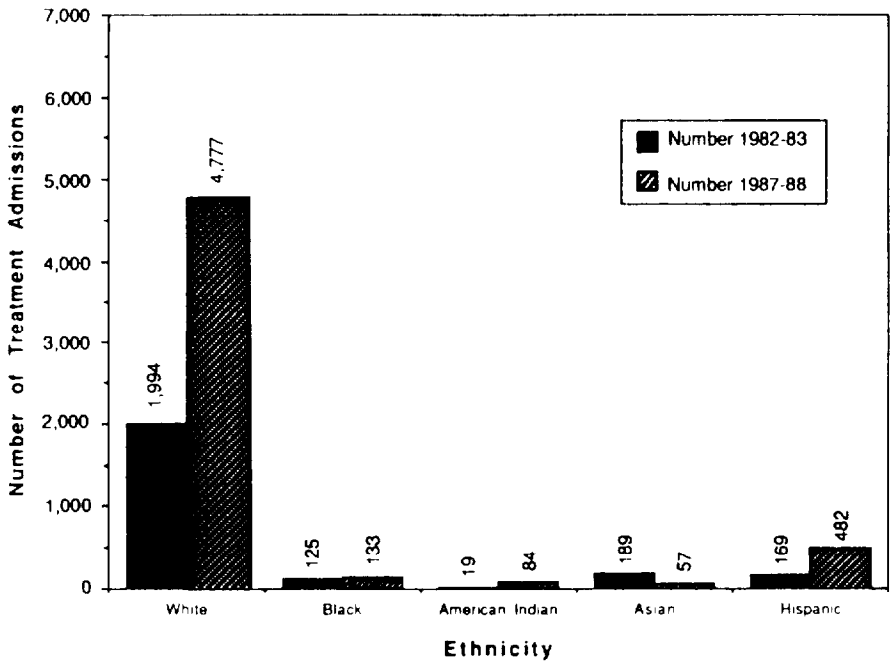


FIGURE 1. *Number of methamphetamine users in treatment by ethnic group*

In contrast, in the five counties of the San Francisco standard metropolitan statistical area (SMSA) (San Francisco, Marin, Contra Costa, Alameda, and San Mateo) methamphetamine ranked third behind heroin and cocaine for drug treatment admissions (Newmeyer 1990). California Department of Alcohol and Drug Programs admissions data show a steady increase in the number of primary amphetamine-type admissions from 1988 through the first half of 1990 (Newmeyer 1990). The profile of recent treatment admittees is overwhelmingly white (about 84 percent) and male (73 percent). Overall, amphetamine-type admissions only accounted for approximately 4 percent of all drug admissions in the SMSA. Gays (homosexual men) in their 20s and 30s accounted for a predominant number of methamphetamine abusers in this area.

National and State data are not comprehensive in describing the local demographics and trends of drug abuse. Certain treatment communities are experiencing an increase in acceptance and abuse among adolescents in the middle and upper socioeconomic classes. Retrospective review of 275 consecutive admissions between 1988 and 1988 to the Redlands Community Hospital inpatient adolescent drug treatment program indicated that 80 percent

of the 12- to 20-year-olds admitted reported methamphetamine as their drug of choice (unpublished data). The majority of these patients were polydrug abusers who also used tobacco, marijuana, and alcohol. The majority of adolescents who preferred methamphetamine also indicated they would not use cocaine even if methamphetamine were not available. Reasons given for the methamphetamine preference were longer duration of effect, availability, and the rather subjective but commonly stated reason that "speed gets me more wired."

In areas of endemic methamphetamine abuse there are certain beliefs held by adolescents that put them at risk for early initiation of methamphetamine abuse. In these areas methamphetamine may act as a gateway drug (initial use leads to subsequent use of other drugs) (DuPont 1984). Several characteristics of methamphetamine abuse support this theory, including the use of methamphetamine as a performance enhancer and as an anorectic agent and the perception by many adolescents that methamphetamine is safer than cocaine (Mandell 1979; Laties and Seiss 1981). Adolescent athletes become aware of the use of legal stimulants for performance enhancement through advertisements in body-building magazines and learn that these are pharmacologically similar to methamphetamine. Methamphetamine also is used by teens to stay awake for late-night studying or to have endurance after sleep deprivation. The majority of adolescent patients in the Redlands Community Hospital program who reported methamphetamine as their drug of choice also reported that they perceived methamphetamine as being safer than cocaine when they began abusing it.

An interesting demographic pattern of clinical significance is noted in the Los Angeles County area, which is experiencing a significant increase in treatment admissions over the past 2 years due to methamphetamine abuse as reported through CAL-DADS (McAllister et al. 1990). In general, indicators of methamphetamine abuse in Los Angeles County are low, and the predominant stimulant of abuse is cocaine. However, in the West Hollywood area there is a much higher prevalence of methamphetamine abuse. This is also an area with a predominantly gay population. In conversations with physicians and substance abuse counselors in this area and in the Bay area of San Francisco, Heischouer learned that methamphetamine is preferred by gays because it allegedly has the ability to enhance and prolong sexual performance. As opposed to the use of opiate or sedative classes of drugs, there are consistent reports of binge use focusing around sexual activity and of decreased caution in general with methamphetamine abuse. Stimulant abuse and compulsive sex behavior is well described (Washton 1989). Unsafe sexual practices put the individual at high risk of contracting human immunodeficiency virus and other sexually transmitted diseases.

Methamphetamine is ideally suited to the current trend in smoking drugs of abuse (Wesson and Washburn 1990) since it is readily volatilized and passes into mainstream smoke (combustion gases that are taken directly into the lung when a product is smoked) at temperatures compatible with smoking in a pipe or chasing the dragon (Chiang and Hawks 1989). Smoking is a method of drug administration that is generally acceptable, easy, and perceived as safe. Smoking methamphetamine is similar to IV use in that the drug gets to the brain in a matter of seconds and produces a rapid and intense effect. The CAL-DADS data show that in 1982-83 there were essentially no reports of smoking methamphetamine by drug abusers entering treatment. By 1987-88 the number smoking and inhaling methamphetamine had increased significantly (figure 2).

Clinical practice confirms this gradual increase in the practice of smoking methamphetamine. Of 30 successive patients with a recent history of methamphetamine abuse admitted to an inpatient drug treatment program in Riverside County, 100 percent reported either smoking methamphetamine at least occasionally or knowing someone who did. These individuals also were

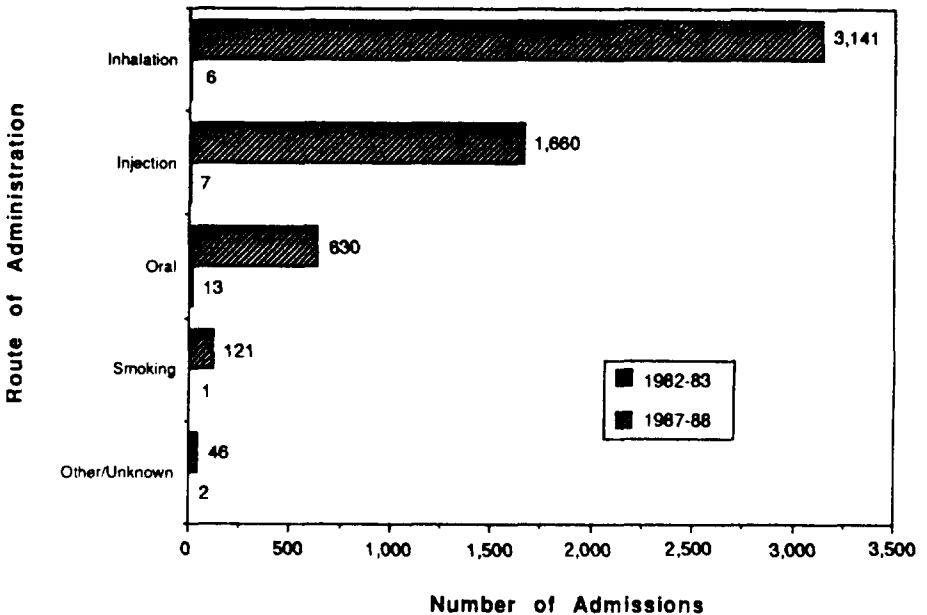


FIGURE 2. *Number of methamphetamine abusers in treatment by route of administration*

aware that, unlike cocaine, methamphetamine in powder or crystalline form is immediately smokable.

CONSEQUENCES OF USE

Trauma

Traumatic incidents frequently are associated with alcohol and other drug abuse and can be used as indicators of drug abuse in a population. The etiologic role of alcohol in trauma is well documented and has been shown to be a contributing factor in 65 to 70 percent of fatal highway accidents (Lindenbaum and Carroll 1989). Although accepted as an etiologic factor, many trauma centers still do not routinely screen for drugs of abuse.

Drug-associated trauma data are not uniformly available; however, an area-specific pattern emerges where these data are available. Data from the trauma registry at a level-one (tertiary, the highest level of care) trauma facility in San Bernardino County show that in the 15- to 24-year-old age group nearly five times as many patients tested positive for methamphetamine compared with cocaine. Also, in 1989, of 675 18- to 24-year-olds who were admitted to the University of California at Davis trauma service, 7 percent tested positive for methamphetamine and 4 percent for cocaine.

Methamphetamine abusers are less likely to interface with emergency care and medical facilities as a result of the acute medical problems (cerebrovascular accidents, acute cardiac ischemia and failure, hyperthermia, seizures) that bring cocaine abusers to these facilities. In a retrospective study of 127 cases of amphetamine (including methamphetamine) toxicity in an emergency department, the major presenting symptom was altered mental status (57 percent); 10 percent were found unresponsive, and the remainder exhibited such physiologic complaints as chest pain, weakness, palpitations, and seizures (Derlet et al. 1989). The CNS symptoms most commonly encountered in the Derlet study included agitation, confusion, delusions, hallucinations, and suicidal ideation.

It has been suggested that the infrequent occurrence of acute medical problems in methamphetamine abusers is a result of the rapid development of tolerance to methamphetamine (Ellenhorn and Barceloux 1988). Tolerance develops to some of the central effect of amphetamines such as its euphorogenic, anorectic, hyperthermic, and lethal actions; however, tolerance does not develop to certain toxic CNS effects (Jaffe 1985). Chronic abusers exhibit limited sympathomimetic effects, with blood pressure not unduly elevated, but frequently suffer from paranoid psychosis and other mental status alterations (Ellinwood 1971).

Trauma and death as a consequence of methamphetamine abuse is increasing in localized areas of California. San Bernardino County Coroner's data consisting of all traffic deaths, homicides, suicides, and unknown causes of death for the past 5 years were reviewed (unpublished data). Although methamphetamine and cocaine positives were approximately equal through 1985, there has been a gradual increase in methamphetamine cases, with methamphetamine present two to three times as frequently as cocaine in 1989. In a retrospective analysis of drug-related homicides and accidental overdoses (Bailey and Shaw 1989), it was reported that cocaine or methamphetamine or both were involved in approximately one-third of all homicides in San Diego County in 1987. The profile for a methamphetamine decedent from the Bailey study is a 32-year-old white male who had used at least one other drug, usually ethanol, codeine, or morphine. The San Diego Sheriffs Crime Laboratory reports that, in cases in 1988, methamphetamine was the most common illicit substance (Rasmussen et al. 1989). Drug-related mortality reported through DAWN shows that methamphetamine was involved in approximately 4 percent of the drug-related deaths in Los Angeles, 18 percent in San Diego, and 17 percent in San Francisco from January through June 1990.

CONCLUSION

It is difficult to generalize when discussing methamphetamine abuse in California. Observation reflects a phenomenon that is geographically influenced and location specific. In some respects, trends and characteristics of methamphetamine abusers in California mimic what is known of the national profile. In general the composite national methamphetamine abuser is predominantly white, male, and with low to middle income. What appears to be emerging in California is a broadening of abuse of methamphetamine in all socioeconomic classes and among women, diversification of use among ethnic minorities, and an increase in special populations using methamphetamine, including adolescents and gays. There is the suggestion of a shift in use from cocaine to methamphetamine in some populations in some areas. California also is experiencing new patterns of drug administration. Based on national data, the typical abuser injects, whereas in California, inhalation, smoking, and ingestion are common (National Institute on Drug Abuse 1989, 1990).

The trend in California has been toward the production of a more neuropharmacologically potent product in a form that has high purity and is easily administered. Consequences of these changes are being reflected in an increase in methamphetamine abusers entering treatment centers and trauma facilities and interfacing throughout the law enforcement and medical care community.

The trends of methamphetamine abuse in California need to be more thoroughly documented and understood. The problem of methamphetamine abuse must be described and quantified before prevention, treatment, and rehabilitation programs can be developed and before resources can be allocated to address the problem. As the drug abuse research community in California begins to understand how methamphetamine is produced and marketed, how the drug is used and abused, and the extent and nature of consequences of abuse, others can benefit from the resultant insight concerning this insidious drug that refuses to fade away.

REFERENCES

- Allen, A., and Cantrell, T. Synthetic reductions in clandestine amphetamine and methamphetamine labs. *J forensic Sci* 42:183-199, 1989.
- Bailey, D.N., and Shaw, R.F. Cocaine and methamphetamine-related deaths in San Diego County (1987): Homicides and accidental overdoses. *J Forensic Sci* 34:407-422, 1989.
- Chiang, C.N., and Hawks, R.L. Introduction and overview. In: Chiang, C.N., and Hawks, R.L. *Research Findings on Smoking of Abused Substances*. National Institute on Drug Abuse Research Monograph 99. DHHS Pub. No. (ADM)90-1690. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1990. pp. 1-4.
- Derlet, R.W., and Heischouer, B. Methamphetamine. Stimulant of the 1990's? *West J Med* 153:625-628, 1990.
- Derlet, R.W.; Rice, P.; Horowitz, B.Z.; and Lord, R.V. Amphetamine toxicity: Experience with 127 cases. *J Emerg Med* 7:157-161, 1989.
- DuPont, R.L. *Getting Tough on Gateway Drugs*. Washington, DC: American Psychiatric Press, 1984.
- Ellenhorn, M.J., and Barceloux, D.F. *Medical Toxicology: Diagnosis and Treatment of Human Poisoning*. New York: Elsevier, 1988. pp. 626-641.
- Ellinwood, E.H. Assault and homicide associated with amphetamine abuse. *Am J Psychiatry* 127:1170-1175, 1971.
- Federal Register. Amendments to the sentencing guidelines for United States courts. Vol. 56, No. 95, Thursday, May 16, 1991,
- Haight, M.A. Drug abuse trends in San Diego County: 1986-1990. In: *Community Epidemiology Work Group: Epidemiologic Trends in Drug Abuse. Proceedings December 1990*. National Institute on Drug Abuse. DHHS Pub. No. (ADM)91-1773. Rockville, MD: Supt. of Docs., U.S. Govt. Print. Off., 1990. pp. 261-274.
- Heischouer, B., and Derlet, R.W. Update on amphetamine abuse. *West J Med* 151:70-71, 1989.
- Jaffe, J.H. Drug addiction and drug abuse, CNS sympathomimetics: Amphetamine, cocaine, and related drugs. In: Gilman, A.G.; Goodman,

- L.S.; Rall, T.W.; and Murad, F., eds. *The Pharmacological Basis of Therapeutics*. New York: MacMillan, 1985. pp. 550-554.
- Kase, C.S.; Foster, T.E.; Reed, J.E.; Spatz E.L.; and Girgis, G.N. Intracerebral hemorrhage and phenylpropanolamine use. *Neurology* 37:399-404, 1987.
- Lake, C., and Quirk, R. Stimulants and look-alike drugs. *Psychiatr Clin North Am* 7:689-701, 1984.
- Laties, V.G., and Seiss, B. Amphetamine use in sports. *Fed Proc* 40:2689-2692, 1981.
- Lindenbaum, A.N., and Carroll, S.F. Alcohol and drug screening in trauma center patients. *J Trauma* 29:1654-1658, 1989.
- Lukas, S.E. *The Encyclopedia of Psychoactive Drugs: Amphetamines: Danger in the Fast Lane*. New York: Chelsea House Publishers, 1985. p. 21.
- Mandell, A.J. Amphetamine abuse and American professional football. *Clin Toxicoll* 5:225-232, 1979.
- McAllister, D.R.; Russell, R.A.; and Webb, F.J. Update on drug abuse in Los Angeles County. In: *Community Epidemiology Work Group: Epidemiologic Trends in Drug Abuse. Proceedings December 1990*. National Institute on Drug Abuse. DHHS Pub. No. (ADM)91-1773. Rockville, MD: Supt. of Docs., U.S. Govt. Print. Off., 1990. pp. 139-150.
- Miller, M.A., and Tomas, J.M. Past and current methamphetamine epidemics. In: *Community Epidemiology Work Group: Epidemiologic Trends in Drug Abuse. Proceedings December 1989*. Rockville, MD: Supt. of Docs., U.S. Govt. Print. Off., 1989. pp. III-58-III-65.
- National Institute on Drug Abuse. *Methamphetamine Abuse in the United States*. DHHS Pub. No. (ADM)89-1608. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1989.
- National Institute on Drug Abuse. *Statistical Series*. Data from the Drug Abuse Warning Network (DAWN). Semiannual Report, Series G, No. 24. DHHS Pub. No. (ADM)90-1664, Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1990.
- Newmeyer, J.A. Drug use in the San Francisco Bay area. In: *Community Epidemiology Work Group: Epidemiologic Trends in Drug Abuse. Proceedings December 1990*. National Institute on Drug Abuse. DHHS Pub. No. (ADM)91-1773. Rockville, MD: Supt. of Docs., U.S. Govt. Print. Off., 1990. pp. 275-285.
- Puder, K.D.; Kagan, D.V.; and Morgan, J.P. Illicit methamphetamine, analysis, synthesis, and availability. *Am J Drug Alcohol Abuse* 14:463-473, 1988.
- Rasmussen, S.; Cole, R.; and Spiehler, V. Methamphetamine prevalence in sheriffs crime lab samples. *J Anal Toxicol* 13:263-267, 1989.
- Smith, R.C. Compulsive methamphetamine abuse and violence in the Haight-Ashbury district. In: Ellinwood, E.H., and Cohen, S., eds. *Current Concepts on Amphetamine Abuse*. National Institute of Mental Health. DHEW Pub.

- No. (HSM)72-9085. Rockville, MD: Supt. of Docs., U.S. Govt. Print. Off., 1972. pp. 205-216.
- Taylor, K.M., and Snyder, S.H. Amphetamine: Differentiation by δ and λ isomer of behavior involving brain epinephrine or dopamine. *Science* 168:1487-1489, 1970.
- Washton, A.M. Cocaine abuse and compulsive sexuality. *Med Aspects Hum Sex* December: 32-39, 1989.
- Wesson, D.R., and Washburn, P. Current patterns of drug abuse that involve smoking. In: Chiang, C.N., and Hawks, R.L., eds. *Research Findings on Smoking of Abused Substances*. National Institute on Drug Abuse Research Monograph 99. DHHS Pub. No. (ADM)90-1690. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1990. pp. 5-11.

AUTHORS

Bruce Heischober, M.D.
Assistant Professor of Adolescent and Emergency Medicine
Department of Emergency and Adolescent Medicine
Loma Linda University Medical Center School of Medicine
11234 Anderson Street
Loma Linda, CA 92350

Marissa A. Miller, D.V.M., M.P.H.
Epidemiologist
Epidemiology Studies and Surveillance Branch
Division of Epidemiology and Prevention Research
National Institute on Drug Abuse
Rockwall II, Suite 815
5600 Fishers Lane
Rockville, MD 20857

Trends and Patterns of Methamphetamine Smoking in Hawaii

Marissa A. Miller

INTRODUCTION

A sharp increase in law enforcement actions related to smoking of d-methamphetamine HCl, known as "ice," was observed and reported by the U.S. Attorney for Hawaii during the last half of 1988. This report was confirmed by Hawaii treatment personnel who observed increasing numbers of clients entering treatment as a result of methamphetamine smoking. At the request of the Hawaii Department of Health, Alcohol and Drug Abuse Branch, a field studies team from the National Institute on Drug Abuse (NIDA) conducted an outbreak investigation during February and March 1989 to characterize the epidemic as to person, place, and time and to document the extent and trend of the problem. A followup data collection was initiated during February 1990.

METHODS

Information was abstracted from treatment records and State treatment admission and discharge summary forms. In addition, a group of methamphetamine smokers currently in treatment were interviewed about their symptomatology and patterns and preferences of drug use. Methamphetamine smokers admitted to treatment between October 1985 and February 1990 in two large treatment programs, the Young Men's Christian Association (YMCA) and Salvation Army (SA), were identified. Methamphetamine smoking was first detected by treatment centers in Hawaii in the summer of 1986 with wider recognition of the problem coming later. YMCA Outreach Services provides community outreach and counseling to individuals younger than 21 primarily in the areas surrounding and including Honolulu. SA offers inpatient, outpatient, and women's drug and alcohol programs and administers services throughout Oahu, including court referral cases.

RESULTS

Treatment and State Admission Data

A total of 172 methamphetamine smoking cases were identified, with 66 (38 percent) from YMCA and 106 (62 percent) from SA (table 1). These methamphetamine smokers at date of admission to treatment ranged in age from 12 to 44 years with a mean of 20.5 years (median 17 years). The age distribution has two peaks, a sharp one at 15 and a more gradual one at 26.5 years. As a whole, 50 percent of the group was younger than age 17, but due to the composition of the treatment population, the YMCA clients tended to be younger. Men comprised 58 percent of the total group (68 percent men in SA and 41 percent men in YMCA). Women tended to be younger than men, with the average age of women being 18.2 years and men 22.2 years. Seventy-five percent of women were younger than 20 years old compared with 50 percent of men. There was no difference between genders for time of admission to treatment, with men and women being admitted throughout the period.

The clients reflected a range of ethnic backgrounds, including 35 percent Hawaiian/part Hawaiian (defined as having at least half Hawaiian ethnicity), 23 percent Filipino, 13 percent Japanese, 10 percent Caucasian, 7 percent Other Asian (including Chinese, Korean, Okinawan, Samoan, and unspecified Asian), 5 percent mixed (defined as three or more ethnicities with none being predominant), 4 percent unknown, 2 percent Hispanic, and 1 percent black. The two treatment programs had different ethnic distributions: YMCA was predominantly Filipino (35 percent) and Hawaiian/part Hawaiian (30 percent), whereas SA was predominantly Hawaiian/part Hawaiian (41 percent), with a broader representation of other groups (11 percent Filipino, 14 percent Japanese, and 11 percent Caucasian). Female clients were primarily of Filipino (32 percent) and Hawaiian/part Hawaiian (30 percent) ethnicity, whereas males were predominantly Hawaiian/part Hawaiian (39 percent) and a variety of other ethnic backgrounds, including Filipino (17 percent), Japanese (13 percent), and Caucasian (9 percent). This ethnic distribution differs from the general population on Oahu, with a higher percentage of Hawaiian/part Hawaiians and Filipinos and a lower percentage of Caucasians and Japanese (table 1).

The epidemiologic curve of treatment admissions shows single cases beginning in October 1985 and continuing sporadically through July 1987 (not depicted in figure 1). The curve shows two peaks: The first begins in September 1988 and runs through April 1989; the second larger peak is centered around October 1989. The admissions for YMCA peak during October 1989, whereas the SA admissions peak slightly earlier in September 1989. Males and females are

TABLE 1. *Demographic characteristics of methamphetamine smokers entering treatment (1986-90) and the general population in Hawaii (1984)*

	Ice Smokers	General Population
N	172	803,135
Mean age	20.5	29.6
Age range	12-44	-
Percent younger than 20 years of age	59	30
Percent male	58	51
Ethnic distribution (percent)		Census 1980 ^a
Filipino	23	12.6
Hawaiian/part Hawaiian	35	10.7
Japanese	13	24.9
Mixed	5	-
Caucasian	10	34.4
Chinese	2	6.9
Hispanic ^b	2	7.2
Black	1	2.3
Korean	1	2.2
Other ^c	4	6.0
Missing	4	-

^aIn the census, persons of mixed origin were classified by self-identification or origin of the mother. In the outbreak investigation, persons of mixed origin were classified by predominant ethnicity as recorded in clinical records or classified as "mixed" if they had three or more ethnicities and no predominance of any ethnic group.

^bHispanic persons may be of any race.

^c"Other" includes Eskimo, Aleutian, American Indian, Vietnamese, Guamanian, Samoan, Other Asian/Pacific islander, and not elsewhere classified. All these categories represented 2 percent or less of the total population individually.

distributed throughout as are YMCA and SA admissions. The two earliest admissions in October 1985 and September 1986 (not pictured in figure 2) are Japanese men ages 19 and 13, respectively. Following these admissions, the curve is dominated by young females during the period October 1986 through May 1988. Also, during this period 11 of 18 admissions (61 percent) are women, with 5 and 4 admissions of Filipino and Hawaiian/part Hawaiian

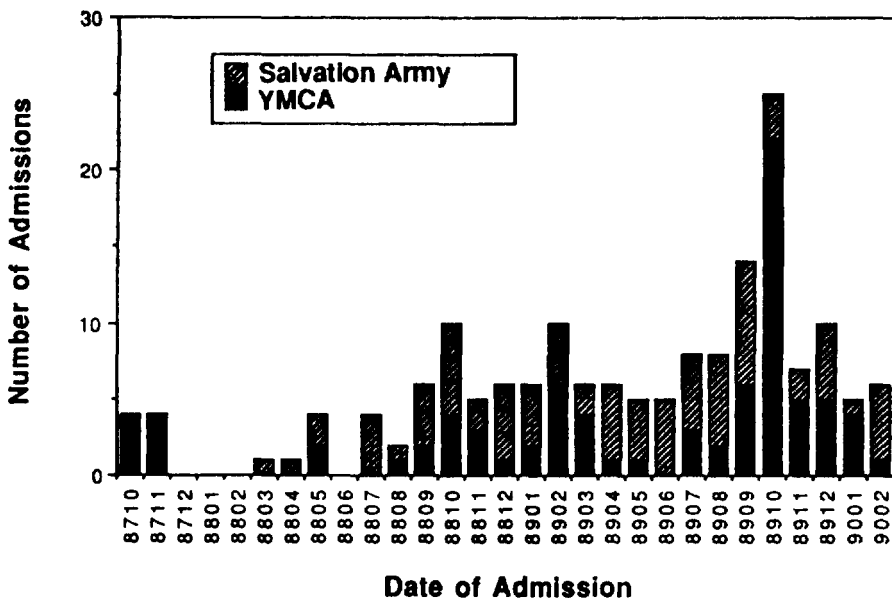


FIGURE 1. Ice admissions epidemic curve by facility

ethnicity, respectively. The average age at admission of these nine women was 15.3 years. In the remainder of the curve from July 1988 through February 1990, the first half is dominated by Hawaiian/part Hawaiians (July 1988 through April 1989), and the latter half is dominated by Filipinos (September 1989 through February 1990). Japanese and Caucasians are scattered throughout.

The earliest reported date of methamphetamine smoking of a client in treatment was 1968, and sporadic single cases continued until 1985 (figure 3). Reported first use began increasing in 1985 and steadily increased until peaking in 1988 followed by a steady decline in 1989 and 1990. Of the 13 sporadic early cases (1968, 1969, 1970, 1972, 1974, 1975, 1978, 1979, 1982, 1983, and 1984), all but two were male, and all but two were older than 25 years at time of admission. The ethnicities of these early cases include Japanese, Caucasian, Hawaiian/part Hawaiian, and Filipino (figure 4). The remainder of the curve (1985 to 1990) comprises all age groups and ethnicities. All the predominant ethnic groups—Filipino, Japanese, Hawaiian/part Hawaiian and Caucasian—peak in 1988. The majority of females reported first use after 1984. The early flat portion of the curve represents clients admitted to treatment at older ages who started using ice at early ages. When the popularity of ice increased

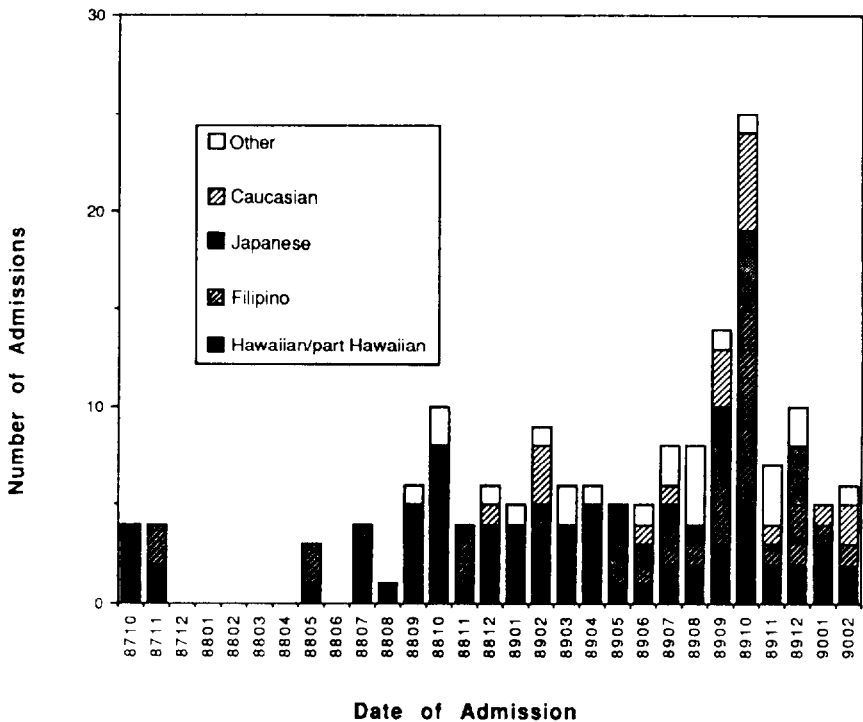


FIGURE 2. *Ice admissions epidemic curve by ethnicity*

during the mid-1980s, the clients admitted to treatment were younger, had started using ice later, and had used for a shorter duration of time before entering treatment programs in comparison with older users. This suggests a change in the epidemiology of ice use from use by a few older persons to a “cultural” or “peer-pressure” spread to younger users and others in the population.

There was a short lag between first use and seeking treatment for these data. Lag between first use and admission to treatment was estimated by subtracting calendar year of first use from calendar year of admission to treatment. This information was available from 91 percent of the records. The mean lag time was 2.1 years (median=1), ranging from 0 to 20 years. There was a difference between the two treatment centers: Clients from YMCA had a shorter lag time (mean=.9, median=1, range=0 to 3) than clients from SA (mean=3.2, median=1, range=0 to 20). There also were differences by gender and age group. Males

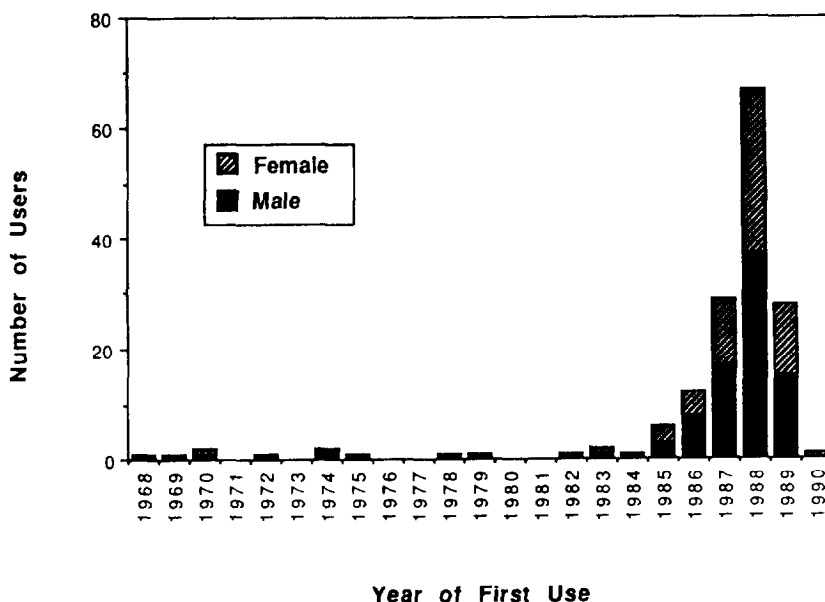


FIGURE 3. *First year of use epidemic curve by gender*

tended to have longer lag times (mean=3, median=1 , range=0 to 20) than females (mean=1, median=1 , range=0 to 3). Increasing age groups exhibited increasing time between first use and seeking treatment. The youngest age group (less than 15 years) had a mean of 1 year progressing to an 8-year mean for the oldest age group (older than 35). Filipinos and Hawaiian/part Hawaiians had among the shortest lag times (1.5 and 1.4 years, respectively), and Japanese and Caucasians had the longest lag times (2.7 and 3.8 years, respectively).

Sixty percent of the clients reported methamphetamine to be their primary drug of abuse. There were small differences in the number of clients in each of the treatment groups reporting methamphetamine to be their primary drug of abuse (55 percent in YMCA and 65 percent in SA). The same was true for both genders (58 percent for males and 62 percent for females). Users younger than age 15 were least likely to report methamphetamine as the primary or secondary drug of abuse (50 percent and 22 percent, respectively). Japanese and Caucasians were the ethnic groups least likely to report methamphetamine as a primary drug problem (47 percent and 55 percent, respectively).

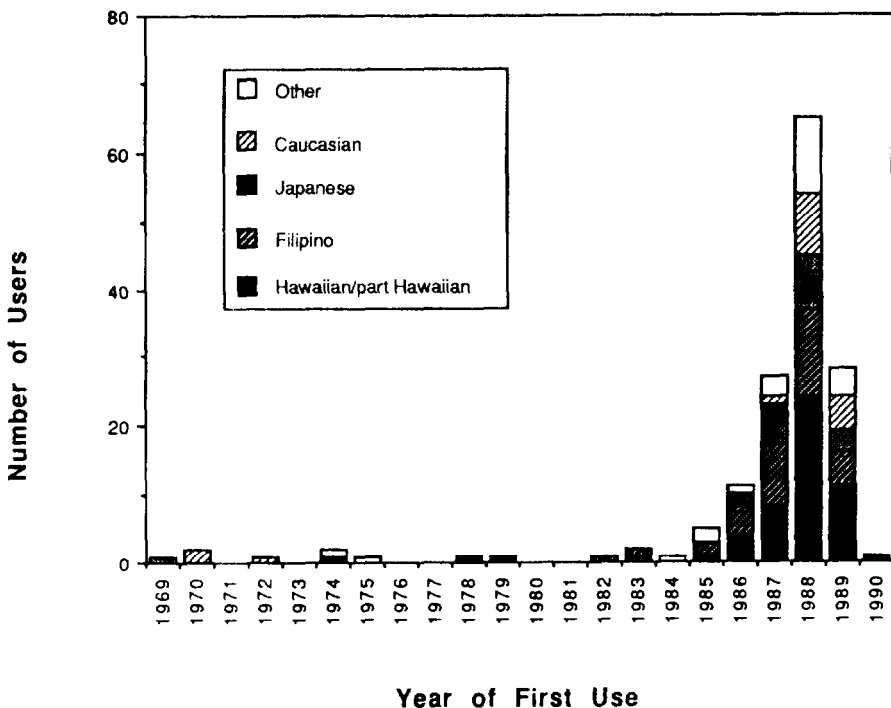


FIGURE 4. *First year of use epidemic curve by ethnicity*

Interview Data

To augment these data, informal interviews were conducted with 35 users in treatment between February 1989 and February 1990, and discussions were held with treatment counselors and law enforcement personnel. These discussions revealed that methamphetamine, a synthetic stimulant, is referred to as “crystal” in and around Honolulu, ice in Waianae and on the leeward and rural parts of Oahu, and “Batu” by the Filipino community. It is a large, usually clear, crystal of high purity (usually greater than 90 percent) in the psychoactively potent d-methamphetamine form that is smoked in a glass pipe.

Sixty-six percent of those interviewed had knowledge of ice by age 20 and began using shortly afterward. Most users (84 percent) reported binge use or repeated administration of methamphetamine, which typically would entail continuous use for an average of 5 days, during which time they would forego both food and sleep. Between binges, users reported extensive sleeping or

what they called “crashing out.” The time between binges was reported to be approximately 3 to 4 days for most users interviewed. Recent use of ice (in the last 30 days before treatment) was heavy, with 74 percent using ice on 15 or more days and 63 percent using 2 or more grams during the month prior to treatment. All but one client preferred to smoke and usually did smoke ice. All those interviewed had previously used at least one drug other than ice, with all having tried alcohol, more than 90 percent having used cocaine and marijuana, and 83 percent having used tobacco. The duration of use of these other drugs was considerable considering the age limitations of the clients, averaging more than 9 years for tobacco, alcohol, and marijuana and more than 5 years for cocaine.

Methamphetamine smokers in treatment self-reported physical symptoms associated with the smoking of methamphetamine, including weight loss, tachycardia, tachypnea, hyperthermia, insomnia, muscular tremors, and, less frequently, blurred vision. The behavioral and psychiatric symptoms most commonly reported included repetitive activity, memory problems, paranoia, stereotypic behavior, delusions of reference, auditory hallucinations, and confusion/fright. Other manifestations of paranoid ideation (e.g., delusions of persecution, visual hallucinations) also were reported. Less common but also reported were olfactory and tactile hallucinations and the feeling that bugs or parasites were crawling over their body or on their skin (formication). Approximately one-third of the clients interviewed reported entering treatment within 12 months of initiating use of methamphetamine, and more than 60 percent entered treatment within 2 years of first use. The majority of clients reported negative effects on their family life (85 percent), social life (79 percent), and work or school performance (73 percent). Other consequences of ice use included injuring others (65 percent), being injured (53 percent), and inflicting injuries on themselves (45 percent). The majority of clients also reported carrying a weapon (74 percent) and dealing drugs (72 percent).

DISCUSSION

The characteristics of the users identified in this field investigation differ from other drug users in treatment in Hawaii and overall in the United States (National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism 1989). The Hawaii drug treatment population in 1987 was 72 percent male, 29 percent age 20 or younger, and 48 percent Caucasian (n=536). As a whole, according to Hawaii State drug abuse experts and treatment counselors, drug users in treatment in Hawaii tend to be in their mid-20s and older, male, Caucasian or Hawaiian/part Hawaiian, and polydrug users. The total U.S. population in treatment for drug abuse the same year was 67 percent male, 57 percent Caucasian, and 22 percent age 20 or younger. The

ice users in this study were younger, with a higher representation of women and a larger proportion of Hawaiian/part Hawaiian than the “typical” Hawaiian or average U.S. drug user.

There appear to be two distinct population peaks in the data collected: (1) females, predominantly younger than 20 years of age and Filipino, with methamphetamine predominating as their primary drug of abuses, and (2) males, most often older than 20 years of age and most often Hawaiian/part Hawaiian, Filipino, or Japanese, with methamphetamine being more often their second or third drug of abuse. Filipinos in this study were shown to rank ice as a more severe problem (82 percent listed ice as their primary drug problem) compared with Hawaiian/part Hawaiians, 47 percent of whom listed ice as their primary problem. The drug-related problems of Filipinos appeared to be predominantly from ice use, whereas the Hawaiian/part Hawaiians seemed more often to have a polydrug abuse problem. Young female Filipinos appeared to be especially vulnerable to the adverse effects of ice, causing them to seek treatment within 1 year of first use.

Anecdotally, young Filipino females were reported to be targets of methamphetamine dealers because of their reliability as customers. Also, females reportedly used ice to lose or control body weight. The presence of young Filipino female users within the early epidemic curve was demonstrated in these data. Older polydrug users had a long lag time before entering treatment, possibly reflecting an ability to use drugs and still function outside of treatment. Japanese users exhibited a long lag time to enter treatment as well, which may reflect a cultural tendency to handle problems within the home or community rather than seeking outside assistance.

There is a dearth of baseline data on the Hawaiian drug-abusing population. From 1988 through 1989 the proportion and total number of ice users increased for YMCA and SA. The proportions increased from 13 to 17 percent and 9 to 19 percent for YMCA and SA, respectively. The data from this study suggest that admissions to treatment due to methamphetamine smoking has peaked or may peak shortly. The frequency curve of methamphetamine admissions by half-year (figure 5) shows a peak during the second half of 1989 and a decline for the first 2 months of 1990 (indicated as “H1 1990” in figure 5). Extrapolation of the same rate of admissions for the first 2 months of 1990 over the hypothesized first 6 months is depicted in figure 5 as “*H1 1990,” which shows an overall decreasing trend. In addition, the curve for users first trying ice peaked in 1988, and the data indicate a 1- to 2-year lag time between first use and entering treatment, which corresponds with the peak and decline described in the admissions curve.

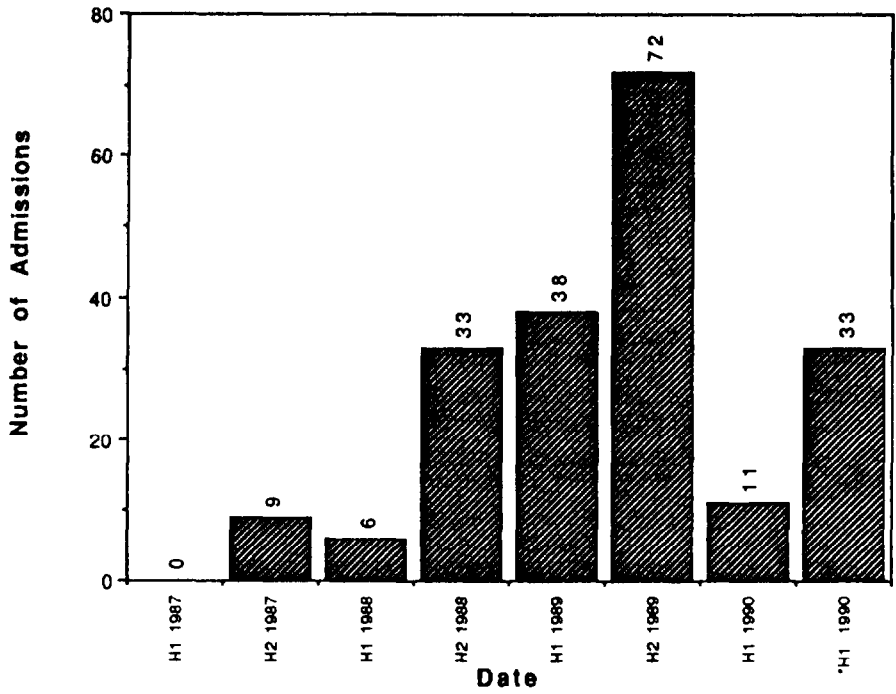


FIGURE 5. *Frequency of methamphetamine admissions by half-year*

*Extrapolated rate of admissions for the first 6 months of 1990 based on actual admissions for the first 2 months of 1990 (depicted as H1 1990)

Surveillance systems monitoring trends of drug use show methamphetamine use to be static across the United States but increasing during the last part of the 1980s in certain cities, particularly on the west coast. The Drug Abuse Warning Network (DAWN) shows statistically significant increases in emergency room mentions of methamphetamine in the San Francisco and Seattle metropolitan areas during the period January 1987 through December 1989 (National Institute on Drug Abuse 1990). However, first quarter 1990 data show a decrease in mentions for San Diego, San Francisco, Los Angeles, and Seattle. The total DAWN system showed no statistical change in methamphetamine use for first quarter 1987 through fourth quarter 1989, but first quarter 1990 results suggest a decreasing trend. San Diego, San Francisco, and Seattle metropolitan areas all showed increases in the proportion of smoked methamphetamine mentions between second quarter 1989 through first quarter 1990 compared with the same period 1 year earlier.

The San Diego smoking cases accounted for 8 percent of the total methamphetamine cases in San Diego during the period between April 1, 1989, and March 30, 1990 (unpublished data). Overall, the smoking route accounted for less than 1 percent (0.5 percent) of the national methamphetamine mentions during this same 12-month period. Intravenous injection remains the most popular and common route of administering methamphetamine in the United States.

The dangers involved with methamphetamine use include both acute and chronic sequellae (Preston et al. 1985; Jaffe 1985; Kramer 1970; Sato 1986). Acute toxicity is similar to that caused by cocaine, and there are studies suggesting permanent neural toxicity from methamphetamine use (see Seiden, this volume). Chronic use typically results in serious psychological consequences. There are also social and behavioral consequences such as loss of friends, alienation of family, job and school failure, and violence that have been associated with chronic methamphetamine use (Kalant and Kalant 1978; Smith 1970; Ellinwood 1971; Asnis and Smith 1978; Beezley et al. 1987).

CONCLUSIONS

At this time the widespread smoking of methamphetamine appears to be unique to Hawaii. However, the widespread use of other forms of methamphetamine and other routes of administration within the continental United States raises concern about the transference of this highly pure and potent form of methamphetamine and the smoking pattern of use. As with cocaine, the smoking route of administration can lead to additional serious adverse health and social consequences. To date, the NIDA drug use surveillance systems have not shown the ice phenomenon to have spread extensively. However, given the lag times between initiation of use of ice and the need to seek treatment, as indicated by the subjects in this investigation, it may be that the drug is being used, but not yet to the threshold necessary for detection by NIDA's national surveillance systems. For these reasons continued vigilance in conducting surveillance is indicated.

REFERENCES

- Asnis, S.F., and Smith, R.C. Amphetamine abuse and violence. *J Psychedelic Drugs* 10:371-377, 1978.
- Beezley, D.A.; Gantner, A.B.; Bailey, D.S.; and Taylor, S.P. Amphetamines and human physical aggression. *J Res Personality* 21:52-60, 1987.
- Ellinwood, E.H., Jr. Assault and homicide associated with amphetamine abuse. *Am J Psychiatry* 127:1170-1175, 1971.

- Jaffe, J.H. Drug addiction and drug abuse, CNS sympathomimetics: Amphetamine, cocaine, and related drugs. In: Gilman, A.G.; Goodman, L.S.; Rall, T.W.; and Murad, F., eds. *The Pharmacological Basis of Therapeutics*. New York: McMillan, 1985. pp. 550-554.
- Kalant, H., and Kalant, O.J. Death in amphetamine users: Causes and rates. In: Smith, D.E.; Wesson, D.R.; Buxton M.E.; Seymour, R.B.; Vugerleider, J.T.; Morgan, J.P.; Mandell, A.J.; and Jara, G. *Amphetamine Use, Misuse, and Abuse: Proceedings of the National Amphetamine Conference*. San Francisco: University of California, 1978, pp. 169-189.
- Kramer, J.C. Introduction to amphetamine abuse. In: Ellinwood, E.H., and Cohen, S., eds. *Current Concepts on Amphetamine Abuse*. National Institute of Mental Health. DHEW Pub. No. (HSM)72-9085. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1970. pp. 177-184.
- National Institute on Drug Abuse. *Statistical Series*. Data from the Drug Abuse Warning Network (DAWN). Semiannual Report, Series G, Number 24. DHHS Pub. No. (ADM)90-1664. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1990.
- National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism. *National Drug and Alcoholism Unit Survey (NDATUS), 1987 Final Report*. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1989.
- Preston, K.L.; Wagner, G.C.; Schuster, C.R.; and Seiden, L.S. Long-term effects of repeated methylamphetamine administration on monoamine neurons in the rhesus monkey brain. *Brain Res* 338:243-248, 1985.
- Sato, M. Psychotoxic manifestations in amphetamine abuse. *Psychopharmacol Bull* 22:751-756, 1986.
- Smith, R.C. Compulsive methamphetamine abuse and violence in the Haight-Ashbury district. In: Ellinwood, E.H., and Cohen, S., eds. *Current Concepts on Amphetamine Abuse*. National Institute of Mental Health. DHEW Pub. No. (HSM)72-9085. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1970. pp. 205-216.

AUTHOR

Marissa A. Miller, D.V.M., M.P.H.
 Epidemiologist
 Epidemiology Studies and Surveillance Branch
 Division of Epidemiology and Prevention Research
 National Institute on Drug Abuse
 Rockwall II, Room 615
 5600 Fishers Lane
 Rockville, MD 20857

Methamphetamine Abuse in Japan

Hiroshi Suwaki

INTRODUCTION

The history of methamphetamine abuse in Japan, where it has been the dominant stimulant of abuse since the end of World War II, is instructive because it shows the emergence of two entirely different patterns of and motivations for substance abuse. Furthermore, it demonstrates the utility and limitation of preventive and educational approaches to the problem.

This chapter first summarizes general trends in substance abuse in Japan to place methamphetamine problems in a historical context and then discusses specific problems in methamphetamine abuse, focusing on its epidemiologic and social problems. Finally, the chapter presents a recent study (Suwaki et al. 1990) of a longitudinal pattern of substance abuse, including methamphetamine. (A person often shifts from one substance of abuse to another or abuses several substances simultaneously).

HISTORICAL TRENDS IN SUBSTANCE ABUSE

Before 1945 substance abuse was not a substantial problem in Japan, with the exception of alcoholism, but from 1945 to 1956 Japan suffered from the new problem of stimulant abuse (methamphetamine is the dominant drug in this category) (figure 1). This problem quickly spread throughout Japan because there were no laws prohibiting the use or sale of this substance. With the passage of the Stimulants Control Law (1951) and its amendments in 1954 and 1955 together with a vigorous policy of enforcement, the abuse of methamphetamine rapidly abated. This epidemic served to awaken the Japanese Government and medical community from its naivete about substance abuse (Suwaki and Bjorksten 1983). Interestingly, cocaine was not included in the Stimulants Control Law but was included in the Narcotics Control Law (1953). Amphetamine and methylphenidate, which along with methamphetamine are the main drugs targeted by the Stimulants Control Law, rarely have been abused in Japan.

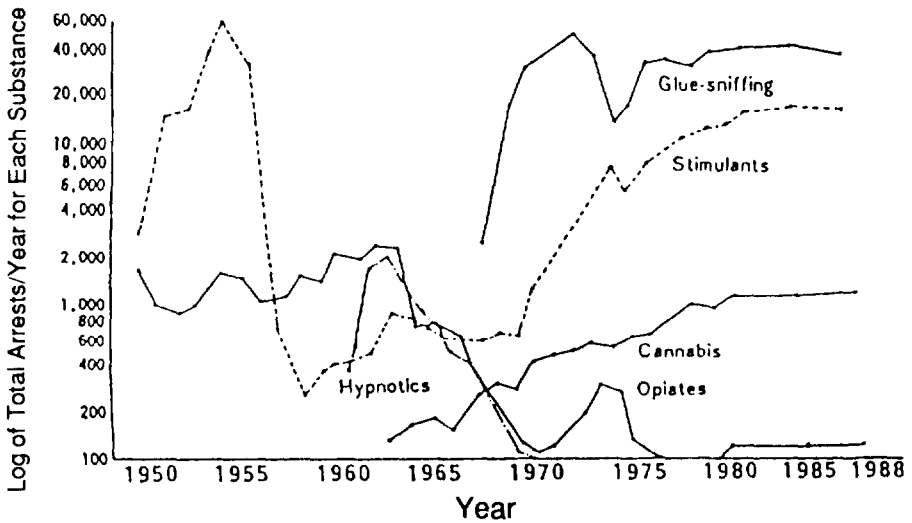


FIGURE 1. Arrests for drug statute violations except alcohol

SOURCE: National Police Agency, Division of Prevention of Crimes, Department for Countermeasures of Drugs, 1989

With the success of efforts to control the methamphetamine epidemic, attention turned to the control of heroin abuse, which also had increased dramatically after 1945. The period of increased heroin use lasted from 1957 to 1963 (Ministry of Health and Welfare 1985). Coordinated Government action began in 1962 with the organization of the Ministers' Council for Narcotics Countermeasures and in 1963 with amendments to the Narcotics Control Law that increased penalties for narcotics violations. Figure 1 demonstrates that these measures, combined with vigorous enforcement, were successful. However, in the author's view, illegal drug traffickers in "Bohryokudan" (a criminal organization similar to the Mafia) then must have begun dealing in methamphetamine instead of heroin, because figure 1 shows that, instead of opiates violations declining, methamphetamine violations again sharply increased in the early 1970s.

The period from 1964 to 1969 often has been referred to as one of "declining drug abuse" (Ministry of Health and Welfare 1985); however, it may be more appropriate to call it the "quiet before the storm." At that time, methamphetamine abuse seemed to stabilize, although at a higher level than in 1959, and narcotics abuse was declining.

However, two important aspects in this period should not be overlooked. First, 300 to 800 methamphetamine-related arrests still were made each year, which suggests “veterans” of methamphetamine abuse survived through this period and eventually sparked the second epidemic. Second, a new phenomenon of drug abuse emerged among teenage delinquents who chose hypnotics and analgesics, which at that time they could buy quite freely in drugstores. This new trend of substance abuse by teenagers was succeeded by the abuse of volatile solvents that are cheaper, easier to obtain, more potent, and quicker to produce a dreamy hallucinatory trip. Volatile solvents abuse among delinquents and school dropouts spread throughout Japan at a high rate from 1967 to 1970 (Suwaki 1982).

The recurrence of methamphetamine abuse began in 1970 and again led to tougher legislation when the Stimulants Control Law was amended in 1973. However, this time the success of the legislative method of control was short-lived. Although this legislation seemed to decrease methamphetamine abuse by about 30 percent, by 1975 levels again had reached that of 1973 and continued to increase despite the law. In the first epidemic, the rapid spread of methamphetamine abuse was due partially to naivete and partially to lack of legislation to control it. The striking success at control during that time seemed to be because any measures could be employed to combat substance abuse. Public education and the passage of legislation worked well. However, the revival of methamphetamine abuse and the increase of solvents sniffing in spite of legal and educational efforts seem to indicate a different attitude toward substance abuse today, one that may be more troublesome and require a different approach.

Since 1980 the numbers of solvents- and methamphetamine-related arrests shown in figure 1 (stimulants category) stabilized at high levels. Arrests for cannabis and opiates violations also show similar tendencies, although these remain at relatively low levels. This recent phenomenon of an apparently stable equilibrium in substance abuse seems to be inherently unstable. Any new substance of abuse or a change in the social situation may upset this equilibrium.

METHAMPHETAMINE ABUSE-EPIDEMIOLOGIC AND SOCIAL PROBLEMS

At the end of the World War II, most Japanese were ignorant about the hazardous properties of methamphetamine, and no laws controlling its sale or distribution existed. Many soldiers and workers in the military had used methamphetamine during the war to remain awake at night and did not think of its use in terms of potential harm or drug dependence. Methamphetamine

became available from those military sources and pharmaceutical companies after the war and could be purchased in drugstores. Thus, at that time the availability of methamphetamine was essentially unlimited and usage dramatically increased until 1955.

Because abuse was believed to be related not only to availability but also to naivete, the Stimulants Control Law passed in 1951 was aimed at both these issues, with the result that abuse rapidly decreased; by 1959 it was below 1950 levels. This is an example of the remarkable effectiveness of legal and educational measures in a population that was ignorant of the hazards of drug abuse and was willing to change its behavior. During the 1945 to 1959 epidemic, people abused methamphetamine in the form of pills as well as by injection.

Figure 1 also shows that after a 10-year lull from 1960 to 1970 methamphetamine abuse (stimulants category) once again rose sharply and has continued to remain at high levels until today, shaping a plateau curve recently. It appears that the current epidemic has an entirely different character from that of the immediate postwar period. Because legal stimulant distribution is tightly controlled today, the sources of methamphetamine are almost entirely illegal. Thus, one factor contributing to the increase in abuse is the availability of methamphetamine from criminal sources, and the high rates of methamphetamine abuse continue in spite of sustained legal and education efforts, suggesting a more malignant motivation than in the previous epidemic. It seems that legal and educational measures can be remarkably effective in controlling drug abuse as it occurs in naive populations, but those measures are less effective in informed ones that consciously choose this pattern of behavior.

In Japan today, almost all methamphetamine is imported, and importation appears to be accomplished by organized crime, which derives a large profit from this source. Table 1 shows that the seaports where illegal methamphetamine arrived are scattered throughout Japan from Hokkaido to Yakushima Island. Figure 2 shows that Taiwan and South Korea are the major countries from which illicit methamphetamine is imported. The location of high abuse areas in Japan can be seen from figures 3 and 4, which show that there was a dramatic spread of abuse into central and northern Japan from 1970 to 1980.

Figure 5 demonstrates that stimulant abusers are Bohryokudan members, unemployed people, and construction workers. One of the greatest concerns is that this abuse pattern may change and spread to other subpopulations. This concern is genuine, as can be seen from figure 6, which shows that the prevalence of abuse in homemakers in 1980 was 7 times that in 1972, though

TABLE 1. *Number and sites of illegally imported methamphetamine seizures (>1 kg)*

Sites	1987	1988
Airports		
Haneda	1	
Narita	1	
Seaports		
Tomakomai	1	
Tokyo	1	1
Kawasaki	1	
Nagoya		1
Osaka		2
Sakai	1	
Kobe	1	1
Shimonoseki		4
Yakushima	1	

SOURCE: National Police Agency, Division of Prevention of Crimes, Department for Countermeasures of Drugs, 1989

in 1988 the number of homemakers arrested remained at 415, almost the same level or a slightly less than in 1980. The number of students arrested for methamphetamine-related violations (158) is also small, only 0.8 percent of total arrests. These data suggest that methamphetamine abusers in Japan are still confined to rather distinct subpopulations and are not evenly distributed throughout the general population.

Table 2 shows the distribution of psychiatric inpatients by diagnosis, age, and sex. The survey was conducted by the Ministry of Health and Welfare on June 30, 1987 (Ministry of Health and Welfare 1987). The number of inpatients who abused methamphetamine was 678; of these, 124 (18.3 percent) were female and 34 (5.0 percent) were younger than 20 years of age. In 1981 the Ministry of Health and Welfare issued an unusual policy statement that urged hospitals to accept more methamphetamine abusers (Ministry of Health and Welfare 1987). Still, the number of inpatients who abused methamphetamine was far less than those who abused alcohol (table 2). Even medical professionals tend to view drug-seeking behavior as more criminal than medical, and the condition on which methamphetamine abusers are accepted into mental hospitals is that they exhibit psychotic symptoms such as hallucinations or confusion.

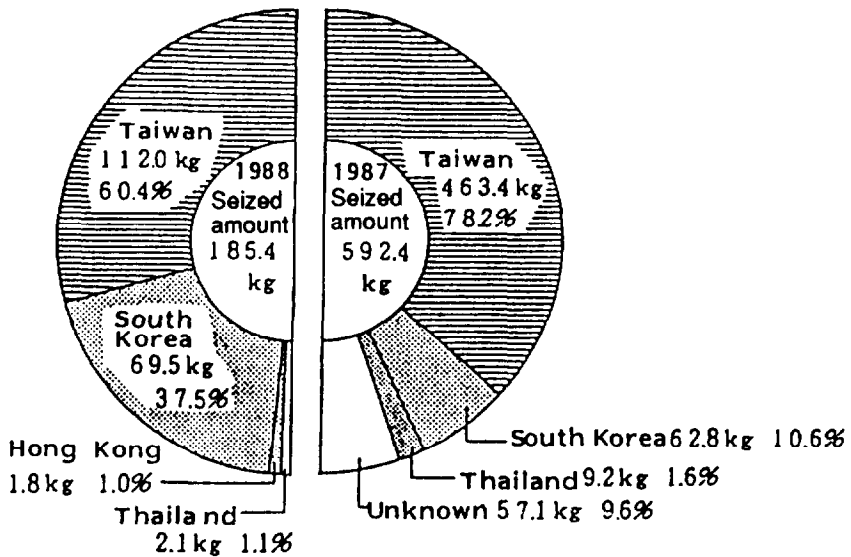


FIGURE 2. Countries from which a large amount of illicit methamphetamine (>1 kg) was exported

SOURCE: National Police Agency, Division of Prevention of Crimes, Department for Countermeasures of Drugs, 1989

Methamphetamine abuse is closely associated with criminal activity, and prisons contain 10 times more methamphetamine abusers than do hospitals, although many of them are casual users. According to a survey of Kochi Prefectural Prison in 1983 (Suwaki et al. 1985), 105 of 405 prisoners (26.1 percent) were convicted under Stimulants Control Law violations, whereas 222 prisoners (55.1 percent) admitted using methamphetamine. In addition, prisoners generally were younger than hospital patients; 61.9 percent were 20 to 29 years old, and 25.2 percent were 30 to 39 years old.

Fukui and colleagues (1988) conducted a survey of substance abuse in psychiatric hospitals and clinics throughout Japan in 1987. There were 776 hospitals and clinics (48.9 percent) that responded to the survey; of these, 310 (39.9 percent) treated substance abusers in the 2-month survey period. Substance abusers totaled 881; of these, 345 (39.2 percent) were on methamphetamine, and 301 (34.2 percent) were on volatile solvents (table 3). Figure 7 shows the age distribution of these substance abusers; many abusers of volatile solvents and cough syrups are in younger age groups, and abusers

Number of people
arrested per 100,000
population

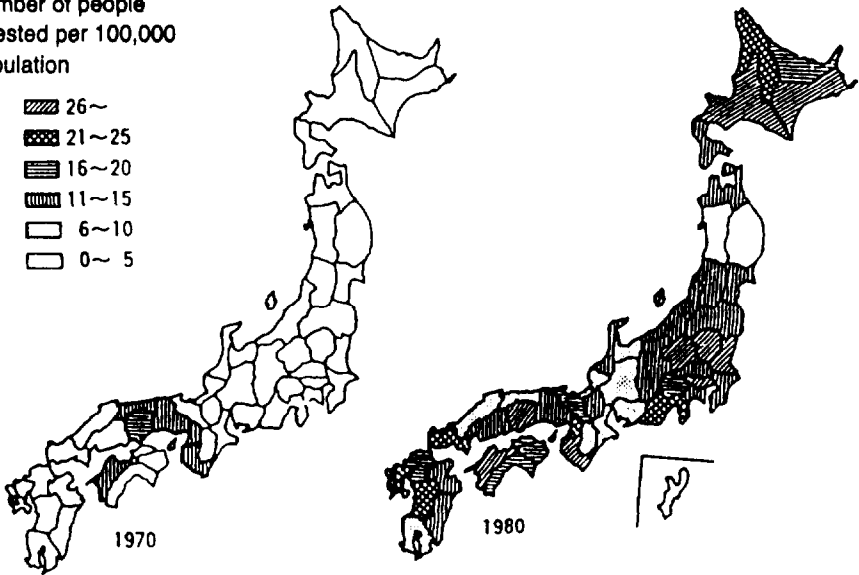
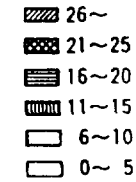


FIGURE 3. *Geographic distribution of methamphetamine-related arrests, 1970 and 1980*

SOURCE: National Police Agency, Division of Prevention of Crimes, 1981

of antianxiety drugs, hypnotics, and analgesics tend to be older. Ages of methamphetamine abusers vary from those in their twenties to those in their fifties. Surprisingly, 13.9 percent of them are in the 50 to 59 age group, although the peak group are those ages 30 to 39. This suggests that many chronic, older patients who abuse methamphetamine are relegated to treatment in mental hospitals due to its effects.

A 55-year-old methamphetamine abuser today would have been a teenager in the previous epidemic. This raises speculation as to how many of today's abusers are holdovers from that period. It is clear that previous efforts at control did not eradicate abuse because abuse levels between 1960 and 1970 still were considerable. It is possible that those "veterans" may have helped spark the present epidemic by continuing to be a ready market for methamphetamine from 1960 to 1970.

Number of people
arrested per 100,000
population

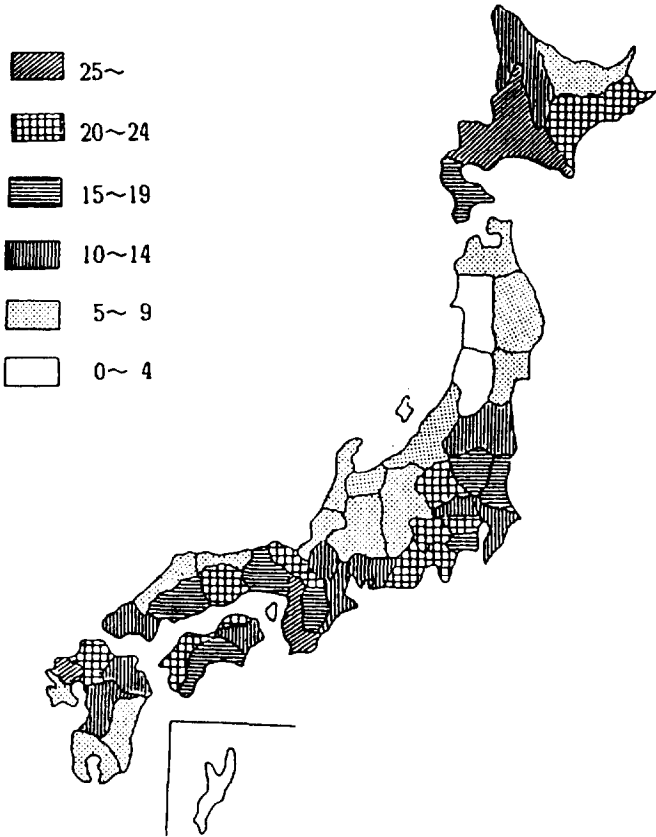


FIGURE 4. *Geographic distribution of methamphetamine-related arrests, 1988*

SOURCE: National Police Agency, Division of Prevention of Crimes, Department for Countermeasures of Drugs, 1989

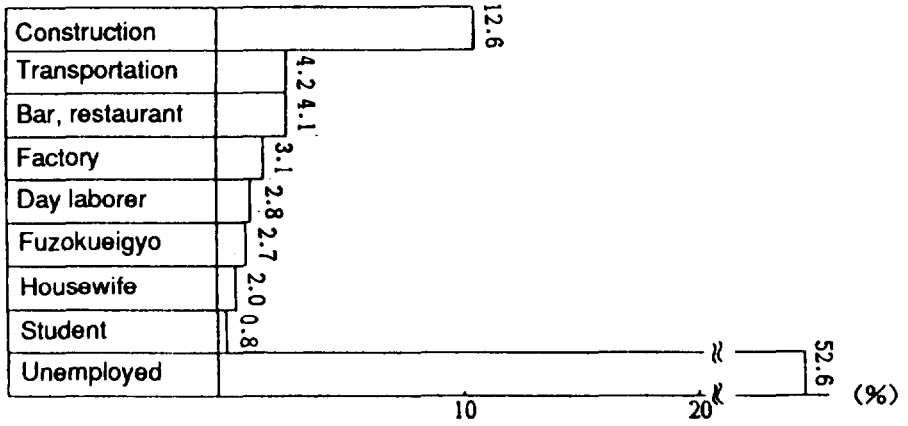


FIGURE 5. *Distribution of occupations of persons arrested for stimulant violations (total n=20,716)*

SOURCE: National Police Agency, Division of Prevention of Crimes, Department for Countermeasures of Drugs, 1989

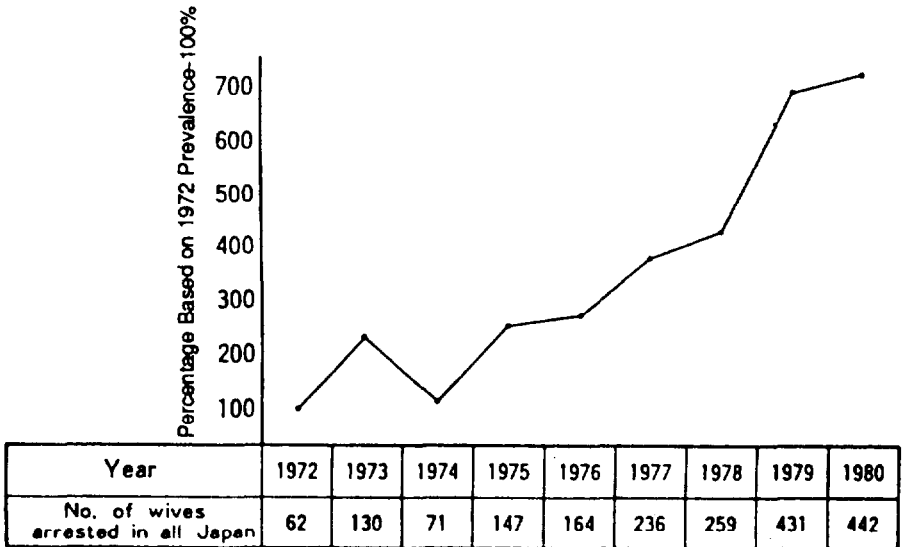


FIGURE 6. *Prevalence of amphetamine abuse among homemakers by year*

SOURCE: National Police Agency, Division of Prevention of Crimes, 1981

TABLE 2. *Distribution of psychiatric inpatient diagnoses by age and sex*

Diagnosis	Total				Men			Women				
	Total	<20	>65	Involuntarily Committed	Total	<20	>65	Total	<20	>65		
Schizophrenia	210,474	1,412	17,872	18,495	120,882	821	6,579	89,812	591	11,293		
Affective disorder	16,263	162	3,834	283	7,735	79	1,249	6,526	83	2,685		
Organic brain disorder	Total	39,902	53	31,560	224	16,599	39	10,928	23,303	14	20,634	
	Dementia	Alzheimer	6,878	3	5,723	8	2,108	0	1,653	4,568	3	4,070
		CVD	19,797	8	16,997	31	7,991	3	6,033	11,806	5	10,984
		Others	6,754	6	5,333	65	2,770	6	1,870	3,984	0	3,483
Others	6,875	36	3,507	120	3,730	30	1,370	2,945	6	2,137		
Substance use disorder	Total	22,479	181	2,819	399	20,832	127	2,567	1,647	54	252	
	Alcohol	20,742	19	2,738	249	19,435	17	2,514	1,307	2	224	
	Methamphetamine	878	34	5	108	554	18	4	124	18	1	
	Others	1,059	128	76	42	843	92	49	216	38	27	
Other psychosis	10,838	262	2,036	318	5,035	129	681	5,903	133	1,355		
Mental retardation	14,699	353	1,132	893	8,701	218	539	5,968	135	593		
Sociopathy	1,956	56	246	91	1,491	33	160	465	23	86		
Neurosis	9,840	566	1,214	85	4,502	299	308	5,338	299	908		
Epilepsy	10,671	227	672	935	6,297	147	331	4,374	80	341		
Others	4,725	514	1,242	67	2,428	297	434	2,299	217	608		
Total	341,917	3,808	62,726	21,550	194,280	2,179	23,774	147,637	1,629	38,954		

SOURCE: Ministry of Health and Welfare, Division of Mental Health, 1987

LONGITUDINAL PATTERN OF SUBSTANCE ABUSE

Finally, the author presents a recent study (Suwaki et al. 1990) of longitudinal patterns of substance abuse, including methamphetamine. Substance abusers often are viewed as abusing only one main substance, and other substances of abuse are likely to be disregarded even when they are abused at the same time. Once a patient is diagnosed with alcoholism or methamphetamine dependence, physicians tend to focus on that diagnosis. Data from hospitals and police offices, to which the author referred in this chapter, also were classified on such identification of each substance of abuse.

However, in our clinic, we often treat young patients who change their drug of abuse from organic solvents to methamphetamine and middle-age methamphetamine abusers who simultaneously consume a large quantity of alcohol. In considering such a situation, it was intended to make clear the pattern of substance abuse, including alcohol, in an individual, covering every substance of abuse and other addictive behaviors such as pathological gambling. Subjects in this study were 225 patients with substance abuse who visited psychiatric hospitals and clinics from December 1987 to December 1988.

In Type 1 alcoholism, alcohol is consumed for a long period as a single substance of abuse. Many Type 1 abusers also had a cigarette smoking habit, but cigarette smoking is not used as a criterion for deciding pattern of abuse, because in the preliminary study of 57 patients, 53 (93.0 percent) had a smoking habit. Type 1b abusers consumed tranquilizers, hypnotics, or analgesics in later stages. Many of them initiated their use by physicians' prescription when they visited hospitals or clinics.

Type 2 abuse is initiated at younger ages and usually involves organic solvents. This type is further subdivided into Type 2a, exclusively solvents; 2b, solvents with alcohol, hypnotics, or analgesics; and 2c, solvents with methamphetamine. The latter two types involve many substances of abuse and constitute a core group of multiple substance abusers in Japan. Type 2c is considered the most vicious pattern of substance abuse in youth.

Type 3 is the pattern of methamphetamine abuse without use of any organic solvents and is subdivided into 3a, without alcohol, and 3b, with alcohol. Most Type 3b patients used alcohol and methamphetamine at the same time.

Type 4 abuse does not include alcohol, organic solvents, or methamphetamine.

TABLE 3. *Distribution of substances of abuse in psychiatric patients with substance use disorder*

Substance of Abuse	Number of Patients	
	(N=881)	Percent
Methamphetamine	345	39.2
Volatile solvents	301	34.2
Hypnotics	85	9.8
Analgesics	84	9.5
Cough syrup	30	3.4
Antianxiety drugs	21	2.4
Others	13	1.5
Unknown	2	0.2

SOURCE: Fukui et al. 1988

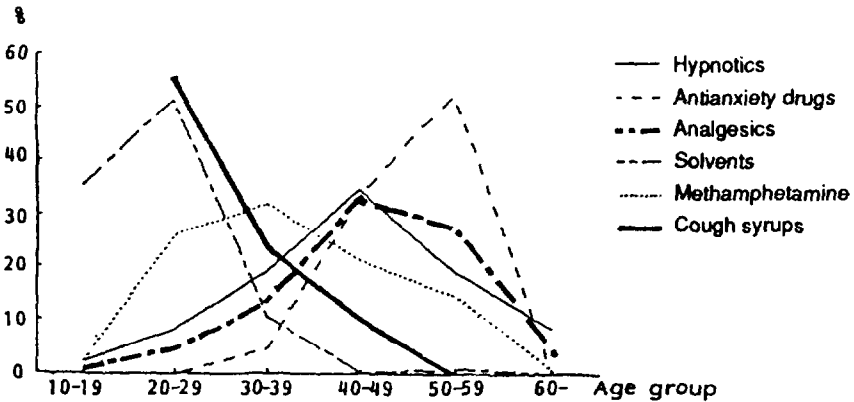


FIGURE 7. *Age distribution of psychiatric patients with substance use disorder*

SOURCE: Fukui et al. 1988

Table 4 shows the longitudinal patterns of substance abuse from the analyses of 225 cases. They were categorized into four types and seven subtypes, based on the longitudinal pattern of abuse, that is, the initial substance of abuse and its continuation, shift to, or combination with other substances.

TABLE 4. *Pattern of substance abuse in psychiatric patients in Japan*

Type	Subtype	Number of Patients (N=225)
1. Alcohol	1a. Alcohol alone	91
	1b. Alcohol with tranquilizers, analgesics	52
2. Solvents initiated	2a. Solvents alone	7
	2b. Solvents with alcohol, tranquilizers, and analgesics	19
	2c. Solvents with amphetamines (alcohol, tranquilizers, analgesics)	28
3. Amphetamine	3a. Amphetamines alone or with tranquilizers and analgesics	7
	3b. Amphetamines with alcohol (tranquilizers, analgesics)	21
4. Other type	Not including alcohol, solvents, or amphetamines	2

SOURCE: Suwaki et al. 1990

Table 5 shows the age of onset in three types of substance abuse: Type 1, alcohol; Type 2, solvents; Type 3, amphetamines. The youngest case began his abuse of organic solvents at age 12, and most of the Type 2 cases began their abuse before age 20. Most of the Type 3 cases began their abuse before 30 years of age. Type 1 cases also initiated their abuse relatively younger than expected, between 20 and 39 years of age. These three types of abuse are relatively distinct from each other in terms of age of onset.

Table 8 shows the present diagnoses of 225 cases of substance abuse. In Types 2b and 2c, the percentage of cases with the diagnosis of solvents abuse decreased to 68.4 percent and 23.1 percent, respectively. On the other hand, 38.8 percent of Type 2b cases were diagnosed with alcohol abuse, and 73.1 percent of Type 2c cases were diagnosed with methamphetamine abuse. This suggests that many solvents abusers shifted the substance of abuse to alcohol or methamphetamine. In Type 3b cases, 80 to 70 percent of them were diagnosed with alcohol and methamphetamine abuse, which suggests that many of them use methamphetamine and alcohol simultaneously. Physical illnesses often were observed in alcohol-related patterns such as Types 1, 2b, 2c, and 3b. In Type 1b (alcohol with hypnotics, tranquilizers, and analgesics), relatively few cases were diagnosed as hypnotics or analgesics abuse. However, the cases that consumed these prescribed drugs on a regular basis were included in the 1b category.

TABLE 5. *Distribution of the age of onset in substance abuse (n= 192)*

Age of Onset	1. Alcohol		2. Solvents		3. Amphetamine	
	Number of Patients		Number of Patients		Number of Patients	
<14	0		13		0	
15 to 19	11		29		9	
20 to 29	59		2		8	
30 to 39	34		0		1	
40 to 49	19		0		0	
50 to 59	5		0		0	
>60	0		0		0	

SOURCE: Suwaki et al. 1990

CONCLUSION

Japan has experienced two epidemics of methamphetamine abuse that are quite different in their backgrounds, Substance abuse problems in a society or substance use behaviors in an individual should be understood in an overall dynamic context that involves the movements and availabilities of other substances of abuse. Japan has reached a plateau in substance abuse for the 10 years in which problems of methamphetamine and volatile solvents abuse stabilized at high levels and those of cannabis and opiates at low levels. Equilibrium among substances of abuse on this plateau is inherently unstable and might be upset by a new epidemic or social conditions.

TABLE 6. *Present diagnoses of substance abuse patients*

Diagnoses	1. Alcohol		2. Solvents			3. Methamphetamine		4. Others
	1a	1b	2a	2b	2c	3a	3b	4
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Substance abuse	91(100)	50(96.2)	0	7(36.8)	5(19.2)	0	13(61.9)	0
Alcohol	0	0	7(100)	13(66.4)	6(23.1)	0	0	0
Volatile solvents	0	0	0	0	19(73.1)	7(100)	15(71.4)	0
Methamphetamine	0	3(5.8)	0	2(10.5)	1(3.8)	0	2(9.5)	2(100)
Hypnotics and tranquilizers	0	4(7.7)	0	1(5.3)	0	0	0	2(100)
Analgesics	3(3.3)	11(21.1)	1(14.3)	4(21.1)	3(11.5)	0	3(14.3)	1(50)
Psychosis	6(6.6)	4(7.7)	0	1(5.3)	0	0	0	0
Neurosis	42(46.2)	14(26.9)	0	3(15.8)	5(19.2)	0	6(28.6)	0
Physical illness	91(100)	52(100)	7(100)	19(100)	26(100)	7(100)	21(100)	2(100)

REFERENCES

- Fukui, S.; Watanabe, N.; Iyo, M.; Konuma, K.; Kurisu, E.; Wada, K.; and Toyama, G. An epidemiologic survey of drug dependence. In: *1987 Report of Studies on Etiological Factors and Pathological Conditions of Drug Dependence*. Tokyo: Ministry of Health and Welfare, 1988. pp. 169-182.
- Ministry of Health and Welfare. *A Brief Account of Drug Abuse and Countermeasures in Japan*. Tokyo: Ministry of Health and Welfare, 1985.
- Ministry of Health and Welfare, Division of Mental Health. *Mental Health in Japan*. Tokyo: Ministry of Health and Welfare, 1987.
- National Police Agency, Division of Prevention of Crimes. *Actual Situations of the Violations Against Stimulants and Narcotics Control Laws and Their Controls in 1980*. Tokyo: National Police Agency, 1981.
- National Police Agency, Division of Prevention of Crimes, Department for Countermeasures of Drugs. *Statistics of the Violations Against Stimulants and Other Drug-Related Laws in 1988*. Tokyo: National Police Agency, 1989.
- Suwaki, H. Solvents and stimulants abuses. *Jpn J Clin Psychiat* 11(8):955-963, 1982.
- Suwaki, H., and Bjorksten, O.J.W. Substance abuse trends in Japan. *Public Health Rev* 11(3):199-222, 1983.
- Suwaki, H.; Horii, S.; Fujimoto, A.; Akita, I.; Yamasaki, M.; Kazunaga, H.; and Shigenari, N. A study of substance abuse pattern with special reference to multiple use problems in Japan. In: *1989 Report of Studies on Etiological Factors and Pathological Conditions of Drug Dependence*. Tokyo: Ministry of Health and Welfare, 1990. pp. 153-161.
- Suwaki, H.; Yoshida, T.; and Ohara, H. A survey of stimulant abusers in prison, probation office, and mental hospitals in Kochi Prefecture. *Jpn J Social Psychiat* 8(2):144-150, 1985.

AUTHOR

Hiroshi Suwaki, M.D.
Professor of Psychology
Kagawa Medical School
1750-1 Mikicho
Kagawa 761-07
JAPAN

Trends and Patterns of Methamphetamine Abuse in the Republic of Korea

Byung In Cho

OVERVIEW

Methamphetamine was first synthesized in the Republic of Korea by individuals who returned home from civilian service for the Japanese Government during World War II and who probably learned the manufacturing process while they were working at chemical plants or substance-producing companies in Japan (Min 1989). It is uncertain when methamphetamine was first introduced or manufactured for illegal business purposes in Korea. Most researchers agree that methamphetamine manufacturing increased in Korea in the early 1970s because at that time Japanese drug control policies stiffened the punishment for illegal substance manufacturers and traffickers in that country (Min 1989). As the Japanese Government prosecuted illegal methamphetamine manufacturers with heavier sentences and stricter enforcement, the Japanese suppliers, presumably the key personnel of major underworld criminal organizations, visited Korea and contacted skilled technicians, resulting in the acceleration of illegal methamphetamine production in Korea.

Since methamphetamine was produced on a contractual basis between Japanese buyers and Korean suppliers, the methamphetamine problem in Korea was thought to be restricted to illegal manufacturing and smuggling. Until the middle 1970s the number arrested for methamphetamine abuse was estimated to be less than 100 per year. By the late 1970s however, Korea and Japan actively blocked methamphetamine smuggling by strengthening border interdiction after the Korean producers also became professional methamphetamine pushers, securing domestic customers and preying on them.

In 1970 the Korean Government began controlling activities involving methamphetamine production and abuse by authority of the Habit-Forming Medicine Control Act. Although that act was replaced by the Psychotropic Medicine Control Act (PMCA) in December 1979, it was not until 1987 that

the annual total of methamphetamine-related arrests exceeded 1,000. Methamphetamine arrestees exceeded 3,300 in 1988, accounting for 84.3 percent of the year's total of accused drug offenders (3,939).

For some time it was believed that the methamphetamine epidemic was a phenomenon unique to the harbor city of Pusan, which previously had been used as a shipping venue by professional methamphetamine smugglers. However, in recent years, PMCA violators have been arrested in almost every part of the nation, indicating that there is no methamphetamine-free area in Korea. Until early 1980 the methamphetamine-abusing population consisted almost exclusively of street gangsters, public entertainers, prostitutes, and truck drivers. However, recent data indicate that college students, homemakers, factory workers, and the unemployed make up the methamphetamine-abusing population throughout Korea.

DATA SOURCE

This chapter summarizes what is known about methamphetamine abuse in Korea in terms of (1) trends in arrested abusers, (2) general characteristics of Korea's methamphetamine problem, (3) characteristics of methamphetamine abusers based on the official documents provided by the Supreme Public Prosecutor's Office, and (4) research findings obtained from a prison survey by the Korean Institute of Criminology (KIC) (1989).

Information on trends in abuse arrests, geographical distribution, and demographic characteristics of methamphetamine offenders were obtained from official documents on PMCA violators compiled by the Supreme Public Prosecutor's Office. These data cover 1980 through the first quarter of 1990.

Data on distribution of methamphetamine offenders by sex, age, and occupation were obtained by examining the prosecution records and court decisions of 817 convicted methamphetamine offenders arrested during 1988 and charged with violation of the PMCA.

Information on the characteristics of methamphetamine abusers was obtained from a prison survey that used questionnaires and interviews with the convicted offenders. Questionnaires were filled out by 260 convicted methamphetamine abusers selected from three major prisons, and 10 offenders were interviewed. The research findings are reported in a special KIC publication (Korean Institute of Criminology 1989).

RECENT TRENDS

Except for 1983 and 1984, the number of arrested methamphetamine offenders has increased steadily. Table 1 shows that arrests increased by 63.9 percent and 67.7 percent in 1986 and 1987, respectively. Furthermore, the rate more than doubled in 1988 compared with 1987; total cases reached 3,320 in 1988.

In 1989 arrest figures declined by 39.9 percent. If this trend continues the methamphetamine epidemic could be curtailed in the near future. The newly established Drug Division of the Supreme Public Prosecutor's Office has made a strong effort to eradicate drug abuse in general and methamphetamine abuse in particular throughout the nation. Nationwide drug control strategies, led by prosecution authorities and the police, severely restricted the activities of syndicated raw material suppliers and several highly sophisticated underground methamphetamine networks. Leading individuals in methamphetamine supply and sales are serving their terms in prisons or are appealing their convictions.

It is assumed that the concentrated and successive drug investigations reduced the total methamphetamine supply on one hand and caused a rapid rise in the drug's price on the other. Thus, the sudden decrease in arrests of methamphetamine abusers probably was caused by decreasing supply and high prices.

As for the methamphetamine and raw materials seized, the amount confiscated in 1989 is calculated to be 821.619 kg (1,814 pounds), which is 2.7 times more than the total amount confiscated during the previous 5 years. Table 2 shows amounts of methamphetamine and raw materials for methamphetamine production seized from 1984 to 1990. Table 3 shows the number of raided clandestine methamphetamine laboratories and the total amount of methamphetamine and raw materials seized in those same years. Table 4

TABLE 1. *Number of people arrested for methamphetamine-related offenses, 1980 to 1990*

Year	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990 ^a
Number of arrestees	78	216	501	420	417	501	821	1,377	3,320	1,994	301
Percent Increase	-	+177	+132	-16.2	-0.7	+20.1	+63.9	+67.7	+141	-39.9	-

The figures for 1990 represent the arrestees during the first quarter of the year.

SOURCE: Supreme Public Prosecutor's Office

TABLE 2. *Amounts (kg/lbs) of methamphetamine and raw materials seized, 1984-90*

Year	Methamphetamine	Raw Material
1984	47.892 (105.72)	-
1985	24.349 (53.75)	-
1986	34.157 (75.40)	-
1987	120.761 (266.58)	.500 (1)
1988	73.538 (162.33)	-
1989	131.619 (290.54)	690.060 (1,523)
1990 ^a	7.372 (16.27)	164.000 (362)
Total	439.688 (970.61)	854.500 (1,686)

^aThe figures for 1990 represent amounts seized during the first quarter of the year.

SOURCE: Supreme Public Prosecutor's Office

TABLE 3. *Methamphetamine laboratories raided and the total amounts (kg/lbs) of methamphetamine and raw materials seized through raids, 1984-90*

Year	Laboratories Raided	Total Amounts Seized
1984	3	2.60 (6.16)
1985	1	11.20 (24.72)
1986	4	23.75 (52.42)
1987	7	29.80 (65.78)
1988	4	115.45 (254.85)
1989	9	637.07 (1,406.33)
1990 ^a	2	171.42 (376.42)
Total	30	991.49 (2,188.71)

^aThe figures for 1990 represent the cases and the amounts seized during the first quarter of the year.

SOURCE: Supreme Public Prosecutor's Office

TABLE 4. *Methamphetamine prices^a at various levels of trade*

Price	City	1988 (Oct.)	1989 (Oct.)	1990 (Jan.)	1990 (Apr.)
Producer's price/kg	Seoul	5,000	6,400	7,000	11,000
	Pusan	4,300	5,700	14,000	21,000-29,000
Wholesale price/100g	Seoul	700	1,000	1,400	4,300
	Pusan	1,400	2,900	5,700	7,000-14,000
Retail price/g	Seoul	70	140	210	700
	Pusan	140	280	430	700-1,400
injection price/0.03g	Seoul	7-14	14-21	28	70
	Pusan	14	43	70	70-140

^aThe price at each trade level was converted into U.S. dollars in accordance with the foreign exchange rate as of June 19, 1990.

SOURCE: Supreme Public Prosecutor's Office

shows the changes in the price of methamphetamine at various levels of trade from October 1988 to April 1990. The price per injection increased by a factor of 10 during that period in Seoul.

Despite these apparently favorable trends, few predictions of future drug use are optimistic. Most experts on drug use in Korea are aware that the use of marijuana and opiate derivatives abruptly increased while the use of methamphetamine decreased. Figure 1 compares the arrests by type of drug abused. It is widely assumed that many methamphetamine abusers gradually began using marijuana or opiate derivatives instead.

It is anticipated that methamphetamine abuse will increase steadily whenever control efforts decline and the supply increases, resulting in price reduction. Some investigators warn of the possibility that the cheaper, foreign-made methamphetamine, possibly from Taiwan or Thailand, would be smuggled into Korea if the price stays high for a prolonged period.

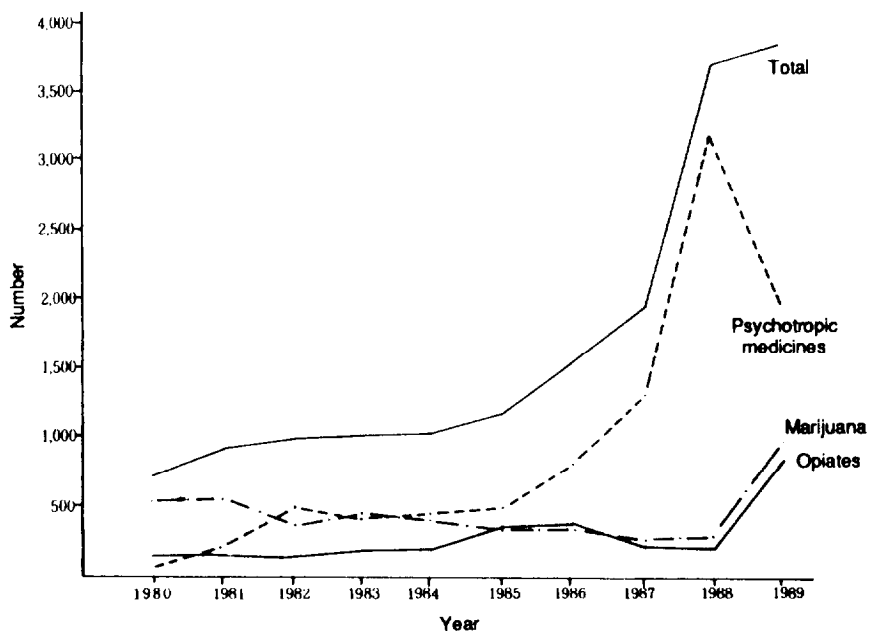


FIGURE 1. *Number of drug arrests and types of drugs involved, 1980-1989*

GENERAL CHARACTERISTICS

Geographic Distribution

Geographic distribution of methamphetamine offenders can be ascertained by reviewing the arrest data compiled by the Supreme Public Prosecutor's Office. Although the figures have fluctuated slightly, about half the arrests for methamphetamine-related offenses were made in the city of Pusan and adjacent districts.

Data presented in table 5 confirm that methamphetamine is being used in every part of Korea. Methamphetamine arrests are increasing rapidly in Kyungki Province, which includes Seoul, rising from 23.4 percent of nationwide drug arrests in 1986 to 34.1 percent in 1989. Kyungbuk Province, including the city of Taegu, also has been identified as a potential area in which the methamphetamine epidemic may rapidly expand.

TABLE 5. *Geographical distribution of methamphetamine offenders*

Province	1986		1987		1988		1989	
	N	%	N	%	N	%	N	%
Kyungki	202	(23.4)	467	(32.0)	624	(18.8)	680	(34.1)
Kyungnam	462	(53.5)	744	(51.0)	2,261	(68.1)	826	(41.4)
Kyungbuk	123	(14.2)	153	(10.5)	295	(8.9)	363	(18.2)
Cheonnam	4	(0.5)	28	(1.9)	27	(0.8)	51	(2.6)
Cheonbuk	6	(0.8)	15	(1.0)	7	(0.2)	20	(1.0)
Kangwon	13	(1.5)	10	(0.7)	27	(0.8)	6	(0.3)
Choongnam	40	(4.6)	34	(2.3)	46	(1.4)	36	(1.8)
Choongbuk	4	(0.5)	8	(0.6)	13	(0.4)	6	(0.3)
Cheju	8	(1.0)	-	-	20	(0.6)	6	(0.3)
Total	862		1,459		3,320		1,994	

SOURCE: Supreme Public Prosecutor's Office

Distribution by Sex, Age, and Occupation

Chronological data on the demographic character of methamphetamine offenders are not available at this time. However, based on the demographic data on those arrested in 1988, a nationwide picture can be projected.

According to table 6, in Korea, **as** in many other countries of the world, males constitute the majority of methamphetamine offenders. The ratio of male to female offenders is 84.7 percent vs. 15.3 percent. As for age distribution, 51.2 percent were between 21 and 30 years of age; the majority of female offenders were disproportionately concentrated under 25 years of age, while the male offenders are relatively evenly distributed across ail ages.

Table 7 shows distribution by occupation of those arrested in 1988. About half those arrested were unemployed. A disproportionate number of female offenders come from the service or entertainment industry (e.g., prostitutes, bar girls), while the occupations of male offenders vary.

ABUSE PATTERNS

Motivations

The KIC survey revealed that 70 percent of the respondents first used methamphetamine between the ages of 16 and 30. The average age of first experience was 28.7 for males and 22.7 for females. As for preliminary

TABLE 6. *Distribution of accused methamphetamine offenders by sex and age, 1988*

Age	Male		Female		Total	
	N	%	N	%	N	%
Younger than 20	264	(9.4)	104	(20.4)	368	(11.1)
21-25	631	(22.4)	208	(40.9)	839	(25.3)
26-30	773	(27.5)	87	(17.2)	860	(25.9)
31-40	803	(28.6)	80	(15.1)	883	(26.6)
41-50	165	(5.8)	21	(4.1)	186	(5.6)
Older than 51	32	(1.2)	6	(1.2)	38	(1.2)
Unknown	142	(5.1)	2	(0.5)	144	(4.3)
Total	2,810	(84.7)	408	(15.3)	3,318	

SOURCE: Korean Institute of Criminology 1989

TABLE 7. *Distribution of methamphetamine offenders by occupation arrested, 1988*

Occupation	Male		Female		Total	
	N	%	N	%	N	%
Unemployed	1,438	(51.2)	236	(46.5)	1,674	(50.5)
Service worker ^a	301	(10.7)	232	(45.7)	553	(16.1)
Factory worker	226	(8.0)	-	-	226	(6.8)
Sales clerk	201	(1.2)	7	(1.4)	208	(6.3)
Farmer	62	(2.2)	-	-	62	(1.9)
Office clerk	57	(1.8)	-	-	56	(1.7)
Technician	51	(1.8)	10	(2.0)	56	(1.7)
College student	33	(1.2)	1	(0.2)	34	(1.1)
Homemaker	-	-	3	(0.6)	3	(0.1)
Others	441	(15.7)	18	(3.5)	459	(13.6)
Total	2,810	(84.7)	508	(15.3)	3,318	(100.0)

^aIn Korea, "service" occupations include such jobs as waiters, pimps, bell boys (males); and waitresses, prostitutes, coffee shop madams (females).

SOURCE: Korean institute of Criminology 1989

knowledge of methamphetamine at the time of first use, 56.6 percent reported that they thought of methamphetamine as a substance for getting high; 32.2 percent thought of it as an excellent remedy for tiredness; and 26.2 percent tried it to enhance sexual pleasure. From these findings, it appears that most methamphetamine abusers began using because of myths and false information. Approximately 90 percent of the respondents reported that they began methamphetamine use due to peer influence.

Methods and Locations

Eighty-one percent of the respondents reported that they first used methamphetamine by intravenous injection, while 15 percent drank it with soft drinks, and 4 percent snorted it. After they became addicts, however, 97 percent used intravenous injection almost exclusively; the abusers agreed that injection is the best method to get high within seconds.

Asked where they used methamphetamine, about 55 percent said they used it in hotels, while bars, cars, and recreation facilities also were used frequently. The KIC research also revealed that 92.6 percent of respondents abused methamphetamine with peers, lovers, or wives rather than alone.

Frequency, Dosage, and Duration

Frequency, dosage, and duration were investigated by inquiring into abuse habits for a month before arrest: 42.8 percent reported that they injected more than once a day; 18.8 percent injected once a day; 14.3 percent injected once every 2 or 3 days; and 8 percent injected once a week. More than 60 percent of respondents used methamphetamine once or more a day.

As for dosage, it has been known that abusers generally use 0.03 g (0.001 ounce) of methamphetamine per injection. However, the KIC research revealed that only 33.8 percent of the respondents administered less than 0.03 g per injection; 28.4 percent of the respondents reported a dosage of 0.1 g (0.03 ounce) or more per injection.

As for duration, 37.4 percent reported that they had used methamphetamine longer than 3 years, while 39.9 percent had used it for 1 to 3 years; only 10.4 percent of respondents reported using methamphetamine less than 6 months.

Methamphetamine Abusers and Other Drugs

The KIC research discovered that 54.3 percent of the respondents also had used at least one other drug prior or subsequent to methamphetamine use: 83.3 percent smoked marijuana; 19.4 percent snorted inhalants (e.g., glue,

butane gas); 18.5 percent used tranquilizers; and 6.3 percent used heroin or cocaine. Respondents reported smoking marijuana or using inhalants prior to methamphetamine use and using heroin or cocaine after an experience with methamphetamine. From these findings, it is hypothesized that the drug addiction process starts with marijuana and inhalants and progresses to use of methamphetamine and other drugs.

CONCLUSION

in general, the drug epidemic in Korea is not serious in number of drug users and the impact on and cost of drug use to society compared with the drug situation in the more industrialized Western countries, Even so, the Korean Government is well aware that drug abuse, particularly methamphetamine abuse, will become uncontrollable unless treated at the beginning stages.

As is the case with other nations, the drug policy of Korea has taken two directions: (1) suppressing the supply of raw materials and the final products of illegal drugs and (2) providing self-reported abusers and addicts with treatment opportunities free of charge and with immunity from criminal punishment.

Whereas the drug control policies focus on border interdiction to prevent illegal trade of methamphetamine and raw materials between nations, the government considers education and prevention as the final solution to the problem. The National Drug Addicts Treatment Center under construction near Pusan is intended as the cornerstone of a more advanced drug policy in the Republic of Korea.

REFERENCES

- Korean institute of Criminology. *A Study on Methamphetamine Abuse and Countermeasures*. Seoul: Korean institute of Criminology, 1969.
- Min, B.H. *Present Situation of Drug Offenders and the Countermeasures*. Research Report 20. Seoul: Legal Research and Training Institute, Department of Justice, 1989.

AUTHOR

Byung In Cho, Ph.D.
Senior Researcher
Korean institute of Criminology
1103 Teacher's Welfare Building
142 Woomyun-Dong
Sucho-gu, Seoul 135-140
REPUBLIC OF KOREA

Community Networks for Response to Abuse Outbreaks of Methamphetamine and Its Analogs

James N. Hall and Pauline M. Broderick

INTRODUCTION

The most recent drug abuse prevalence surveys as well as morbidity and mortality indicators demonstrate that the Nation's cocaine epidemic has started to decline. In assessing potential drug problems for the 1990s, it is important to recognize the increased significance of local and regional drug issues.

Previously, drug problems have been associated with major urban centers, particularly on the east and west coasts. In recent years, all communities are at risk of drug abuse outbreaks. Several factors contribute to this trend. The increased domestic production of marijuana and synthetic drugs from clandestine laboratories means that even isolated rural areas may be centers of illicit drug production and trafficking. The rapid distribution of crack cocaine via the US. interstate highway system demonstrates that more aggressive drug marketing strategies place all communities at risk.

Community-based networks are a vital resource for countering the problems of alcohol and other drug abuse. Indeed, such organizations represent the "homefront" of the "war on drugs." The impact of these networks is particularly appropriate for addressing the spread of domestically produced methamphetamine (speed, crank, crystal, or ice) and its analog MDMA (XTC or ecstasy). The localized nature of methamphetamine abuse has been a unique aspect of its epidemics.

A 1989 National Institute on Drug Abuse (NIDA) study concluded that the most important factor in determining a community's risk for methamphetamine abuse is the presence of local clandestine laboratories that produce the drug (National Institute on Drug Abuse 1989a). Patterns of the drug's abuse tend to be concentrated in selected cities and regions. However, locations of such drug outbreaks have shifted over the past 30 years. Since 1960, areas affected by abuse of synthetic stimulants have moved from coast to coast as well as to the Midwest and, more recently, to the South.

In the early 1960s pharmaceutical stimulants were prescribed widely as appetite suppressants for the treatment of obesity. Diversion of these legally prescribed products became rampant and ultimately led to stricter government regulations and more cautious prescribing for medical use. Later in that decade, “street speed” from clandestine laboratories was introduced by motorcycle gangs, which quickly gained control of the manufacture and distribution of illicit amphetamine products. The mobility of these laboratories and their affiliation with biker groups in different regions of the country Contributed to the changing geography of the methamphetamine problem. Today, methamphetamine producers and sellers still include biker gangs but also have expanded to include large and small independent criminal enterprise groups.

San Francisco and the Pacific Northwest were the center of amphetamine abuse in the late 1960s and early 1970s. Trafficking spread to the Midwest throughout the 1970s and by the early 1980s Philadelphia and Minneapolis led the Nation in consequences of methamphetamine problems. In 1987 San Diego surpassed all other U.S. cities in the consequences of methamphetamine abuse (National Institute on Drug Abuse 1989a).

Table 1 tracks methamphetamine-related emergency room (ER) mentions reported to NIDA’s Drug Abuse Warning Network (DAWN) from 1985 to 1989. Such mentions increased from 1,370 in 1985 to 2,439 in 1988 and then decreased slightly to 2,135 in 1989. It should be noted that these totals are from only those hospitals that have consistently reported to DAWN during the 5-year period covered and represent only a sample of the national total. Of the 1989 mentions, 77 percent were from only five cities-San Diego (25 percent), San Francisco (22 percent), Dallas (11 percent), Phoenix (11 percent), and Los Angeles (8 percent). Likewise, table 2 reveals that 74 percent of the 180 methamphetamine-related deaths reported by medical examiners (MEs) to DAWN in 1989 were from the three California cities of San Diego (36 percent), San Francisco (24 percent), and Los Angeles (14 percent).

Demographic profiles of abusers from various sources reflect a similar at-risk group. The National Institute on Drug Abuse (1989b) reported that abusing populations are predominantly white, lower middle-income, high school-educated (or less), young adults ranging in age from 20 to 35 years. Table 3 reflects a similar demographic pattern of 1988 DAWN emergency room mentions and ME-reported deaths for methamphetamine. More recently, adolescent use appears to be on the rise (Adams et al. 1990). Although most drug abuse monitoring systems focus on major metropolitan areas, anecdotal surveillance and reports from State epidemiology work groups indicate that methamphetamine is spreading rapidly to rural communities in the West, Midwest, and South (Westrate 1989).

TABLE 1. *Methamphetamine-related ER mentions, 1985-1989*

Total DAWN System and Metropolitan Areas	1985	1986	1987	1988	1989
Total ER Mentions	1,370	1,472	2,062	2,439	2,135
San Diego	112	218	528	778	524
San Francisco	360	240	218	256	461
Dallas	72	230	284	308	243
Phoenix	51	85	208	345	234
Los Angeles	65	87	117	176	166
Seattle	30	32	58	86	121
Denver	65	102	84	71	97
Philadelphia	285	161	206	102	79

SOURCE: NIDA Drug Abuse Warning Network, March 1990 data file for ERs and April 1990 data file for MEs

TABLE 2. *Methamphetamine-related deaths, 1985-1989*

Total DAWN System and Metropolitan Areas	1985	1986	1987	1988	1989
Total ME Mentions (excludes New York)	65	116	141	163	180
San Diego	9	27	39	52	64
San Francisco	13	37	51	53	44
Los Angeles	3	23	18	18	25
Philadelphia	34	23	14	15	13
Oklahoma City	0	2	6	0	8
Phoenix	0	0	3	7	8

SOURCE: NIDA Drug Abuse Warning Network, March 1990 data file for ERs and April 1990 data file for MEs

The inhalation (“smoking”) of melted d-methamphetamine hydrochloride (ice) reached epidemic proportions in Hawaii between 1987 and 1990 (Cave 1990). This highly pure, recrystallized methamphetamine product is believed to be manufactured in Korea and trafficked by Filipino crime groups. Abuse of ice in the United States still appears to be isolated to Hawaii according to Federal drug use tracking systems (Drug Enforcement Administration 1990). Scattered

TABLE 3. *Demographics of methamphetamine-related ER patients and ME decedents, 1988, by percent*

Category	White	Male	Number (Age Range)
ER Patients	76	62	51 (20-29 years old)
Decedents	75	83	43 (30-39 years old)

SOURCE: NIDA Drug Abuse Warning Network *Statistical Series, 1-8 Annual Data, 1988, 1989a*

reports of ice use along the west coast and in the South generally have referred to abuse of a less pure form of methamphetamine than that being abused in Hawaii and Asia. Yet the potential for a mainland US. ice epidemic exists if supplies of the drug become available. It is believed that crack users might be attracted to the economy offered by the long duration (4 to 6 hours) of the drug's stimulant effects.

The abuse of the methamphetamine analog MDMA has not been adequately tracked. Newmeyer (1986) has identified the problems of applying traditional drug abuse epidemiology systems in monitoring patterns of MDMA abuse. The general perception is that the drug is widely used, particularly among college Students in the West and South. However, as Fuller (1989) notes, there are few hard data regarding the geographic distribution of MDMA use or its patterns of abuse. Consequently, community networks may be able to identify local outbreaks of MDMA abuse years before national drug abuse surveillance systems, such as DAWN and Federal prevalence surveys, may report it.

COMMUNITY-BASED STRATEGIES

It is increasingly apparent that Comprehensive, community-based strategies represent a strong deterrent in the prevention of drug abuse. Recognizing that problems associated with drug abuse are multifaceted indicates that a variety of solutions from many different disciplines are appropriate. Even more important is the need to coordinate these solutions into a comprehensive approach. Such strategies are formulated by networks that may exist among Federal, State, and local agencies within the same field (e.g., law enforcement) or from cross-disciplinary alliances, including health and human services, criminal justice, education, and environmental agencies. Some of these types of networks include:

- Private-sector drug prevention coalitions
- Local drug epidemiology networks

- Alcohol and other drug abuse and mental health agencies
- Criminal justice interagency networks

Private-Sector Coalitions

Private-sector drug prevention coalitions have been formed in at least 35 US cities during the past few years (personal communication, M. Culp, August 1990). These groups have proven effective in organizing and promoting public policy requiring comprehensive approaches and interagency cooperation, although their organizational structures and foci may vary from city to city. One of the most important functions performed by these coalitions is community consensus development. Consequently, it is important that they develop formats based on community needs. It is also vital that community coalitions establish as broad a membership base as possible, drawing from every sector of the community. Many of these local coalitions grew out of parent action groups, which recognized the need to expand family-oriented antidrug efforts to comprehensive community strategies.

Local Drug Epidemiology Networks

A local drug epidemiology network (DEN) is a committee comprising representatives from health, criminal justice, and other community agencies affected by drug abuse. The DEN gathers, monitors, and analyzes drug abuse indicator data from these various community institutions. The DEN tracks drug-related medical emergencies and deaths reported by hospital ER facilities and ME departments and reviews addiction treatment admissions data for substance abuse patterns and client demographic information. Criminal justice data may include information on arrestees, drug-related crime, and price and purity statistics from drug seizure. Local drug abuse research from academic institutions helps complete a comprehensive profile of community substance abuse patterns. Local trends may be tracked from semiannual or quarterly reports generated by the DEN.

Local epidemiology may reveal an emerging drug problem, such as methamphetamine abuse, much sooner than it would be detected from national data or surveys. Local drug epidemiology assists public policy planners by identifying where to provide services. Community epidemiology networks **also** provide a vital communication link for health, criminal justice, and education professionals. Traditionally, these groups have worked independently and missed the benefits of comprehensive strategies derived from interagency cooperation.

Alcohol and Other Drug Abuse and Mental Health Agencies

Networks of alcohol and other drug abuse and mental health organizations include community councils of treatment and prevention service provider agencies. Local substance abuse planning boards are responsible for identifying community needs and preparing recommendations on resource allocations and budgets for addiction treatment. Community addiction services boards may administer central intake units that offer diagnosis and assessment services independent of the treatment program where therapy is provided. Independent assessment centers provide efficient Utilization of a community's limited addiction therapy resources.

Criminal Justice Networks

Interagency law enforcement networks promote cooperation among Federal, State, and local agencies. Networks linking enforcement, courts, corrections, and probation help coordinate the various local service components of the criminal justice system. It is important that each part of the justice system be aware of the needs and limitations of the other components. Local networks provide that opportunity.

ROLE OF NETWORKS

Community networks may assume various roles in countering drug abuse outbreaks of methamphetamine and its analogs. These roles include:

- Conducting surveillance
- Planning and implementing prevention programs
- Developing intervention Strategies
- Adapting addiction treatment
- Enforcing legal sanctions

Surveillance

The earliest detection of local methamphetamine problems often begins from anecdotal mentions from school personnel, drug hotlines, or treatment admissions counseors. Yet it is important that there be a recognized reporting center for such information, Professionals may hesitate to contact police solely on the basis of unconfirmed reports. Consequently, local DENs are ideal forums to receive such information. Once the DEN is alerted, it may further investigate the availability of methamphetamine products through its multi-indicator system.

Surveillance includes identification of sources for precursor chemicals and laboratory equipment. Below are lists of popular chemicals used as precursors, solvents, and metal/salt or acid-based reagents in the illicit manufacture of methamphetamine (Oregon Department of Human Resources 1988). These substances have many industrial applications; therefore, monitoring their distribution is often more appropriate than outlawing their sale. Indeed, legitimate chemical supply houses should be included in the surveillance process. Law enforcement officers should be alerted to these chemicals in the event of their discovery during routine property searches. Laboratory analysis of seized methamphetamine will help identify precursor chemicals being used locally.

Metal/Salt Reagents

Aluminum foil
Magnesium
Palladium
Mercuric chloride
Sodium cyanide
Red phosphorous
Thionyl chloride
Lead acetate
Iodine
Lithium aluminum hydride
Sodium

Solvents

Freon
Chloroform
Methanol
Isopropanol
Ethyl ether
Acetone
Pyridine
Hexane
Benzene

Precursors

Phenylacetic acid
Phenyl-2-propanone
Methylamine
Ephedrine
Benzyl chloride
Acetaldehyde

Acid-Based Reagents

Hydrochloric acid
Acetic anhydride
Sodium hydroxide
Hydriodic acid
Acetic acid
Hydrogen peroxide
Sulfuric acid
Ammonia

The detection of clandestine laboratories may be facilitated by distinct odors emanating from such operations. Information campaigns may alert the public to signs of clandestine laboratory operations and may solicit reporting of suspected activity to law enforcement agencies. Such campaigns should emphasize the health and safety hazards associated with the presence of illicit drug laboratories. Public electrical utilities may help identify an unusually large

consumption of energy indicating the possible location of a methamphetamine laboratory. Recently, this type of assistance led to the seizure of a methamphetamine laboratory in Racine, WI.

Surveillance for methamphetamine requires an understanding of how the drug is trafficked both from local laboratories and nationally via interstate highways. The recent spread of methamphetamine from Southern California eastward parallels movement along interstate Highways 10 and 44. In the North, a similar pattern may be observed along Interstate 90. It is important that law enforcement agencies share information about general trafficking patterns with community networks. This type of intelligence need not include specific facts nor jeopardize ongoing investigations.

Communities at risk for methamphetamine abuse should monitor all available drug prevalence surveys for changes in patterns of stimulant use. Morbidity and mortality indicators also may alert local networks to the arrival or spread of methamphetamine abuse. These data sources include ME departments, hospital ERs, and addiction treatment programs. Patterns first may be reported as secondary or tertiary drug problems, particularly among cocaine clients. Methamphetamine use may be reported by arrestees for drug and nondrug offenses. The National Institute of Justice's Drug Utilization Forecast (DUF) system is an excellent example of drug abuse surveillance methods among the criminal justice population. The DUF program interviews and conducts urine drug screens among arrestees on a voluntary, anonymous basis. Early detection of methamphetamine and its analogs, as well as other new street drugs, is more likely to be revealed first in the DUF interviews rather than in the toxicology test results.

A special problem related to the surveillance of methamphetamine involves the many different street names by which the drug is known. Users rarely refer to the drug by its five-syllable chemical name. Street names for methamphetamine include crank, crystal, speed, crystal meth, glass, peanut butter speed, ice, go-fast, zip, chris, cristy, go, or meth. Some of these names are more popular in one community than in others. In San Diego the drug usually is called crystal; in Portland, OR, the name crank is used most often; in Dallas it is known as speed. Because of the variety of terms used, it is likely that data collection and reporting of methamphetamine abuse may not always properly classify the substance described. Consequently, it is important that ER staff, treatment counselors, educators, and law enforcement personnel be familiar with the various street names,

Prevention Requirements

Prevention of methamphetamine abuse requires a comprehensive understanding of the drug's desired and adverse effects, its unique patterns of abuse, the at-risk populations most likely to be using it, and its special risks related to transmission of the human immunodeficiency virus. Recovering methamphetamine addicts interviewed in a 1988 study (National Institute on Drug Abuse 1989b) identified the need for methamphetamine-specific prevention strategies. They reported seeing national antidrug messages about cocaine, crack, alcohol, and marijuana on television, billboards, and in newspapers but never hearing about methamphetamine. Consequently, they naively assumed that the drug must not be dangerous.

The localized nature of methamphetamine epidemics emphasizes the need for creative prevention strategies created by community-based networks. Such groups are in the best position to determine the most appropriate way of marketing and disseminating drug prevention messages. An example of a local prevention effort focused on MDMA is the "Agony of Ecstasy" campaign created by the "I Care" program of the East Baton Rouge Parish School Board in Louisiana. Local networks also are ideal groups for evaluating the effectiveness of prevention campaigns.

Intervention Strategies

Intervention for methamphetamine abuse involves identification of users and addicts as well as development of effective communications and options available to help them change their behavior. Local drug abuse networks may help community groups identify the specific signs and symptoms of methamphetamine abuse most likely to be observed by various institutions such as health and human service agencies, the criminal justice system, employers, and families and other social organizations. An understanding of the drug's unique abuse patterns will assist in developing such guidelines. Once identified, methamphetamine abusers need to be educated about the hazards of continued use in terms relevant to their own experiences and their observations of other users. A well-formulated continuum of care based on availability of local services should include resources for private counseling, self-help groups, and inpatient and outpatient addiction therapy. These services provide options for helping individuals change drug-using behavior. An example of a community network's intervention training program is Project First Aid for Addiction, developed by the Miami, FL, Coalition for a Drug-Free Community. Project First Aid for Addiction is a 3-evening educational series designed to teach the nature of addiction and how family members and friends may intervene with an addict.

Networks of addiction treatment programs and health departments may anticipate and allocate therapy resources at the onset of a methamphetamine abuse outbreak. Gawin and Ellinwood (1988) **have** reported that stimulant abuse produces some unique problems such as anhedonia (lack of pleasure in acts that are normally pleasurable) and anergia (inactivity, lack of energy). Kleber and **Gawin** (1984) have indicated that many substance abuse treatment programs are patterned after therapy for alcohol or opiate addiction and applied without adaptation for stimulant abuse. Experience with treating cocaine addiction will prove helpful. Nevertheless, an important role of local networks is to provide specialized training for stimulant addiction treatment to counselors in communities affected by methamphetamine abuse.

Adapting Addiction Treatment

Gawin and Ellinwood (1988) report that stimulant abuse treatments are being developed and applied, including adaptations of most major types of psychotherapy as well as pharmacotherapy. They also indicate that outpatient treatment is often successful, although early relapse is a strong possibility, and brief, episodically evoked craving recurs after withdrawal. Although it gradually diminishes in frequency, such craving can reemerge months or years after cessation of stimulant use. Such craving emerges as a crucial component of strategies for relapse prevention for stimulant abuse, which otherwise resembles the postwithdrawal treatment for other addictions.

Legal Sanctions

Community networks may assist law enforcement officers by promoting communication about methamphetamine problems among drug abuse professionals from various disciplines. Sharing information is an important source of intelligence for law enforcement activities. Networks may identify key resource persons and provide training for police about typical user profiles, trafficking patterns, and clandestine laboratory operations. Westrate (1989) has identified outlaw motorcycle gangs as the largest organized group involved with methamphetamine trafficking. In some areas, they control the market, whereas elsewhere they share the market with other types of traffickers. Motorcycle gangs appear to be strongest in areas that are not influenced by traditional organized crime groups or other ethnic criminal organizations. Generally, the most productive methamphetamine laboratories have been sited in secluded, rural areas away from the metropolitan distribution areas that these laboratories service.

Clandestine laboratory seizure requires specialized training in detection and safety precautions as well as hazardous waste cleanup and disposal. Federal

networks have been most helpful in conducting laboratory enforcement schools. The Drug Enforcement Administration has sponsored more than 23 such schools instructing more than 800 enforcement personnel from Federal, State, and local agencies. In addition, the Bureau of Justice Assistance has trained more than 230 State and local personnel. Community networks may help identify local experts to provide similar training programs. State epidemiology networks provide an excellent central reporting mechanism for tracking methamphetamine seizures and arrests. Two recent ice seizures in Florida were first reported to the State's Epidemiology Work Group by local law enforcement agencies in two rural counties.

Drug abuse problems frequently have been viewed as a national crisis requiring Federal solutions. This perception is particularly understandable with drugs of foreign origin such as cocaine or heroin. However, domestically produced drugs tend to have more regional patterns of abuse. Consequently, local strategies may more rapidly identify, prevent, intervene in, and stop expansion of the problem. Local networks encourage communication and cooperation among key professionals from various disciplines and develop comprehensive strategies. NIDA's drug abuse telecommunication network promotes exchanges among local networks in various parts of the country. A vital role for Federal institutions is to stimulate, train, and assist with the implementation of local initiatives for solving community drug problems. This approach is of particular significance for problems related to drugs of domestic origin such as methamphetamine and its analogs.

REFERENCES

- Adams, E.H.; Blanken, A.J.; Ferguson, L.D.; and Kopstein, A. "Overview of Selected Drug Trends." Unpublished paper. Division of Epidemiology and Prevention Research, National Institute on Drug Abuse, 1990.
- Cave, L.J., ed. NIDA monitors Hawaiian "ice" epidemic, *NIDA Notes*. Vol. 5, No. 2. National Institute on Drug Abuse. DHHS Pub. No. (ADM)90-1488. Washington, DC: Supt. of Docs., US. Govt. Print. Off., 1990. pp. 22-23.
- Drug Enforcement Administration, A special report on "ice" (d-methamphetamine hydrochloride)." In: *Epidemiologic Trends in Drug Abuse, Proceedings of the Community Epidemiology Work Group, December 1989*. National Institute on Drug Abuse. DHHS Pub. No. 90-721-75720058. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1990. pp. III-69-III-83.
- Fuller, R.W. Recommendations for future research on amphetamines and related designer drugs. In: Asghar, K., and De Souza, E., eds. *Pharmacology and Toxicology of Amphetamine and Related Designer Drugs*. National Institute on Drug Abuse Research Monograph 94. DHHS Pub. No.

- (ADM)89-1640. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1989. pp. 341-357.
- Gawin, F.H., and Ellinwood, E.H., Jr. Cocaine and other stimulants: Actions, abuse, and treatment. *N Engl J Med* 318:1173-1182, 1988.
- Kleber, H.D., and Gawin, F.H. Cocaine abuse: A review of current and experimental treatments. In: Grabowski, J., ed. *Cocaine: Pharmacology, Effects, and Treatment of Abuse*. National Institute on Drug Abuse Research Monograph 50. DHHS Pub. No. (ADM)87-1326. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1984. pp. 111-129.
- National Institute on Drug Abuse. *Methamphetamine Abuse in the United States*. DHHS Pub. No. (ADM)89-1608. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1989b.
- National Institute on Drug Abuse. *Statistical Series 1-8, Annual Data, 1988*. DHHS Pub. No. (ADM)89-1634. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1989a.
- Newmeyer, J.A. Some considerations on the prevalence of MDMA use. *J Psychoactive Drugs* 18:361-362, 1986.
- Oregon Department of Human Resources, Health Division. *Clandestine Drug Lab Committee, Final Report*. Portland, OR, 1988.
- Westrate, D.L. "Methamphetamine Trafficking and Abuse." Statement to the Select Committee on Narcotics Abuse and Control, US. House of Representatives, October 24, 1989.

AUTHORS

James N. Hall, B.A.
Executive Director

Pauline M. Broderick, B.P.S.
Director of Research

Up Front Drug Information Center
Suite 602
5701 Bisoayne Boulevard
Miami, FL 33137

National
Institute on
Drug
Abuse

Research

MONOGRAPH SERIES

While limited supplies last, single copies of the monographs may be obtained free of charge from the National Clearinghouse for Alcohol and Drug Information (NCADI). Please contact NCADI also for information about availability of coming issues and other publications of the National Institute on Drug Abuse relevant to drug abuse research.

Additional copies may be purchased from the U.S. Government Printing Office (GPO) and/or the National Technical Information Service (NTIS) as indicated. NTIS prices are for paper copy; add \$3 handling charge for each order. Microfiche copies are also available from NTIS. Prices from either source are subject to change.

Addresses are:

NCADI
National Clearinghouse for Alcohol and Drug Information
P.O. Box 2345
Rockville, MD 20852
(301) 468-2600
(800) 729-6686

GPO
Superintendent of Documents
U.S. Government Printing Office
Washington, DC 20402
(202) 275-2981

NTIS
National Technical Information Service
U.S. Department of Commerce
Springfield, VA 22161
(703) 487-4650

For information on availability of NIDA Research Monographs 1 through 24 (1975-1979) and others not listed, write to NIDA, Community and Professional Education Branch, Room 10A-54, 5600 Fishers Lane, Rockville, MD 20857.

- 25 BEHAVIORAL ANALYSIS AND TREATMENT OF SUBSTANCE ABUSE. Norman A. Krasnegor, Ph.D., ed.
GPO out of stock NCADI out of stock
NTIS PB #80-112428/AS \$31
- 26 THE BEHAVIORAL ASPECTS OF SMOKING. Norman A. Krasnegor, Ph.D., ed. (reprint from 1979 Surgeon General's Report on Smoking and Health)
GPO out of stock NTIS PB #80-118755/AS \$23
- 30 THEORIES ON DRUG ABUSE: SELECTED CONTEMPORARY PERSPECTIVES. Dan J. Lettieri, Ph.D.; Mollie Sayers; and Helen W. Pearson, eds.
GPO out of stock NCADI out of stock
Not available from NTIS
- 31 MARIJUANA RESEARCH FINDINGS: 1980. Robert C. Petersen, Ph.D., ed.
GPO out of stock NTIS PB #80-215171/AS \$31
- 32 GC/MS ASSAYS FOR ABUSED DRUGS IN BODY FLUIDS. Rodger L. Foltz, Ph.D.; Allison F. Fentiman, Jr., Ph.D.; and Ruth B. Foltz, eds.
GPO out of stock NCADI out of stock
NTIS PB #81-133746/AS \$31
- 36 NEW APPROACHES TO TREATMENT OF CHRONIC PAIN: A REVIEW OF MULTIDISCIPLINARY PAIN CLINICS AND PAIN CENTERS. Lorenz K.Y. Ng, M.D., ed.
GPO out of stock NCADI out of stock
NTIS PB #81-240913/AS \$31
- 37 BEHAVIORAL PHARMACOLOGY OF HUMAN DRUG DEPENDENCE. Travis Thompson, Ph.D., and Chris E. Johanson, Ph.D., eds.
GPO out of stock NCADI out of stock
NTIS PB #82-136961/AS \$39
- 38 DRUG ABUSE AND THE AMERICAN ADOLESCENT. Dan J. Lettieri, Ph.D., and Jacqueline P. Ludford, M.S., eds. A RAUS Review Report.
GPO out of stock NCADI out of stock
NTIS PB #62-148198/AS \$23

- 40 ADOLESCENT MARIJUANA ABUSERS AND THEIR FAMILIES. Herbert Hendin, M.D; Ann Pollinger, Ph.D.; Richard Ulman, Ph.D.; and Arthur Carr, Ph.D., eds.
GPO out of stock NCADI out of stock
NTIS PB #82-133117/AS \$23
- 42 THE ANALYSIS OF CANNABINOIDS IN BIOLOGICAL FLUIDS. Richard L. Hawks, Ph.D., ed.
GPO out of stock NTIS PB #83-138044/AS \$23
- 44 MARIJUANA EFFECTS ON THE ENDOCRINE AND REPRODUCTIVE SYSTEMS. Monique C. Braude, Ph.D., and Jacqueline P. Ludford, M.S., eds. A RAUS Review Report.
GPO out of stock NCADI out of stock
NTIS PB #85-150563/AS \$23
- 45 CONTEMPORARY RESEARCH IN PAIN AND ANALGESIA, 1983. Roger M. Brown, Ph.D.; Theodore M. Pinkert, M.D., J.D.; and Jacqueline P. Ludford, M.S. eds. A RAUS Review Report.
GPO out of stock NCADI out of stock
NTIS PB 184-184670/AS \$17
- 46 BEHAVIORAL INTERVENTION TECHNIQUES IN DRUG ABUSE TREATMENT. John Grabowski, Ph.D.; Maxine L. Stitzer, Ph.D.: and Jack E. Henningfield, Ph.D., eds.
GPO out of stock NCADI out of stock
NTIS PB #84-164688/AS \$23
- 47 PREVENTING ADOLESCENT DRUG ABUSE: INTERVENTION STRATEGIES. Thomas J. Glynn, Ph.D.; Carl G. Leukefeld, D.S.W.; and Jacqueline P. Ludford, M.S., eds. A RAUS Review Report.
GPO out of stock NCADI out of stock
NTIS PB #85-159663/AS \$31
- 48 MEASUREMENT IN THE ANALYSIS AND TREATMENT OF SMOKING BEHAVIOR. John Grabowski, Ph.D., and Catherine Bell, M.S., eds.
GPO out of stock NCADI out of stock
NTIS PB #84-145184/AS \$23
- 50 COCAINE: PHARMACOLOGY, EFFECTS, AND TREATMENT OF ABUSE. John Grabowski, Ph.D., ed.
GPO Stock #017-024-01214-9 \$4 NTIS PB #85-150381/AS \$23

- 51 DRUG ABUSE TREATMENT EVALUATION: STRATEGIES, PROGRESS, AND PROSPECTS. Frank M. Tims, Ph.D., ed.
GPO out of stock NTIS PB #85-150365/AS \$23
- 52 TESTING DRUGS FOR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. Joseph V. Brady, Ph.D., and Scott E. Lukas, Ph.D., eds.
GPO out of stock NTIS PB #85-150373/AS \$23
- 53 PHARMACOLOGICAL ADJUNCTS IN SMOKING CESSATION. John Grabowski, Ph.D., and Sharon M. Hall, Ph.D., eds.
GPO out of stock NCADI out of stock
NTIS PB #69-123186/AS \$23
- 54 MECHANISMS OF TOLERANCE AND DEPENDENCE. Charles Wm. Sharp, Ph.D., ed.
GPO out of stock NCADI out of stock
NTIS PB #89-103279/AS \$39
- 55 PROBLEMS OF DRUG DEPENDENCE, 1984: PROCEEDINGS OF THE 46TH ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed.
GPO out of stock NCADI out of stock
NTIS PB #89-123194/AS \$45
- 56 ETIOLOGY OF DRUG ABUSE: IMPLICATIONS FOR PREVENTION. Coryl LaRue Jones, Ph.D., and Robert J. Battjes, D.S.W., eds.
GPO Stock #017-024-01250-5 \$6.50 NTIS PB #89-123160/AS \$31
- 57 SELF-REPORT METHODS OF ESTIMATING DRUG USE: MEETING CURRENT CHALLENGES TO VALIDITY. Beatrice A. Rouse, Ph.D.; Nicholas J. Kozel, M.S.; and Louise G. Richards, Ph.D., eds.
GPO out of stock NTIS PB #88-248083/AS \$23
- 58 PROGRESS IN THE DEVELOPMENT OF COST-EFFECTIVE TREATMENT FOR DRUG ABUSERS. Rebecca S. Ashery, D.S.W., ed.
GPO out of stock NTIS PB #89-125017/AS \$23
- 59 CURRENT RESEARCH ON THE CONSEQUENCES OF MATERNAL DRUG ABUSE. Theodore M. Pinkert, M.D., J.D., ed.
GPO out of stock NTIS PB #89-125025/AS \$23

- 68 PRENATAL DRUG EXPOSURE: KINETICS AND DYNAMICS. C. Nora Chiang, Ph.D., and Charles C. Lee, Ph.D., eds.
GPO out of stock NTIS PB #89-124564/AS \$23
- 61 COCAINE USE IN AMERICA: EPIDEMIOLOGIC AND CLINICAL PERSPECTIVES. Nicholas J. Kozel, M.S., and Edgar H. Adams, M.S., eds.
GPO out of stock NTIS PB #89-131866/AS \$31
- 62 NEUROSCIENCE METHODS IN DRUG ABUSE RESEARCH. Roger M. Brown, Ph.D.; David P. Friedman, Ph.D.; and Yuth Nimit, Ph.D., eds.
GPO out of stock NCADI out of stock
NTIS PB #89-130660/AS \$23
- 63 PREVENTION RESEARCH: DETERRING DRUG ABUSE AMONG CHILDREN AND ADOLESCENTS, Catherine S. Bell, M.S., and Robert Battjes, D.S.W., eds.
GPO out of stock NTIS PB #89-103287/AS \$31
- 84 PHENCYCLIDINE: AN UPDATE. Doris H. Clouet, Ph.D., ed.
GPO out of stock NTIS PB #89-131858/AS \$31
- 65 WOMEN AND DRUGS: A NEW ERA FOR RESEARCH. Barbara A. Ray, Ph.D., and Monique C. Braude, Ph.D., eds.
GPO Stock #017-024-01283-1 \$3.50 NTIS PB #89-130637/AS \$23
- 66 GENETIC AND BIOLOGICAL MARKERS IN DRUG ABUSE AND ALCOHOLISM. Monique C. Braude, Ph.D., and Helen M. Chao, Ph.D., eds.
GPO out of stock NCADI out of stock
NTIS PB #89-134423/AS \$23
- 68 STRATEGIES FOR RESEARCH ON THE INTERACTIONS OF DRUGS OF ABUSE. Monique C. Braude, Ph.D., and Harold M. Ginzburg, M.D., J.D., M.P.H., eds.
GPO out of stock NCADI out of stock
NTIS PB #89-134936/AS \$31
- 89 OPIOID PEPTIDES: MEDICINAL CHEMISTRY. Rao S. Rapaka, Ph.D.; Gene Barnett, Ph.D.; and Richard L. Hawks, Ph.D., eds.
GPO out of stock NTIS PB #89-158422/AS \$39
- 70 OPIOID PEPTIDES: MOLECULAR PHARMACOLOGY, BIOSYNTHESIS, AND ANALYSIS. Rao S. Rapaka, Ph.D., and Richard L. Hawks, Ph.D., eds.
GPO out of stock NTIS PB #89-158430/AS \$45

- 71 OPIATE RECEPTOR SUBTYPES AND BRAIN FUNCTION. Roger M. Brown, Ph.D.; Doris H. Clouet, Ph.D.; and David P. Friedman, Ph.D., eds.
GPO out of stock NTIS PB #89-151955/AS \$31
- 72 RELAPSE AND RECOVERY IN DRUG ABUSE. Frank M. Tims, Ph.D., and Cari G. Leukefeid, D.S.W., eds.
GPO Stock #017-024-01302-1 \$6 NTIS PB #89-151963/AS \$31
- 73 URINE TESTING FOR DRUGS OF ABUSE. Richard L. Hawks, Ph.D., and C. Nora Chiang, Ph.D., eds.
GPO Stock #017-024-01313-7 83.75 NTIS PB #89-151971/AS \$23
- 74 NEUROBIOLOGY OF BEHAVIORAL CONTROL IN DRUG ABUSE. Stephen I. Szara, M.D., DSc., ed.
GPO Stock #017-024-01314-5 83.75 NTIS PB #89-151989/AS \$23
- 75 PROGRESS IN OPIOID RESEARCH. PROCEEDINGS OF THE 1988 INTERNATIONAL NARCOTICS RESEARCH CONFERENCE. John W. Holaday, Ph.D.; Ping-Yee Law, Ph.D.; and Albert Herr, M.D., eds.
GPO out of stock NCADI out of stock
Not available from NTIS
- 78 PROBLEMS OF DRUG DEPENDENCE, 1988: PROCEEDINGS OF THE 48TH ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed.
GPO out of stock NCADI out of stock
NTIS PB #88-208111/AS \$53
- 77 ADOLESCENT DRUG ABUSE: ANALYSES OF TREATMENT RESEARCH. Elizabeth R. Rahdert, Ph.D., and John Grabowski, Ph.D., eds.
GPO Stock #017-024-01348-0 \$4 NCADI out of stock
NTIS PB #89-125488/AS \$23
- 78 THE ROLE OF NEUROPLASTICITY IN THE RESPONSE TO DRUGS. David P. Friedman, Ph.D., and Doris H. Clouet, Ph.D., eds.
GPO out of stock NTIS PB #88-245683/AS \$31
- 79 STRUCTURE-ACTIVITY RELATIONSHIPS OF THE CANNABINOIDS. Rao S. Rapaka, Ph.D., and Alexandros Makriyannis, Ph.D., eds.
GPO out of stock NTIS PB #89-109201/AS \$31

- 80 NEEDLE SHARING AMONG INTRAVENOUS DRUG ABUSERS: NATIONAL AND INTERNATIONAL PERSPECTIVES. Robert J. Battjes, D.S.W., and Roy W. Pickens, Ph.D., eds.
GPO out of stock NTIS PB #88-236138/AS \$31
- 81 PROBLEMS OF DRUG DEPENDENCE, 1987: PROCEEDINGS OF THE 49TH ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed.
GPO Stock #017-024-01354-4 \$17 NTIS PB #89-109227/AS
Contact NTIS for price
- 82 OPIOIDS IN THE HIPPOCAMPUS. Jacqueline F. McGinty, Ph.D., and David P. Friedman, Ph.D., eds.
GPO out of stock NTIS PB #88-245691/AS \$23
- 83 HEALTH HAZARDS OF NITRITE INHALANTS. Harry W. Haverkos, M.D., and John A. Dougherty, Ph.D., eds.
GPO out of stock NTIS PB #89-125496/AS \$23
- 84 LEARNING FACTORS IN SUBSTANCE ABUSE. Barbara A. Ray, Ph.D., ed.
GPO Stock #017-024-01353-6 \$6 NTIS PB #89-125504/AS \$31
- 85 EPIDEMIOLOGY OF INHALANT ABUSE: AN UPDATE. Raquel A. Crider, Ph.D., and Beatrice A. Rouse, Ph.D., eds.
GPO Stock #017-024-01360-9 \$5.50 NTIS PB #89-123178/AS \$31
- 86 COMPULSORY TREATMENT OF DRUG ABUSE: RESEARCH AND CLINICAL PRACTICE. Carl G. Leukefeid, D.S.W., and Frank M. Tims, Ph.D., eds.
GPO Stock #017-024-01352-8 \$7.50 NTIS PB #89-151997/AS \$31
- 87 OPIOID PEPTIDES: AN UPDATE. Rao S. Rapaka, Ph.D., and Bhoia N. Dhawan, M.D., eds.
GPO Stock #017-024-01366-6 \$7 NTIS PB #89-158430/AS \$45
- 88 MECHANISMS OF COCAINE ABUSE AND TOXICITY. Doris H. Clouet, Ph.D.; Khursheed Asghar, Ph.D.; and Roger M. Brown, Ph.D., eds.
GPO Stock #017-024-01359-5 \$11 NTIS PB #89-125512/AS \$39
- 89 BIOLOGICAL VULNERABILITY TO DRUG ABUSE. Roy W. Pickens, Ph.D., and Dace S. Svikis, B.A., eds.
GPO Stock #017-022-01054-2 \$5 NTIS PB #89-125520/AS \$23

- 90 PROBLEMS OF DRUG DEPENDENCE, 1988: PROCEEDINGS OF THE 50TH ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed.
GPO Stock #017-024-01362-5 \$17
- 91 DRUGS IN THE WORKPLACE: RESEARCH AND EVALUATION DATA. Steven W. Gust, Ph.D., and J. Michael Walsh, Ph.D., eds.
GPO Stock #017-024-01384-6 \$10 NTIS PB #90-147257/AS \$39
- 92 TESTING FOR ABUSE LIABILITY OF DRUGS IN HUMANS. Marian W. Fischman, Ph.D., and Nancy K. Mello, Ph.D., eds.
GPO Stock #017-024-01379-0 \$12 NTIS PB #90-148933/AS \$45
- 93 AIDS AND INTRAVENOUS DRUG USE: FUTURE DIRECTIONS FOR COMMUNITY-BASED PREVENTION RESEARCH. C.G. Leukefeid, D.S.W.; R.J. Battjes, D.S.W.; and Z. Amsel, D.Sc., eds.
GPO Stock #017-024-01388-9 \$10 NTIS PB #90-148941/AS \$39
- 94 PHARMACOLOGY AND TOXICOLOGY OF AMPHETAMINE AND RELATED DESIGNER DRUGS. Khursheed Asghar, Ph.D., and Errol De Souza, Ph.D., eds.
GPO Stock #017-024-01386-2 \$11 NTIS PB #90-148956/AS \$39
- 95 PROBLEMS OF DRUG DEPENDENCE, 1989: PROCEEDINGS OF THE 51ST ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed.
GPO Stock #017-024-01399-4 \$21 NTIS PB #90-237660/AS \$67
- 96 DRUGS OF ABUSE: CHEMISTRY, PHARMACOLOGY, IMMUNOLOGY, AND AIDS. Phuong Thi Kim Pham, Ph.D., and Kenner Rice, Ph.D., eds.
GPO Stock #017-024-01403-6 \$8 NTIS PB #90-237678/AS \$31
- 97 NEUROBIOLOGY OF DRUG ABUSE: LEARNING AND MEMORY. Lynda Erinoff, Ph.D., ed.
GPO Stock #017-024-01404-4 \$8 NTIS PB #90-237886/AS \$31
- 98 THE COLLECTION AND INTERPRETATION OF DATA FROM HIDDEN POPULATIONS. Elizabeth Y. Lambert, M.S., ed.
GPO Stock #017-024-01407-9 84.75 NTIS PB #90-237694/AS \$23
- 99 RESEARCH FINDINGS ON SMOKING OF ABUSED SUBSTANCES, C. Nora Chiang, Ph.D., and Richard L. Hawks, Ph.D., eds.
GPO Stock #017-024-01412-5 \$5 NTIS PB #91-141119 \$23

100 DRUGS IN THE WORKPLACE: RESEARCH AND EVALUATION DATA. VOL. II. Steven W. Gust, Ph.D., and J. Michael Walsh, Ph.D., eds.

101 RESIDUAL EFFECTS OF ABUSED DRUGS ON BEHAVIOR. John W. Spencer, Ph.D., and John J. Boren, Ph.D., eds.
GPO Stock #017-024-01426-7 \$6 NTIS PB #91-172858/AS \$31

102 ANABOLIC STEROID ABUSE. Geraline C. Lin, Ph.D., and Lynda Erinoff, Ph.D., eds.
GPO Stock #017-024-01425-7 \$6 NTIS PB #91-172866/AS \$31

103 DRUGS AND VIOLENCE: CAUSES, CORRELATES, AND CONSEQUENCES. Mario De La Rosa, Ph.D.; Elizabeth Y. Lambert, M.S.; and Bernard Gropper, Ph.D., eds.
GPO Stock #017-024-01427-3 \$9 NTIS PB #91-172841/AS \$31

104 PSYCHOTHERAPY AND COUNSELING IN THE TREATMENT OF DRUG ABUSE. Lisa Simon Onken, Ph.D., and Jack D. Blaine, M.D., eds.
GPO Stock #017-024-01429-0 \$4 NTIS PB #91-172674/AS \$23

105 PROBLEMS OF DRUG DEPENDENCE, 1990: PROCEEDINGS OF THE 52ND ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed.
GPO Stock #017-024-01435-4 \$22

106 IMPROVING DRUG ABUSE TREATMENT. Roy W. Pickens, Ph.D.; Carl G. Leukefeld, D.S.W.; and Charles R. Schuster, Ph.D., eds.
GPO Stock #017-024-01439-7 \$12

107 DRUG ABUSE PREVENTION INTERVENTION RESEARCH: METHODOLOGICAL ISSUES. Carl G. Leukefeld, D.S.W., and William J. Bukoski, Ph.D., eds.
GPO Stock #017-024-01441-9 \$9

108 CARDIOVASCULAR TOXICITY OF COCAINE: UNDERLYING MECHANISMS. Pushpa V. Thadani, Ph.D., ed.
GPO Stock #017-024-01446-0

109 LONGITUDINAL STUDIES OF HIV INFECTION IN INTRAVENOUS DRUG USERS: METHODOLOGICAL ISSUES IN NATURAL HISTORY RESEARCH. Peter Hartsock, Dr.P.H., and Sander G. Genser, M.D., M.P.H., eds.
GPO Stock #017-024-01445-1

110 THE EPIDEMIOLOGY OF COCAINE USE AND ABUSE. Susan Schober, Ph.D., and Charles Schade, M.D., M.P.H., eds.

111 MOLECULAR APPROACHES TO DRUG ABUSE RESEARCH: VOLUME I. Theresa N.H. Lee, Ph.D., ed.

112 EMERGING TECHNOLOGIES AND NEW DIRECTIONS IN DRUG ABUSE RESEARCH. Rao S. Rapaka, Ph.D.; Aiexandros Makriyannis, Ph.D.: and Michael J. Kuhar, Ph.D., eds.

113 ECONOMIC COSTS, COST-EFFECTIVENESS, FINANCING, AND COMMUNITY-BASED DRUG TREATMENT. William S. Cartwright, Ph.D., and James M. Kaple, Ph.D., eds.

114 METHODOLOGICAL ISSUES IN CONTROLLED STUDIES ON EFFECTS OF PRENATAL EXPOSURE TO DRUGS OF ABUSE. M. Mariyne Kibbey, Ph.D., and Khursheed Asshar, Ph.D., eds.



DHHS Publication No. (ADM) 91-1836
Alcohol, Drug Abuse, and Mental Health Administration
Printed 1991