Ice: A New Dosage Form of an Old Drug

ARTHUR K. CHO

Ice, which has been described as the drug of the 1990s, is a pure form of (+)methamphetamine hydrochloride; it is more dangerous because of its purity and because it can be inhaled. Taken by this route, the drug causes an effect similar to that from an intravenous dose, and much more intense than that from ingestion. The detailed mechanism of action differs from that of cocaine, but the overall stimulant effect of methamphetamine is similar. Methamphetamine effects, however, persist for hours, whereas cocaine effects are over in minutes. Ice is, therefore, just another agent for abuse by those seeking psychostimulation and, as with cocaine, compulsive abusers of amphetamines consume the drug repeatedly and continuously. Unlike cocaine, methamphetamine is a synthetic compound and is manufactured in illicit laboratories within the United States.

IN RECENT MONTHS, NEWS MAGAZINES (*1, 2*) AND PROFESsional periodicals (*3*) have reported on the entry of "ice" into the recreational drug scene. The compound has become the number one drug problem in Hawaii, surpassing cocaine, and there is concern that it will become the "drug of the 90s" (*3*). In this article, I describe the background of this drug and its relation to the currently more popular stimulant, cocaine.

Ice is a pure preparation of methamphetamine hydrochloride and was originally manufactured in South Korea and Taiwan. There is evidence that "technology transfer" is occurring; an ice laboratory was seized in northern California in January 1990 (*4*). The drug is a psychostimulant and the racemate is known by the street names of speed, crank, and crystal. Methamphetamine and amphetamine, its *N*-desmethyl analog, have been abused for several decades (*5, 6*). Epidemics of abuse occurred in Japan in the 1950s, in Sweden in the 1950s and early 1960s, and in the United States in the 1960s and early 1970s.

History

The amphetamines and related phenylisopropylamines (Fig. 1) have been known as stimulants for centuries. This group of compounds includes alkaloids such as ephedrine, obtained from *Ephedra mahuang*, and norpseudoephedrine, or cathine, obtained from *Catha edulis*. The stimulant properties of ephedrine were described by the Chinese more than 5100 years ago, and cathine was used in East Africa in the early 1300s for the feeling of strength and suppression of fatigue and appetite that its users experienced. Ephedrine was also used therapeutically to treat the bronchoconstriction associated with asthma and other pulmonary problems. The chewing of coca leaves to extract cocaine dates back to A.D. 500 to 600 (*7*). On this time scale, the abuse of amphetamine is a relatively recent event, as the early reports on its abuse occurred in the 1940s and 1950s. Amphetamine was introduced in 1932 (*8*) as a synthetic analog of ephedrine to be used as a bronchodilator for treatment of nasal and bronchial congestion associated with colds. At one time amphetamine was commercially available in an inhaler (*9*) containing 250 mg of the drug in a cotton plug. When the actions of amphetamine on the central nervous system were discovered, the plug was either extracted or directly ingested by abusers. The drug was also used to treat narcolepsy and as an anoretic for weight reduction. For these purposes the compound was available in 5- and 10-mg tablets.

Methamphetamine was introduced at about the same time as amphetamine and has comparable bronchodilator effects but is more potent in its psychostimulant actions. Both drugs are used recreationally, but a new dosage form and route of administration of methamphetamine have been introduced, and these present new hazards. The new dosage form is the relatively pure, crystalline hydrochloride salt, called ice because of its transparent, sheet-like crystals. The new route of administration is smoking; the hydrochloride salt is sufficiently volatile to vaporize in a pipe (*10*) so that it can be inhaled. This route of self-administration allows rapid absorption into the bloodstream from where the drug moves quickly into the brain, bypassing organs such as the liver, which tends to reduce the proportion entering the brain. Abusers have apparently found that smoking methamphetamine gives a response similar to that of an intravenous dose without the hazards associated with syringe needles.

Abuse

The amphetamines cause a number of effects that are sought by the abuser, for example, a sense of increased energy, self-confidence, and well-being; heightened awareness; loss of appetite; and euphoria. These effects are enantioselective: the (+)isomer is about five times as active as the (−)isomer. In addition to these effects, the drugs cause bronchodilation and an increase in heart rate and blood pressure. In previous years, amphetamine abusers have included occasional users who wanted to stay awake, obese persons who wanted to lose weight, and compulsive users. The compulsive users, or "speed freaks," took intravenous doses repeatedly over a period of days to weeks during "speed runs" (*6, 11, 12*).

The speed freak sought the flash or intensely pleasurable feeling that occurred briefly even before the injection was complete (*13*). The flash is transient, and to regain this sensation the abuser would repeat the injection. Because of the acute tolerance, or tachyphylaxis, to amphetamine that develops, the doses were increased. Chronic

The author is in the Department of Pharmacology, UCLA School of Medicine Center for Health Sciences, Los Angeles, CA 90024.

abusers were reported to take as much as 15 g per day in doses exceeding 1 g every 4 hours over a 24-hour period (*12*). A conventional dose of methamphetamine for central nervous system stimulation is about 10 mg, and doses of 150 mg to 1 g would be highly toxic to an occasional user. A speed run usually lasted 24 to 48 hours but could last for 12 days (*12*), so that the quantity of the drug consumed could be substantial. During this time the subjects would not eat or sleep because of the stimulant and anoretic effects of the drug. At the end of a run the subject usually would sleep continuously for days and awaken depressed and hungry. The cure for depression would then be another dose of amphetamine. An amphetamine psychosis, similar to paranoid schizophrenia, could occur during a run (*14*). Most but not all subjects recover from this psychosis after the drug is cleared. During this psychotic period, however, subjects can become violent, and homicides have been attributed to the effects of the drug (*15*). It should be pointed out that compulsive abusers of amphetamine, like compulsive abusers of cocaine (*6*), make up a small percentage (5 to 10%) of the total number of abusers and an even smaller percentage of those who use amphetamines for therapeutic purposes.

Pharmacology

The detailed pharmacological actions of the amphetamines have been the subject of extensive study (*7, 16, 17*), and this research has shown that they affect the presynaptic terminal of catecholamine (CA) neurons. Amphetamines and other phenylisopropylamines are called indirect agents because they exert their effects primarily through release of CA neurotransmitters rather than by acting directly on CA receptors (*16, 18*). The CA neurotransmitters, norepinephrine and dopamine, are found in the peripheral and central nervous systems. In the peripheral nervous system, norepinephrine is the neurotransmitter of the sympathetic nervous system, stimulation of which initiates a complex series of events in preparation for an emergency (the flight or fight response). This response includes bronchodilation and increased heart rate, cardiac output, and blood pressure. In the central nervous system, the CA dopamine (DA) is associated with mood, excitation, motor movements, and regulation of appetite.

The amphetamines exert their actions on these systems by causing neurotransmitter release from the presynaptic terminal, resulting in stimulation of the postsynaptic receptor. The compounds interact

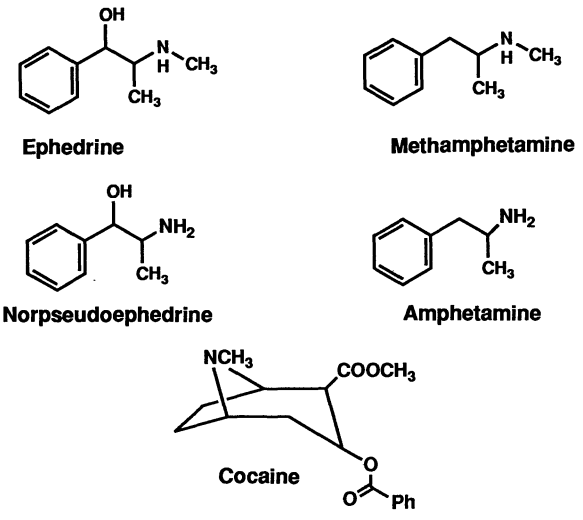

Fig. 1. Chemical structures of methamphetamine and related compounds; Ph, phenyl.

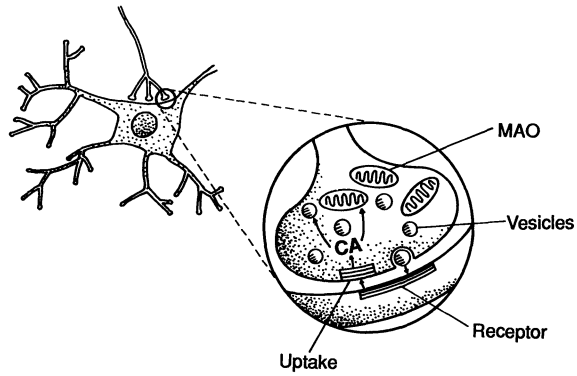

Fig. 2. A catecholaminergic synapse and the functions affected by amphetamine. In the process of neurotransmission, CA neurotransmitter (DA or norepinephrine) is released by a calcium-dependent mechanism into the synaptic cleft from storage vesicles that have merged with the terminal membrane. The CA stimulates the postsynaptic receptor and initiates the simulatory response. CA is removed from the synapse mostly by transport back into the presynaptic terminal. The transport process is called uptake. Once inside the terminal, the CA can be destroyed by MAO present on mitochondria or it can be stored in vesicles. Amphetamines interact with the transporter, inhibit the storage process, and inhibit MAO. The latter two actions increase the cytoplasmic concentration of neurotransmitter, and this increase results in the outward-directed transport of neurotransmitter into the synapse and stimulation of the receptor. Cocaine also increases synaptic levels of neurotransmitter, but does so by inhibiting the uptake transporter.

with several components of the CA terminal, including the neuronal transporter (uptake I transporter), the vesicular storage system, and monoamine oxidase (MAO) (Fig. 2). Amphetamine and methamphetamine are substrates for the transporter and can be transported into the presynaptic terminal. Once inside, they inhibit the storage of DA by vesicles and its degradation by MAO, thereby increasing cytoplasmic levels of neurotransmitter. The neurotransmitter binds to the inward-facing transporter and is transported out of the terminal into the synaptic cleft, where it activates the postsynaptic receptor (*18, 19*). Consistent with the in vivo effects, these biochemical actions of amphetamine are stereoselective; the (+)enantiomer is two to five times as potent as the (−)enantiomer.

The indirect action of amphetamine may also underlie the tachyphylaxis that develops to the drug (*17*). The quantity of CA available in the terminal for release is limited to that which leaks from storage vesicles and that which is not oxidized by MAO. Because the action of the amphetamines depends on this limited pool, subsequent doses release smaller and smaller quantities of neurotransmitter. Once the neurotransmitter depleted, a finite time is required for the terminal to replenish itself by synthesis. These factors could account for the increasing doses required during a speed run, the depression associated with the end of the run, and the recovery after several days due to resynthesis. An alternative explanation would be a decrease in the number, or down-regulation, of receptors in response to excessive transmitter release.

Although their overall actions are similar, there is a fundamental difference in the mechanisms by which amphetamine and cocaine increase neurotransmitter levels in the synaptic cleft. Cocaine appears to inhibit the removal of transmitter that is released by neuronal activity (Fig. 2) and its action is dependent on extracellular Ca^{2+} (*20*), whereas amphetamine causes transmitter to be transported extraneuronally (*21*). Cocaine is also a local anesthetic and affects neurons and other excitable tissue such as cardiac tissue by another mechanism involving the removal of transmitter. The discriminative psychostimulant properties of cocaine are similar to those of amphetamine, and there is evidence that subjects cannot distinguish between the two after intravenous dosage (*6, 22*).

There is evidence for neurotoxicity associated with repeated

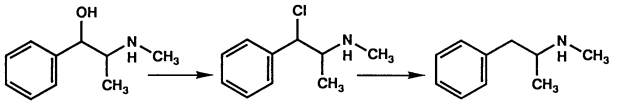

Fig. 3. Synthesis of methamphetamine by reduction of ephedrine.

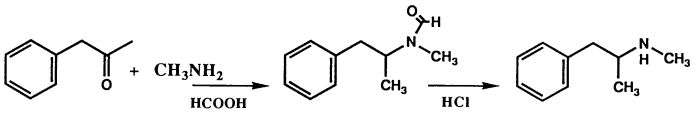

Fig. 4. Synthesis of methamphetamine by condensation of phenylacetone and methylamine.

exposure to high doses of amphetamine (*23*). Repeated administration of methamphetamine or amphetamine to experimental animals has resulted in long-lasting depletion of DA and, to a lesser extent, 5-hydroxytryptamine, in certain regions of the brains of experimental animals (*24*). This toxicity is associated with massive DA release after prolonged high-level exposure to these drugs, but the actual mechanism is not clear. One hypothesis is that the DA released into the synaptic cleft is oxidized to a toxic metabolite such as 6-hydroxydopamine, which destroys the terminal by generating toxic oxygen metabolites (*23*). There is also evidence that the mechanism of toxicity may be much more complex, involving participation by excitatory amino acids such as glutamate (*25*).

One of the ironic observations made in this last study (*25*) is that phencyclidine, an abused substance known as "PCP" or "angel dust," is a protective agent against this amphetamine neurotoxicity in experimental animals. Neurotoxicity consistent with the involvement of DA neurons has not been reported in humans. As with cocaine, methamphetamine affects infants born of users. In addition to problems at birth (*26*), there are developmental difficulties associated with these "cocaine babies." These infants have neurological and social development problems. As they develop, they have a difficult time in social situations and are given to fits of uncontrolled rage (*27*).

Pharmacokinetics

The pharmacokinetics, or absorption and elimination, of these drugs are also important in the context of their abuse. Because of their relatively high lipophilicity, the amphetamines rapidly penetrate body compartments, including the brain, and after intravenous dosage the effects are seen within seconds. When inhaled as a vapor with a pipe, the drug condenses in the lungs, and the high vascularity and surface area of the lungs ensure rapid entry into the bloodstream and thence to the brain. Absorption through this route of administration has been shown to be very efficient. For cocaine, it is quite comparable to the intravenous route (*28*).

The pathways for elimination of the amphetamines differ markedly from those for cocaine. Cocaine is a diester and is rapidly hydrolyzed in the plasma (*29*) so that its plasma half-life is about 12 min (*28*). The amphetamines, on the other hand, are eliminated unchanged to a considerable extent but are also metabolized by enzymes whose distribution and activity are much more limited. As a result, the amphetamines have much longer half-lives—approximately 12 and 8 hours in humans for methamphetamine and amphetamine, respectively (*30*). The actions of methamphetamine will therefore persist much longer than those of cocaine, a desirable feature for the abuser. The long half-life of the amphetamines, together with the repeated self-administration of high doses during a speed run, results in substantial accumulation of the drug. This is less of a problem with cocaine because of its rapid hydrolysis to inactive metabolites. Amphetamine and methamphetamine are converted to pharmacologically active metabolites that include ephedrine derivatives (*31–33*). Amphetamine does not appear to be a major metabolite of methamphetamine, accounting for less than 20% of the administered methamphetamine (*30, 31*). Methamphetamine generates the pharmacologically active *p*-hydroxymetabolites in higher proportion than amphetamine (10% for methamphetamine versus 0.4% for amphetamine) (*33*). These metabolites accumulate with repeated high doses.

Chemistry

Methamphetamine is manufactured in large quantities in clandestine laboratories in the United States. Methamphetamine laboratories have been described that have second-generation "cookers" or chemists who have learned the process from parents (*2*). Clandestine laboratories can be mobile. For example, one was a motor home appropriately modified to minimize detectable fumes (*2*). The manufacture is a $3-billion industry concentrated in Texas and Southern California (*2*). In contrast, cocaine is only available as a natural product from Central and South America, and the processing that takes place in the United States is limited to conversion of the hydrochloride salt to crack, the volatile free base that is associated with addiction and toxicities.

The purity of ice can be attributed in part to its route of synthesis, which is thought to be based on the reduction of ephedrine (*34*) (Fig. 3). The advantage of ephedrine as the starting material is that the process does not involve a condensation or coupling of more than one chemical species, and side products are limited. Also, because ephedrine is a stereochemically pure natural product, the process generates the more potent dextrorotatory enantiomer of methamphetamine, not a racemic mixture. The absolute configuration of the alpha carbon of (−)ephedrine and (+)pseudoephedrine are the same, so that (+)methamphetamine can be prepared from either compound. The more common approach for methamphetamine synthesis in the United States has been by a condensation reaction between phenylacetone and methylamine (Fig. 4). This procedure generates the racemic mixture and, unless carefully purified, a higher proportion of contaminants. The purity of these illicit drugs is highly variable, and the Drug Enforcement Administration (DEA) has reported purities of methamphetamine samples ranging from 88 to 20% (*35*). The contaminants differ with the synthetic route used and some are known to be pharmacologically active (*36, 37*). The *N*-formyl derivative of methamphetamine has been reported to have anoretic properties and 2-(phenylmethyl)-phenylethylamine is reported to have strong stimulant activity (*36*). Some of these contaminants appear to be quite potent, but their detailed pharmacology and their contributions to the overall pharmacology and toxicology of the dose are not clear.

Economics

The manufacture of methamphetamine is a $3-billion industry with indications of expansion. Unlike cocaine, the compound is readily synthesized from commercially available starting materials. A cursory glance through research chemical catalogs (the most expensive source of chemicals) should indicate that chemicals for the synthesis of methamphetamine from phenylacetic acid would cost about $700 per pound if one assumed a 10% overall yield. The street value of this product would be $225,000, based on a price of

$50 per 100 mg (*1*). With these profit margins, manufacturers could reduce the price substantially to increase the number of consumers. Because of these economic incentives and the escalation of the war on cocaine, the likelihood of increased methamphetamine supply and demand is very high.

Conclusions

Ice is not a new drug, but it is one that has been and continues to be abused. As with crack, the drug can be self-administered by smoking, a procedure that provides a dosage comparable to an intravenous one and that allows the abuser to experience a flash without the hazards of intravenous use. The persistence of methamphetamine in the body as compared to that of cocaine will greatly enhance the medical problems associated with the drug. For example, because of longer exposure times, children born of methamphetamine users may have greater development problems than cocaine babies. Symptoms of acute toxicity from methamphetamine, such as excitation and cardiovascular problems, will persist and may require medical intervention. Psychiatric, social, and law enforcement problems will also occur as a result of amphetamine psychoses. The continuing high incidences of clandestine laboratory seizures suggest that methamphetamine synthesis is a lucrative activity. Because data from the DEA indicate that methamphetamine is the most common product of illicit drug laboratories in the United States, interdiction at the border is likely to have little impact on its supply.

The ice problem, therefore, is a slightly different form of a drug abuse problem that has been with us for decades, if not centuries. Human beings appear to have a proclivity for chemically induced stimulation. Most people are apparently satisfied by xanthines, such as the caffeine and theophylline found in coffee and tea, but others seek much more intense stimulation. Although early users of the more potent alkaloids took them orally, current abusers compulsively self-administer these chemicals under conditions of maximal exposure to gain this intense sensation. As a result, they expose themselves and, in some instances, their unborn children to toxic levels of these chemicals.

Approaches to the treatment of compulsive abusers must be considered. Treatment regimens for acute and chronic intoxication are needed, as is a better understanding of the social and psychological basis of this form of stimulant abuse. The new hazard that ice represents is its route of administration. The public must be informed that the dangers of inhaling potent, centrally active compounds are far greater than the dangers of oral dosage. In contrast to drug busts and seizure of large quantities of drugs, these approaches to the drug abuse problem are long term and expensive and do not provide easily documentable results. It may thus be difficult to justify the required expenditure of funds on these approaches. Nevertheless, until we understand the basis for stimulant abuse, we will forever be engaged in wars on the manufacture of different stimulant chemicals. If the war on drugs is directed to South America now, will Southern California and Texas be next?

REFERENCES AND NOTES

1. M. A. Lerner, D. Bank, P. Leyden, B. Martin, *Newsweek* (27 November 1989), p. 37.
2. J. Beaty, *Time* (24 April 1989), p. 1013.
3. P. Zurer, *Chem. Eng. News* **67**, 6 (30 October 1989).
4. *Los Angeles Times*, staff and wire reports, 22 January 1990, p. A19.
5. K. Blum, *Handbook of Abusable Drugs* (Gardner, New York, 1984), pp. 306–312.
6. F. H. Gawin and E. H. Ellinwood, *N. Engl. J. Med.* **318**, 1173 (1988).
7. B. Angrist, in *Stimulants: Neurochemical, Behavioral and Clinical Perspectives*, I. Creese, Ed. (Raven, New York, 1983), pp. 1–30.
8. J. V. Spotts and C. A. Spotts, *Use and Abuse of Amphetamine and Its Substitutes*, National Institute on Drug Abuse Research Issues Number 25 (U.S. Department of Health, Education and Welfare, Washington, DC, 1980).
9. J. D. Griffith, in *Drug Addiction II: Amphetamine, Psychotogen and Marihuana Dependence*, W. R. Martin, Ed. (Springer-Verlag, Berlin, 1977), pp. 277–296.
10. C. N. Chiang and R. Hawks, personal communication; H. Sekine and Y. Nakahara, *J. Forensic Sci.* **32**, 1271 (1987).
11. S. Cohen, *The Substance Abuse Problems* (Haworth, New York, 1981), pp. 146–149.
12. J. C. Kramer, V. S. Fischman, D. C. Littlefield, *J. Am. Med. Assoc.* **201**, 305 (1967).
13. C. Cox and R. G. Smart, *Can. Med. Assoc. J.* **102**, 724 (1970).
14. D. S. Bell, *J. Psychiatry* **3**, 701 (1965).
15. E. H. Ellinwood, Jr., *Am. J. Psychiatry* **127**, 1170 (1971).
16. T. Lewander, in *Drug Addiction II: Amphetamine, Psychotogen and Marihuana Dependence*, W. R. Martin, Ed. (Springer-Verlag, Berlin, 1977), pp. 33–181.
17. E. Costa and S. Garattini, Eds. *Amphetamines and Related Compounds* (Raven, New York, 1970), pp. 317–329.
18. R. Kuczenski, in *Stimulants: Neurochemical, Behavioral and Clinical Perspectives*, I. Creese, Ed. (Raven, New York, 1983), pp. 31–61.
19. M. W. Fishman, in *Psychopharmacology: The Third Generation of Progress*, H. Y. Meltzer, Ed. (Raven, New York, 1987), pp. 1543–1553; L. M. Gunne, in *Drug Addiction II: Amphetamine, Psychotogen and Marihuana Dependence*, W. R. Martin, Ed. (Springer-Verlag, Berlin, 1977), pp. 247–266.
20. Y. L. Hurd and U. Ungerstedt, *Synapse* **3**, 48 (1989).
21. J. F. Fischer and A. K. Cho, *J. Pharmacol. Exp. Ther.* **208**, 203 (1979); M. Raiteri, F. Cerrito, A. M. Cervoni, F. Levi, *ibid.*, p. 195; C. O. Rutledge, *Biochem. Pharmacol.* **27**, 511 (1978).
22. M. W. Fishman *et al.*, *Arch. Gen. Psychiatry* **33**, 983 (1976).
23. L. S. Seiden and G. A. Ricuarte, in *Psychopharmacology: The Third Generation of Progress*, H. Y. Meltzer, Ed. (Raven, New York, 1987), pp. 359–366.
24. R. W. Fuller and S. K. Hemick-Lemcke, *Neuropharmacology* **21**, 433 (1982); A. J. Hotckiss and J. W. Gibb, *J. Pharmacol. Exp. Ther.* **214**, 257 (1980).
25. P. K. Sonsalla, W. J. Nicklas, R. E. Heikkila, *Science* **243**, 398 (1989).
26. L. Ryan, S. Ehrlich, L. Finnegan, *Neurotoxicol. Teratol.* **9**, 295 (1987).
27. B. Kantrowitz, P. Wingert, N. de la Pena, J. Gordon, T. Padgett, *Newsweek* (12 February 1990), p. 62.
28. A. R. Jeffcoat, M. Perez-Reyes, J. M. Hill, B. M. Sadler, C. E. Cook, *Drug Metab. Dispos.* **17**, 153 (1989).
29. T. G. Vitti and R. L. Boni, in *Pharmacokinetics and Pharmacodynamics of Psychoactive Drugs*, G. Barnett and C. N. Chiang, Eds. (Biomedical Publications, Foster City, CA, 1985), pp. 427–440.
30. T. B. Vree and J. M. van Rossom, in *Amphetamines and Related Compounds*, E. Costa and S. Garattini, Eds. (Raven, New York, 1970), pp. 165–190.
31. J. Caldwell, L. G. Dring, R. T. Williams, *Biochem. J.* **129**, 11 (1972).
32. A. K. Cho and J. Wright, *Life Sci.* **22**, 363 (1978).
33. H. Yamada and H. Yoshimura, *Eisei Kagaku* **36**, 383 (1989).
34. R. S. Frank, *J. Forensic Sci.* **28**, 18 (1983).
35. T. C. Kram, *ibid.* **22**, 508 (1977).
36. W. H. Soine, *Med. Res. Rev.* **6**, 41 (1986).
37. T. C. Kram and A. V. Kruegel, *J. Forensic Sci.* **22**, 40 (1977).