J Forensic Sci, Jan. 1978, Vol. 23, No. 1

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The Forensic Toxicology of Cocaine (1971-1976)

It is the general purpose of this study-report to assess the role of cocaine in postmortem, medicolegal investigation, and a primary, particular objective is to determine whether cocaine is significant as a causative agent in a growing number of sudden, unexplained deaths. The significance can be evaluated in terms of either the absolute number of deaths directly attributable to cocaine ingestion or relative to fatalities caused by other abused and misused drugs. A total of only 111 cases involving cocaine occurred at 27 study sites, encompassing a jurisdictional population of 79.2 million over a five- to six-year period ending in mid-1976. Further, of the total cases, only 26 involved cocaine alone.

The report is a retrospective, collaborative survey aimed at answering the above questions and possibly providing incidental data that may assist forensic toxicologists and pathologists in a more rational approach to the analysis and interpretation of "cocaine cases." It is not designed nor intended as a review of cocaine toxicology-pharmacology nor as a critique of analytical toxicology methods.

The study was prompted by growing professional publicity during the past two years indicating that a massive resurgence of cocaine availability and nonmedical use was underway [*1-4*]. In addition, a controversy centered around the toxicology of the drug has developed between advocates of its recreational use, who claim it to be completely safe, and opponents, who cite the historical record as well as apparent current dangers as seen through the Drug Abuse Warning Network (DAWN)[2] and the experience of many professionals working in drug abuse treatment and rehabilitation programs. Toxicology data to support or refute these claims have not been available, and although coroner and medical examiner's offices are only concerned with fatal cases (and therefore this report ignores overdose intoxications and adverse reactions in which the subject recovers), the fatalities do provide a means of examining the most extreme hazards of cocaine use. It is inevitable that if cocaine is widely available and abused, and also toxic, then it will come to the attention of forensic pathologists and toxicologists. Sudden, unexplained deaths are subject to extensive medical and circumstantial investigation to determine manner and cause of death and, as such, are often able to provide accurate, objective information to elucidate many of the questions posed regarding cocaine use. For any drug used and abused for recreational purposes there will be an accompanying body of folklore and case law that serves to support all shades of subjective opinion but seriously clouds and hinders scientific knowledge. Data from cases subject to postmortem, medicolegal investigation can shed important light through the cloud and help clarify misconceptions. This is an important justification for this study-report.

Although books and papers [*1-3,5*] continue to be published apparently describing new

Received for publication 25 April 1977; accepted for publication 1 Aug. 1977.

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[2] DAWN is a nationwide drug abuse monitoring system operated through the combined facilities of the Drug Enforcement Agency and the National Institute on Drug Abuse.

aspects of cocaine, it can be firmly stated that fatalities from the drug are certainly not new. As early as 1891, Mattison [*6*], in a discussion of cocaine poisoning, reported four well-documented fatalities that occurred in 1887 and three in 1888. Mayer [*7*], in a 1924 article, recounts 21 deaths attributed to cocaine toxicity, and all editions of Webster's classic text *Legal Medicine and Toxicology* [*8*] discuss fatal cocaine poisonings from the turn of the century through the 1920s. It is not a benign drug, and this fact is clearly supported by its known pharmacology [*9*]. Although generally regarded clinically as a local anesthetic, its potent central nervous system (CNS) effects cause greatest concern for toxicity. The subject is likely to be excited and confused and suffer seizures as early effects of central stimulation, but this is followed rapidly by depression, eventually involving medullary centers so that death results from respiratory failure. In addition, cocaine interferes with uptake of norepinephrine by adrenergic nerve terminals, and resulting cardiovascular responses such as tachycardia, sudden increase in blood pressure, and vasoconstriction can pose serious problems. Intravenous doses of cocaine may adversely affect heart muscle function directly and cause very rapid death. These carefully studied toxicological responses are not essentially debatable, but they do indicate a need to document authentic case data to support the basic research pharmacology findings. There has been no major effort in this area in recent years, although isolated cases have been reported in the medical literature since 1970 [*4,10–13*]. This study-report is also an attempt to fill this gap.

Description and Scope of Survey

The survey and data evaluation were carried out between mid-August, 1976, and January, 1977, and were designed to address the general questions discussed above and to document in detail any cases in which cocaine was the specific, causative toxic agent. Certain personal background information was gathered for each individual victim and for the circumstances surrounding the death to determine if there were any common factors or trends that could be useful indicators for predicting cocaine fatalities.

Medical examiner- and coroner-toxicologists and pathologists at 27 sites across the United States and Canada participated in the study. The sites and jurisdictional areas are shown in Fig. 1, and Table 1 presents the population represented in the survey along with the number of investigated cocaine-associated deaths at each site. A total of 62.9 million people, or 29.8% of the United States' population, were involved. This is not only a statistically useful, large percentage, but it also includes all sites from which cocaine deaths had been reported to the DAWN program and many others, such as New York City and Los Angeles, where drug abuse is a known social problem. This bias was offset by including sites thought less likely to yield cases and, overall, more likely to provide a balanced national geographic and demographic picture. Most of the sites are covered by medical examiner or coroner offices of high professional standing, long experience, and capability, and their cases often represent those most thoroughly and scientifically investigated. It is also, perhaps, significant that almost all of the toxicologists and pathologists interviewed were aware of the cocaine problem and therefore on guard for its potential involvement in their cases.

Two questionnaires were used to gather the data at each site. One provided information concerning analytical toxicology and laboratory resources, and the other was used to record individual case data. Only those cases in which cocaine, its metabolites, or both were detected and identified by toxicological analysis were included in the study. Personal visits were made to each site, and the files for those cases involving cocaine were examined. Only the information indicated on the questionnaires was recorded, and the anonymity and confidentiality of the deceased were scrupulously maintained. None of the data can be traced from this report to any individual.

The total number of cases finally collected in the survey is 111. Table 1 shows the num-

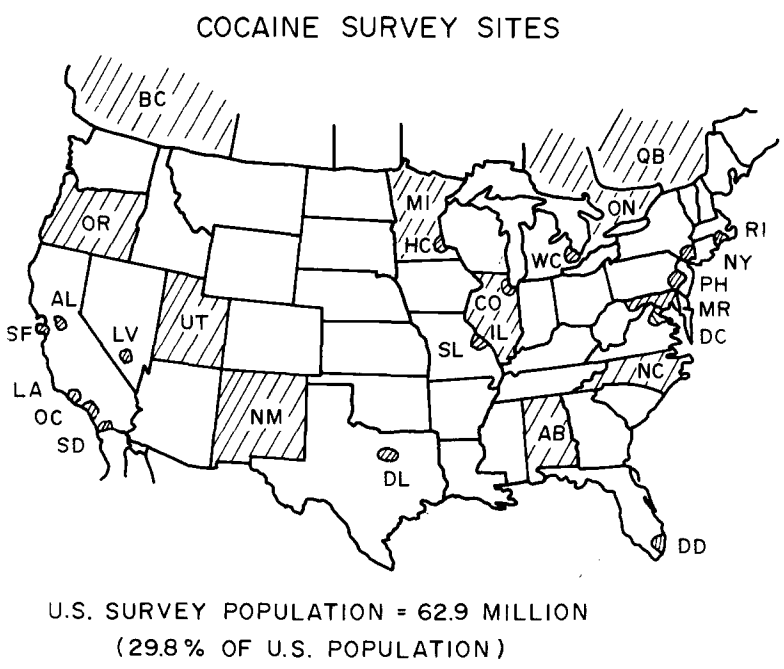

FIG. 1—*Map of survey sites.*

ber from each site. There are some surprising results. The relatively high number of cases from New York City and Los Angeles County is, perhaps, not unexpected, but no cases at all were recorded in Philadelphia, Minneapolis, or Las Vegas, and only one and three from Wayne County (Detroit) and Cook County (Chicago), respectively, is notable. (All these areas have acknowledged drug abuse problems.) Similarly, to find rural Utah and New Mexico with case numbers virtually matching populous urban areas of California and Florida is very striking. Information gained by interview with forensic scientists and, in some instances, with law enforcement officials at several sites confirmed the local case incidence and the overall inference that cocaine use and subsequent fatal episodes are not uniform for urban or rural areas throughout the United States. Its occurrence does not appear to be reliably predictable from general demographic considerations or drug abuse history for a particular area.

One hundred eleven cases in a six-year period is a small number of fatalities when compared to almost any other major drug of abuse (for example, heroin or barbiturates), but, more importantly for this study, it is a small number for useful statistical analysis. This is particularly true when it is recognized that of the 111, death was caused by drugs in 86 cases and by cocaine alone in only 26 cases (Fig. 2). Although the gathered data are uniform and therefore suitable for analysis, the study encompasses a highly specialized population: victims in fatal cases involving cocaine. Therefore great care must be exercised not to extrapolate the data in any attempt to establish a perspective or assessment of cocaine use generally. However, with these limitations in mind, many useful facts and conclusive statements can be made from the study cases. As shown in Fig. 2, 25 cases (22.5% of the total survey) were fatalities with a cause other than drugs. Of course, cocaine and sometimes other drugs were detected in all these cases but not in concentrations considered by the toxicologist or pathologist to be sufficient to cause death. In any event, 60% of these cases were either homicides or suicides, and almost all of them were violent deaths via gunshot or stab wounds.

TABLE 1—*Cocaine survey: participating sites, jurisdiction population, and investigated cocaine-associated deaths.*

Site	Jurisdiction Population, $\times 10^6$	Documented Cocaine-Associated Deaths, 1971-1976, *n*
Alabama (AB)	3.5	2
Alameda County, Calif. (LA)	1.1	6
Clark County, Nev. (LV)	0.3	0
Cook County, Ill. (CO)	5.4	3
Dade County, Fla. (DD)	1.5	6
Dallas County, Te. (DL)	1.3	2
Hennepin County, Minn. (HC)	1.0	0
Illinois state (IL)	6.0	0
Los Angeles County, Calif. (LA)	7.0	10
Maryland state (MR)	4.0	5
Minnesota state (MI)	3.0	0
Montreal, Province of Quebec	6.0	6
New Mexico state (NM)	2.1	5
New York City (NY)	7.6	31
North Carolina state (NC)	5.0	1
Orange County, Calif. (OC)	1.5	8
Oregon state (OR)	2.0	0
Philadelphia County, Pa. (PH)	2.0	0
Rhode Island state (RI)	1.0	0
San Diego County, Calif. (SD)	1.4	5
San Francisco County, Calif. (SF)	0.7	5
St. Louis, Missouri County, Mo. (SL)	0.6	0
Toronto, Province of Ontario	8.3	2
Utah state (UT)	1.2	6
Vancouver, Province of British Columbia	2.0	0
Washington, D.C. (DC)	0.7	7
Wayne County, Mich. (WC)	3.0	1
Total	79.2	111

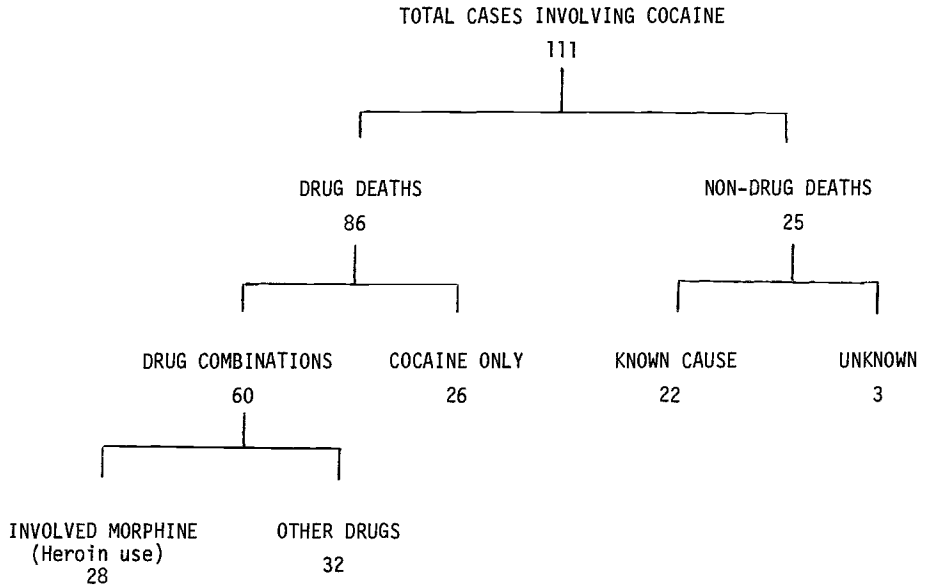

FIG. 2—*Segregation of study cases according to drug or nondrug deaths.*

The increasing frequency of occurrence of cocaine in sudden, unexplained death cases is indicated in Table 2. The increase is sharp, but care must be taken before inferring that the figures indicate a dramatic increase in cocaine use. This may be so, but there are other possible influences, particularly the increasing awareness of medicolegal investigators and the development of improved analytical methods available to toxicologists during the past six years.

TABLE 2—*Occurrence of cocaine cases by year, including total cases from all study sites for the period 1971 through the first six months of 1976.*[a]

Year	Cases, *n*
1971	2
1972	3
1973	11
1974	25
1975	37
1976	29

[a] Four cases prior to 1971 have not been included in the figures.

Analytical Toxicology Methods for Cocaine

All but two of the toxicology laboratories at the 24 survey sites in the United States currently use routine analytical screening methods that would detect cocaine, or its metabolite benzoylecgonine, or both, if present, in the autopsy specimen tested. Not less than 5 ml of blood or urine was generally the sample of choice, with stated sensitivity limits for cocaine of 2.0 μg/ml or less. Three sites included liver tissue samples in the initial drug screening analysis for cases in which no specific drugs were suspected. For urine samples, immunological methods were most commonly employed, followed by thin-layer chromatography (TLC) and gas chromatography (GC), with ultraviolet spectrophotometry being used at two sites. The enzyme multiplication immunological technique (EMIT) was used at nine laboratories and radioimmunoassay at one other site. The EMIT system has the advantage of rapid, direct testing of the sample and detection of the cocaine metabolite benzoylecgonine. However, for practical purposes, it is insensitive to parent cocaine. It has been in use at most of the nine sites since 1974. The other methods used all require extraction of the drug or metabolite from the biological sample before chromatographic analysis. At 11 laboratories benzoylecgonine was included, but the remaining 15 sites relied on detection of the parent cocaine. At two sites XAD-2 resin was used to separate the drug from the biological matrix. All of the other laboratories used organic solvent extraction after adjusting the sample to approximately pH 9 with buffer. Some saturated the aqueous sample phase with salt before extraction to improve recovery of the drug and metabolite. Chloroform, *n*-butyl chloride, or diethyl ether were the most commonly used solvents. Cocaine was often back-extracted into dilute acid and recycled with solvent as a purification step before chromatography. It was noted that the stability of cocaine in hydrochloric acid greater than 0.5*N* is not reliable. The degeneration of cocaine in biological samples in vitro by hydrolysis was also cause for concern. Sodium fluoride, as recommended by Jatlow et al [*14*], should be used as a preservative to prevent this problem.

Quantitative analysis for cocaine and its metabolite was generally achieved by gas chromatography with an internal standard. At only four sites were other techniques employed: ultraviolet spectrophotometry, two; EMIT, one; and GC-mass spectrometry, one. It is interesting that GC-mass spectrometry was available at 12 of the 27 survey sites, but at only one was it routinely used for quantitative work by multiple-ion monitoring. At all

sites the instrument was used for specific, qualitative identification purposes. Eight different internal standards were in use: nalorphine, imipramine, mepivacaine, methaqualone, cholestane, trihexyphenidyl, lidocaine, and SKF 525-A. Data given in this report indicating the prevalence of lidocaine as a cutting agent should be a caution against its use as an internal standard for cocaine analysis. It should also be noted that a number of collaborators expressed dissatisfaction with SKF 525-A because of apparent unpredictable variation in its extraction characteristics and its susceptibility to thermal degradation during GC analysis.

Excellent critical reviews of available analytical methods, with their advantages and limitations, have been written by Jatlow [*15*] and by Bastos and Hoffman [*16*]. The extraction procedure followed by GC-mass spectrometry qualitative and quantitative analysis described and used by Hawks [*17*] might be considered current state-of-the-art and is potentially usable by toxicologists at at least half of the study laboratories. For those with GC, there are a number of published, proven methods available [*18–21*]. Of particular note are those of Jain et al [*18*] and Jatlow and Bailey [*19*]; the latter requires a nitrogen-phosphorus detector, but the former uses a simple derivatization technique to allow the use of flame ionization.

Practical means for the analysis of cocaine and its primary metabolite are available and were in use at almost all of the study sites. In summarizing initial screening procedures and the likelihood of cocaine eluding detection, it is almost certain that at 22 of the 27 laboratories collaborating in the study cocaine involvement in a fatal case would not have been missed, especially since the advent of immunological testing in 1973-1974. The high percentage of study cases in which cocaine was suspected by the investigator or pathologist prior to toxicology analysis adds to this confidence. Similarly, it lends support to the veracity of reports from those sites stating that no cocaine cases were encountered in the six-year study period. It could be recommended that initial screening methods should be capable of detecting less than 1.0 μg/ml cocaine in blood; this is based on known maximum blood concentrations achieved following effective doses of the drugs and the number of study cases in which the blood level was less than 1.0 μg/ml.

History of the Deceased

General inspection and overview of the survey cases reveal that the deceased were principally young, white males. The great majority were less than 30 years old and almost two thirds of the total were white, with an approximate 3:1 bias in favor of males.

Figure 3 shows the distribution of age groups as a percentage of the total cases (1 case

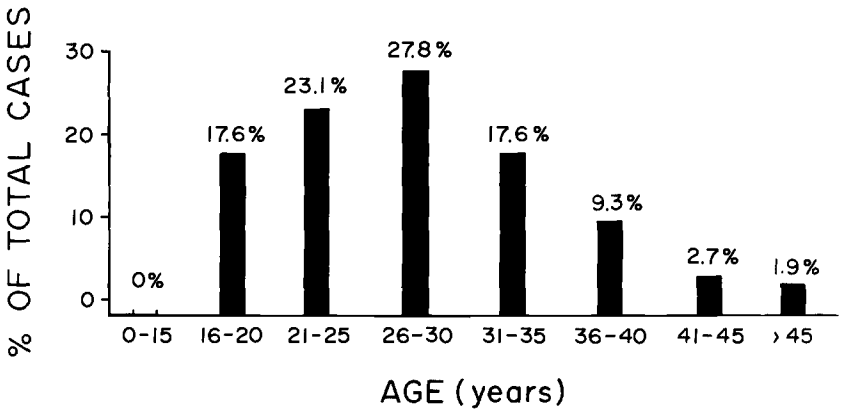

FIG. 3—*Distribution of age groups.*

= 0.9%) and clearly illustrates the young ages. Although more than a quarter are between 26 and 30 years old, 51% are in their twenties and 68.5% are under 30 years. There is a negligible number of cases older than 40 years. Further analysis of the data did not show any other significant facts concerning age. For example, the 26 cases in which only cocaine was involved were almost evenly distributed between ages 16 and 35 years, and for those 28 cases associated with heroin use, as indicated by the detection of morphine in the postmortem blood and tissues, there was no real, discernible difference from the pattern shown in Fig. 3.

The racial characteristics of the victims were known in all but four cases; 63.1% were white, 22.5% were black, and 10.8% were of Spanish-American descent. There were no native-American Indians or Asian-Americans. Whites were represented in greater proportion (80.8%) and blacks in lesser proportion (11.5%) in the 26 cocaine-only cases, whereas the opposite is true for those victims involved with heroin use: almost one third (32.1%) were black against 52.7% white. The deceased of Spanish-American descent are represented in any category in about the same proportion as in the total survey.

There is a marked bias towards males among the deceased in the study: there were 81 (73.0%) males and 30 (27.0%) females, for a male/female ratio *M/F* of 2.7. A very similar ratio (*M/F* = 2.9) exists for the cases in which only cocaine was involved and for those in which morphine was detected (*M/F* = 2.5). There was an even greater preponderance of males among the nondrug deaths (*M/F* = 5.25).

The occupation status of the deceased was known for 69 of the 111 cases; 77% of the 69 held jobs at the time of their deaths. Approximately 35% could be classified as manual, blue-collar workers. There were relatively few professionals, clerical workers, or students represented. Occupation was known for half of the cocaine-only deaths, but no particular group predominated.

To determine the previous health and drug use experience of the deceased, their medical and psychiatric histories were evaluated whenever possible. This information was generally available as part of the investigator's case report to the medical examiner or coroner. For the purpose of this study, medical and psychiatric histories were coded into categories assembled from common medical ailments and typical conditions associated with emotional disturbances. These were extended in keeping with case findings as the survey proceeded. Within the definition of these categories, the total deceased population was generally medically healthy prior to their demise. There was no definable history of recent acute or chronic illness for 85.6% of the cases. For those who did have a history, there was no marked, single ailment or class of diseases. All but two of the 26 cases involving only cocaine had no medical history. Contrary to the lack of medical illness, 61.3% of the deceased had emotional or behavioral problems almost exclusively centered around drug abuse or misuse.

Evidence of alcohol abuse was conspicuously absent, being noted in only 2.4% of the 86 drug death cases. The victims were not a population seeking psychiatric help for emotional disturbance or overt mental illness, nor did they appear to belong to the segment of society who find tranquilizers a necessary supporting adjunct to daily living. Morphine as a result of heroin use was the most commonly detected drug, in combination with cocaine. It was detected analytically in 33% (28) of the drug-death cases. Lidocaine (encountered as the usual cutting agent for cocaine and not in the course of medical treatment of the victim), methadone, and hypnotic sedatives were the only other noteworthy drugs associated with the study cases. There were less than five occurrences each for diazepam, amitriptyline, phenothiazines, and propoxyphene, drugs often used to treat minor pain, tension, depression, and neuroses. Only 1.2% had a history of prior suicide attempts, which is consistent with the low number of study cases classified as suicide—16 (14.4%).

There were 23 cases in the total survey in which the deceased had a known, documented history of cocaine abuse. These data are presented in Table 3, which shows the cases as 26.7% of the total drug-caused deaths (21% of the entire survey). All these drug-caused

TABLE 3—*Cases involving prior history of drug abuse.*

Prior History	Drug-Death Cases	
	%[a]	*n*
Heroin abuse	34.8	30
Cocaine abuse	26.7	23
Unspecified drug abuse	25.6	22
Alcohol abuse	2.3	2

[a] Percentage values do not tally because of overlap between categories.

deaths of cocaine abusers were classified by the pathologist as accidents. The remaining nondrug deaths were classified as natural, one; homicide, two; and suicide, one (gunshot wound). As might be anticipated, the incidence of intranasal administration is much higher in those cases with a history of cocaine abuse than for the total cases in the survey (Table 4). In addition, this group is characterized by a higher percentage (56.5%) of intravenous administration at the final episode. Throughout this study-report it will be seen that intravenous use of cocaine, knowingly or otherwise, is a common occurrence even among identified cocaine abusers, as illustrated in Table 4. This is consistent with the

TABLE 4—*Route of administration of cocaine for various categories of the survey cases.*

Route of Administration	Total Survey Cases, %	Cocaine-Only Drug Deaths	Drug-Combination Deaths, %	Cases Deceased Had History of Cocaine Abuse, %
Undeterminable	54.1	15.4	56.8	17.4
Intravenous	31.5	61.5	30.0	56.5
Nasal	7.2	7.7	8.3	17.4
Oral	6.3	15.4	3.3	8.7
Rectal	0.9	...	1.6	...

statements of Wesson and Smith [*22*] reporting the "street-use" of cocaine. None of the group of known cocaine abusers in the study had any reported medical history, in contrast to 14.4% of the cases in the total survey. Similarly, there was no remarkable frequency of psychiatric history for this group, other than their drug abuse problems.

Attendant Circumstances in Cocaine-Associated Deaths

The manner of death as classified by the medical examiners and coroners for all the study cases is shown in Table 5. The high number of accidental and undetermined deaths is notable because it clearly indicates the unintentional aspect of most of the cases and the appropriately conservative view taken by most pathologists when assessing deaths involving drugs of abuse. The study population cannot be generally characterized as suicides. Although the proportion of cases classified as accident and undetermined was the same among those involving only cocaine as for the total survey cases, those classed as suicides were more prevalent (22.9%) in the cocaine-only deaths. There is no obvious explanation for this. If those cases in which heroin use was implicated are examined, it will be seen that only 1 case of 28 (as compared to 16 cases of the 111 survey total) was a suicide, and the accidental deaths rise to 71.4%, again indicative of the cautious approach adopted by pathologists towards classifying sudden deaths involving opiate narcotics.

TABLE 5—*Classified manner of death for total survey cases.*

Manner	Cases	
	n	%
Suicide	16	14.4
Accident	48	43.2
Homicide	13	11.7
Natural	5	4.6
Undetermined	29	26.1
Total	111	100

The route of administration of the cocaine is shown in Table 4. For most of the cases (54.1%) these data could not be reliably determined. When information was available, it was usually from one or more of three sources: (1) witnesses' statements; (2) pathology-toxicology findings at autopsy, such as injection sites, needle tracks, or cocaine detected on nasal swabs; and (3) drug injection kit paraphernalia found with the body. It is perhaps important to reiterate that, as indicated in Table 4, intravenous self-administration is frequently used. This is particularly true for those cases in which morphine was detected, but there were no means to determine whether the cocaine and heroin were acquired and used as a single powder containing both drugs or as separate preparations. There are a total of 28 cases in which morphine, related to heroin use, was detected analytically. This is a quarter of the total survey cases, or one third of the drug deaths. The relationship between heroin and cocaine use, at least for this postmortem population, is therefore persuasive.

There is a significant bias towards the oral route for those cases involving only cocaine. Oral ingestion was documented for 15.4% of these cases, but this can be partially explained by the fact that most were obvious suicidal ingestions of very large amounts of the drug or accidental deaths in which the packaged drug was swallowed for smuggling purposes or to elude detection when arrested. While the percentage (7.7%) of the group in which the cocaine was taken by nasal insufflation closely matches the incidence within the total survey, it does refute the commonly held opinion by drug users that this route is reliably safe. These case data highlight the principles of pharmacology that deny the naive assumption that a particular route of administration can be considered an absolute safeguard against toxicity.

There was nothing remarkable or unique concerning the location at which the cocaine use or fatal incident took place; 65.9% were private residences (house or apartment) and 9.4% occurred at a motel or hotel. Only 11.8%, ten of the drug-death cases, reached a hospital before they died. This small number of cases presenting at the hospital is undoubtedly a reflection of the short survival interval seen in a majority of the total study cases and illustrates the potency of the drug.

The range of apparent survival times following cocaine ingestion or the recorded interval between the last time the deceased was seen alive and was found dead is depicted graphically in Fig. 4. One case represents 1.7% of the total drug-death cases composing the graph. The earlier time intervals are undoubtedly the most accurate in reflecting survival time, because for the longer periods, particularly beyond 10 h, it becomes increasingly likely that death occurred earlier and the body remained undiscovered. Within these constraints, it can be seen from Fig. 4 that almost two thirds of the victims (65%) died in less than 5 h, and most of these (31.7% of the total drug deaths) died in the first hour after drug administration. The peak in the 9- to 10- h period results from classifying cases in this interval that were reported as overnight deaths. Obviously, for many of them the time interval should be less. For the 26 cases in which only cocaine was involved, the time

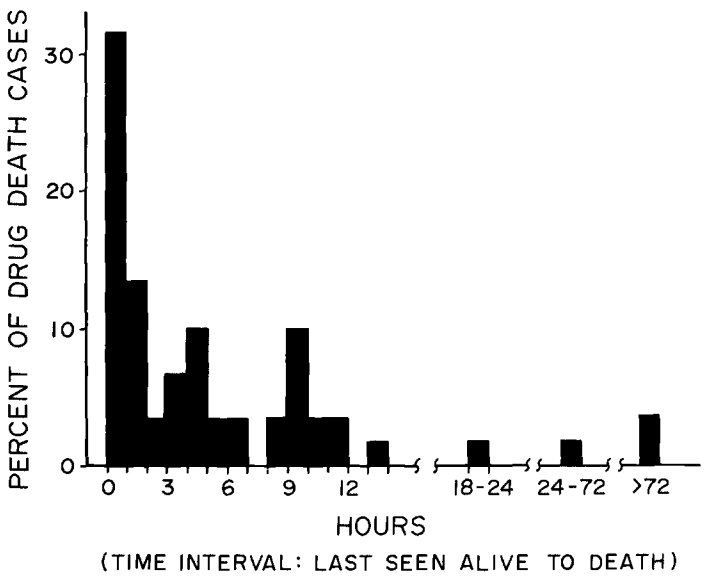

FIG. 4—*Distribution of survival times.*

interval distribution is significantly shortened, with 73.9% of these victims dying in less than 2 h and more than half within 1 h. For the cases involving morphine there was no discernible difference from the total drug deaths shown in Fig. 4. Examination of the data in an attempt to correlate the survival times with route of administration of the drug was not fruitful; but inasmuch as all routes, including nasal ingestion, were distributed across the short times (less than 5 h), the potential for insufflation to produce toxicity was again highlighted.

Although only half of the deaths in which cocaine was the only drug (13 of 26 cases) had terminal symptoms reliably observed and reported, they were remarkably consistent. They were entirely CNS-mediated actions—most commonly, seizures followed by respiratory arrest and coma before death. Cardiac arrest was reported on three occasions. These observations present a logical picture in considering the principal, known pharmacological actions of cocaine as well as lidocaine, which is often used as a cutting agent. Almost no other signs and symptoms (for example, vomiting and dizziness) were reported.

Forensic Pathology

All but two (one from natural causes and one from gunshot wounds) of the 111 study cases were suspected by the pathologist or investigator to involve drugs, and in no less than 100 cases cocaine was anticipated. Of the 86 deaths classified as drug fatalities, 90% were subject to a complete medicolegal autopsy. Of these, 70% of the autopsies were performed within 24 h, and 20% were performed within 6 h of discovery or report of the death. This prompt response by medical examiners and coroners is particularly important when the potential for postmortem in-vivo and in-vitro degradation of cocaine is considered. For those cases in which only cocaine was detected, 86% were autopsied within 24 h. The gross observations by the pathologist at autopsy were generally nonspecific, consisting almost uniformly of pulmonary edema and passive pulmonary, visceral, and cerebral congestion. However, for the cocaine deaths, a high percentage showed evidence of recent intravenous self-administration, which correlates well with the high incidence of intravenous drug use by this group of victims, as reported by witnesses and investigators.

In the cases where an authenticated prior history of cocaine use was established, the pathologist obtained nasal swabs for analysis and carefully examined the nostrils, nasal cartilage, cavity, and nasopharynx. It is interesting that not one of the deceased had a perforated nasal septum. In addition, as a part of this study, it was reported by personal communication[3] that ear, nose, and throat surgeons at Yale University School of Medicine and Hospital had never seen a case of nasal necrosis resulting from cocaine use. It would seem, then, that perhaps this supposed adverse effect associated with nasal insufflation of cocaine is an exaggeration.

The pathologists' microscopic study of autopsy specimen sections were all either reported as unremarkable or confirmed the gross observations. No cases were reviewed in which microscopic findings were unusual or surprising.

Fatal Blood and Tissue Concentrations

As seen in Fig. 2, 86 of the total 111 study cases were classified as drug deaths. Only 53 cases of the 86 had quantitative cocaine blood concentrations determined. The distribution of these concentrations as a percentage of the drug-death cases is shown in Fig. 5.

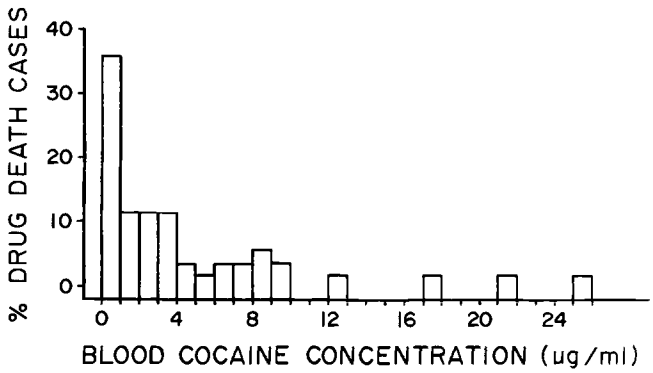

FIG. 5—*Distribution of blood cocaine concentrations for all drug deaths.*

It should be noted for reference that one case is equivalent to 1.9% of the total. Almost three quarters of the cases, 70%, had blood concentrations less than 4.0 μg/ml, with one third between 1.0 and 4.0 μg/ml and fully 36% with 1.0 μg/ml or less. Only four of the 53 cases had blood concentrations greater than 10 μg/ml, and one of these had the highest recorded value of 25 to 26 μg/ml. The routes of administration for these four cases were either unknown or intravenous.

Blood cocaine concentration data were reported for 23 of the 26 cases in which only cocaine was involved (Fig. 6). Any inferences should be made cautiously because of the small number of cases composing the graph (1 case = 4.3%), but there is a definite trend towards higher blood concentrations in these cases as compared to all the drug deaths. This can be shown by comparing 70% of the cases in each category; for all drug deaths, this percentage had concentrations less than 4.0 μg/ml, whereas for those cases with only cocaine present, this percentage is not accounted for until concentrations up to 9.0 μg/ml are included. In addition, only 7.5% of the total drug deaths had blood concentrations greater than 10 μg/ml, whereas in the cocaine-only deaths 17.3% were above this concentration.

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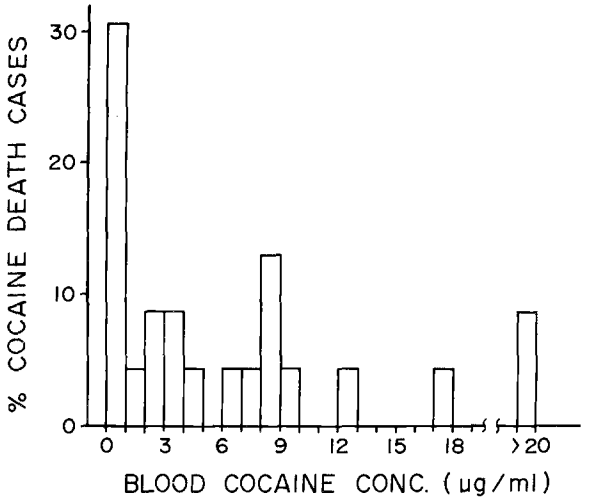

FIG. 6—*Distribution of blood cocaine concentrations for all cocaine-only deaths.*

To assess the significance of the blood concentrations in fatal cases, reported values from controlled animal and human clinical studies may be helpful. In monkeys, a regimen of approximately 40 mg of cocaine every 4 h, with a maximum daily intake of 80 to 100 mg/kg body weight, has been shown by Deaneau et al [*23*] to culminate in convulsions and death within 30 days. In human subjects receiving cocaine applied to the nasal mucosa up to 1.5 mg/kg body weight, VanDyke et al [*24*] and Byck et al [*25*] have reported plasma concentrations persisting for 4 to 6 h in the range of 120 to 474 ng/ml. The highest blood concentrations achieved by experienced cocaine users following large street doses injected intravenously is in the range of 3 to 7 μg/ml, and for monkeys receiving 15 mg/kg body weight intraperitoneally, concentrations were 0.7 to 1.0 μg/ml.[4] Obviously, many factors can affect these broad estimated ranges, not least of which may be the ability of an individual to hydrolyze cocaine by plasma cholinesterase. Jatlow [*14*] has suggested possible impairment of this metabolic pathway in succinyl-choline-sensitive individuals that could result in an unusually elevated plasma cocaine concentration and a possible life-threatening situation.

An attempt has been made to analyze the liver tissue concentrations of cocaine relative to blood concentrations to determine whether liver is a useful specimen for toxicology and whether the ratio of blood/liver values is a practical indicator of toxicity, particularly as cocaine is one of the few drugs that undergo metabolism in blood and has a half-life of approximately 1.5 h [*14,15*]. Data for the total survey cases are shown in Fig. 7. There are only 15 cases for which both blood and liver concentrations are reliably known. In general, blood concentrations were higher than the liver, there being only 5 of the 15 cases in which the liver concentration was greater. Figure 7 clearly shows the desirability of blood analysis. For those cases involving only cocaine, the blood concentration was greater than that of the liver in all instances, and the mean blood/liver ratio of this population was 1.4.

Only two other drugs were considered when the significance of the toxicology findings in the 111 study cases was evaluated: morphine and alcohol. There were 28 cases in which morphine was detected, and all were classified as drug deaths. The blood cocaine concentrations are notably different from the total survey cases and the cocaine-only cases in that all of them are less than 4.0 μg/ml, and almost 60% are between 1.0 and 4.0 μg/ml.

[4] Personal communication, Dr. Richard Hawks, National Institute of Drug Abuse.

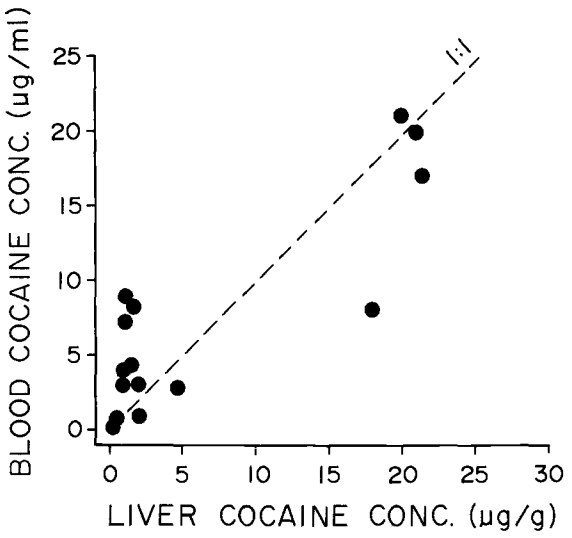

FIG. 7—*Blood/liver ratios for cocaine concentrations in all drug deaths.*

There is little doubt that the contribution of morphine to the overall toxicity in these cases is important.

Although alcoholism and alcohol abuse was not a major finding in the medical and psychiatric histories of the survey case population, 22 (25.6%) of the 86 drug-death cases were positive for alcohol, and in six of these (approximately 7%) alcohol and cocaine were the only drugs detected. There were only eight cases in which both alcohol and morphine, in addition to cocaine, were detected in significant amounts. The blood alcohol concentrations for the 22 cases ranged from 0.02 to 0.43%. If the one case at 0.43% is neglected, then the mean value is 0.10% and the median of the range, 0.12%—concentrations that would cause CNS depression and could add to the adverse CNS effects of cocaine. The presence of ethanol in pharmacologically effective concentrations is important, but a general conclusion from the study that alcohol in combination with cocaine is a dominant or predictable finding in cocaine-associated deaths is not justified.

Fatalities Involving Nasal Administration of Cocaine

There were 8 cases of the total 111 in the study for which it was known that the cocaine was ingested by nasal insufflation ("snorting," "sniffing coke"). Although cocaine was shown to be present, the immediate cause of death in one of the eight cases was determined to be factors other than drugs. Of the remaining seven cases, cocaine was the only drug detected in two of these drug deaths. As shown in Table 4, this is 7.7% of the 26 cocaine-only cases. The classified manners of death for these drug-caused cases were accidental, five; undetermined, two; and suicides, none. Of the drugs detected in these cases, two involved cocaine alone, two involved only cocaine and lidocaine, and three involved only cocaine and morphine (heroin).

Nasal swabs taken at autopsy were positive in one of the two cocaine-only cases. For the two fatalities in which lidocaine was detected, it is known that the lidocaine was used to cut the cocaine and that the mixed drugs in powder form were sniffed. No medical treatment was given in these cases and, therefore, no lidocaine was mistakenly administered to the victims as an emergency medical measure. It is known through Drug Enforcement Agency reports that lidocaine or procaine may be mixed with heroin or cocaine for sale. In

consequence, finding these drugs or their metabolites by postmortem analytical toxicology does not differentiate the dose-form or formulation, and it is virtually impossible to assign separate toxicological significance to each of the drugs in any of the cases. The postmortem blood concentrations of cocaine were high, however, ranging from 2.8 to 5.9 μg/ml. There was only one case in the nanogram range, at 200 ng/ml. This is in sharp contrast to reports that nasal administration of single doses between 20 and 40 mg results in maximum plasma concentrations of approximately 50 to 100 ng/ml [*25*], and doses as high as 1.5 mg/kg body weight provide peak concentrations of approximately 120 to 500 ng/ml at 15 to 60 min [*24*].

Although intravenous self-administration was the predominant route in the survey cases, and only seven confirmed drug-deaths were associated with nasal insufflation, the survey case data underscore the possibility of the user achieving very high, toxic blood concentrations by nasal administration of the drug, and it must not be assumed that use of this route is a guarantee of safety.

Summary and Conclusions

A retrospective, collaborative study-report has been presented in which 27 medical examiners' and coroners' offices across the United States and Canada participated. The geographic area surveyed includes 62.9 million people, or 29.8% of the U.S. population, and provided a total of 111 sudden, unexplained deaths in which cocaine was involved but only 26 cases in which cocaine was the only drug detected. Drugs were causative in 86 of the 111 deaths. Within the full spectrum of the 111 study fatalities, there were 25 cases, both accidental and intentional, resulting from a variety of causes other than drugs. These are not large numbers, either absolute or relative to fatalities from other drugs such as sedative-hypnotics, analgesics, or opiate narcotics that are commonly encountered by forensic toxicologists and pathologists. However, there is evidence that the number of cocaine deaths is increasing. The following summary presents the more prominent features distilled from this study.

1. The national picture of cocaine deaths is not uniform and many cities and counties with known major drug abuse problems do not report any fatal cocaine cases. The incidence of cocaine-related deaths is, therefore, not predictable, either from geographic or demographic considerations.

2. Analytical toxicology methods adequate for the detection and quantitative determination of cocaine in postmortem biological specimens are available at most laboratories. Immunological techniques (EMIT) and gas chromatography following solvent extraction or column chromatography separation were the most common. Sensitivity limits for a 5-ml blood sample were generally in the range of 1.0 to 2.0 μg/ml. Benzoylecgonine was never analyzed quantitatively.

3. The deceased population were predominantly young, white males with a record of drug abuse. Most victims were less than 30 years old, males out-numbered females almost three to one, and most victims were employed in a variety of blue-collar jobs at the time of their deaths.

4. They were a medically healthy group without significant psychiatric problems other than drug abuse, but this abuse did not include alcoholism or excessive use of tranquilizers, although many of them were certainly drinkers.

5. There is a notable number of heroin users among the victims. This conclusion is based on case history, established route of administration of the drug, and postmortem analytical toxicology data (morphine was detected analytically in one third of the 86 drug deaths). The intravenous route of administration was prominent throughout the entire study population; 61.5% of the cases involving only cocaine and 30.0% of the drug combination deaths used this method.

6. The manner of death for almost half of the deceased was classified as accidental, and for approximately one quarter it was undetermined. They were not generally suicides.

7. Fatal toxicity from cocaine is rapid, with extremely fast onset of symptoms. Two thirds of the victims died in less than 5 h and one third within the first hour following administration of the drug. There is no evidence from the study that any particular route of administration played a dominant part with respect to survival time. Terminal symptoms were always CNS-mediated and generally involved seizures followed by respiratory arrest.

8. Cocaine involvement was suspected in most of the study cases by the investigator or pathologist prior to toxicology. Complete and prompt autopsies were performed, often including examination of nasal passages. Perforated nasal septum was never found. Gross observations and microscopic findings were unremarkable and without diagnostic character.

9. In 70% of the 86 drug-death cases, the blood concentrations of cocaine were under 4.0 μg/ml and in more than one third were 1.0 μg/ml or less. For fatalities involving only cocaine, 70% of the cases had blood concentrations less than 9.0 μg/ml. Blood concentrations were generally higher than liver tissue values in the same case, confirming blood to be the sample of first choice for analysis; however, an appreciation of the in-vitro instability of cocaine unless the sample is preserved by sodium fluoride is important.

10. Analytically detected lidocaine apparently originated almost exclusively as a cutting agent for cocaine rather than through attempted therapeutic intervention. Alcohol was present in significant concentration in about one quarter of the drug deaths and had a mean blood value of 0.10%.

11. For eight of the study cases it was established that the cocaine was ingested intranasally. The blood concentrations in six of these cases were very high: 2.8 to 5.9 μg/ml. Only one case had the minimum concentration of 200 ng/ml. The overall study findings, and seven of these eight cases in particular, clearly refute any lay or drug-user opinions that nasal insufflation of cocaine is completely safe. This belief is not true, and there is no pharmacology-toxicology rationale to suggest that toxic circulatory system concentrations of the drug cannot be achieved by this route.

This report should not be construed as an assessment of cocaine use in the United States and Canada. That is not its purpose, and, in any event, the deceased study population cannot reflect general use of the drug. Whatever the magnitude and frequency of cocaine use may be, the study does clearly indicate that drug abusers are dying from cocaine intoxication, either alone or more usually in combination with other agents. It is a drug that should not be lightly regarded as an in-vogue recreational pastime without potential serious consequences, and, as with many other abused substances, it properly and only belongs in the field of medicine.

Acknowledgments

It would not have been possible to conduct this study without the generous, professional support of many forensic scientists and librarians, technical, and clerical staff at each of laboratory survey sites. The work and contributions of the following individuals are gratefully acknowledged:

Alabama	June K. Jones	forensic toxicologist
Alameda County, Calif.	Philip Reynolds	forensic toxicologist
	Allan B. McNie	forensic pathologist
Clark County, Nev.	Thorne J. Butler	forensic pathologist and toxicologist
Cook County, Ill.	George N. Christopoulos	forensic toxicologist

Dade County, Fla.	Arthur J. Fisk	forensic toxicologist
Dallas County, Tex.	James C. Garriott	forensic toxicologist
Hennepin County, Minn.	Robert DeGregory	forensic toxicologist
Illinois	John J. Spikes	forensic toxicologist
Los Angeles County, Calif.	George R. Nakamura	forensic toxicologist
	Thomas T. Noguchi	forensic pathologist
Maryland	Yale H. Caplan	forensic toxicologist
Minnesota	Lowell C. VanBerkom	forensic toxicologist
Montreal, Province of Quebec	Jean Jacques Rousseau	forensic toxicologist
New Mexico	James C. Standefer	forensic toxicologist
New York state	Milton L. Bastos	forensic toxicologist
North Carolina	Arthur J. McBay	forensic toxicologist
	R. Page Hudson	forensic pathologist
Orange County, Calif.	Robert H. Cravey	forensic toxicologist
Oregon	John P. Aitchison	forensic toxicologist
Philadelphia County, Pa.	Jane H. Speaker	forensic toxicologist
Rhode Island	Richard J. Bushee, Jr.	forensic toxicologist
	William Q. Sturner	forensic pathologist
San Diego County, Calif.	Richard F. Shaw	forensic toxicologist
San Francisco County, Calif.	James A. Wright	forensic toxicologist
	Boyd G. Stephens	forensic pathologist
St. Louis, Missouri County	George E. Gantner	forensic pathologist
Toronto, Province of Ontario	George Cimbura	forensic toxicologist
	Douglas M. Lucas	laboratory director
Utah	Ladislav Kopjak	forensic toxicologist
Vancouver, British Columbia	Edwin J. Fennell	forensic toxicologist
	Mel Y. W. Yip	forensic toxicologist
Washington, D.C.	Robert F. Reisch	forensic toxicologist
	James L. Luke	forensic pathologist
Wayne County, Detroit, Mich.	Joseph R. Monforte	forensic toxicologist
	Werner U. Spitz	forensic pathologist

This study was supported, in part, by a National Institute on Drug Abuse Contract No. 271-76-3327.

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