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Cocaine: 1977

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COCAINE: 1977

EDITORS: Robert C. Petersen, Ph.D.
Richard C. Stillman, M.D.

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FOREWORD

Increasing chemical sophistication has brought a bewildering array of drugs that produce feelings people like. Despite this increase in the number of abusable psychoactive drugs, a few plant substances have been the dominant psychochemical influence in many cultures over millennia. One of these is the coca bush. Unlike tobacco, marihuana, and opium, it has been geographically restricted -- primarily to the Andes mountains of South America, where its leaves continue to be chewed by millions of Indians on a daily basis.

For most Americans, it comes as a surprise to realize that much traditional drug use around the world has been and continues to be work-related, rather than recreational. Contrary to expectations based on modern pharmacology, this is true of such drugs as cannabis, opium, tobacco, and it is even more characteristic of the coca leaf. In fact, the most compelling analogy to Andean coca chewing is American coffee drinking as a work adjunct.

In most cultures over most of history, use of such substances as coca, cannabis and opium has existed in a cultural context which tended to moderate and restrict use.

During the last century, traditional patterns of drug use have been increasingly, often profoundly, modified. The availability of the concentrated psychoactive ingredients of traditional drug substances in purified form together with such new routes of administration as intravenous injection has markedly altered the drug picture. Simultaneously with these pharmacological developments, traditional cultures all over the world have been losing their power. In addition, the numbers of people exposed to each psychoactive substance have grown dramatically.

Cocaine, the principal psychoactive ingredient of the coca plant, has been a part of this trend. The purified drug was isolated a little more than a hundred years ago. The leaves of the coca plant are typically chewed or used for a tea in traditional settings of use. By contrast, their psychoactive ingredients, from fifty to a hundred times more concentrated, may be "snorted" (like snuff), injected or smoked. The traditional customs that have governed coca use in South America's mountains are largely absent with respect to cocaine.

Despite the spurt of scientific interest in cocaine when it was first isolated and despite the drug's limited medical use as a local anesthetic, our knowledge of cocaine as a psychoactive substance is modest. For most of the last half century, use was restricted to a comparative few. The amount of research that was conducted using modern pharmacological techniques was correspondingly small. Four years ago, the awareness of increasing cocaine use and the realization of how little we know led the National Institute on Drug Abuse to launch the present high priority cocaine research effort. About a million dollars a year has been spent in the intervening period to support 40 research projects exploring aspects of cocaine from the chemistry of the substance to the characteristics of users.

This volume summarizes our current understanding of cocaine. One of the most notable aspects of our knowledge is that so much is not yet known. We are still, to a large extent, ignorant of the actual and potential health hazards posed by this fascinating substance, even though it was used by about two million Americans this past year. Despite obvious knowledge limitations, we do know a few things that are important: We know, for example, that cocaine can kill -- not commonly but occasionally and perhaps not predictably. Despite the street lore to the contrary, death sometimes occurs even when the drug is snorted rather than injected. We also know that cocaine is among the most powerfully reinforcing of all abused drugs. Although not physically addictive in the sense that the opiates are, there is good evidence that the desire to continue use when available is remarkably strong. The relatively benign picture presented by occasional use of small quantities might be markedly altered were the single euphoric illicit dose now costing about $10 available at the licit cost of about ten cents.

While the evidence accumulated thus far does not justify the claim that the American public is now suffering greatly as a consequence of cocaine use, it is evident that much more needs to be known before any actions are taken that might result in a wider availability at lower cost.

In the tradition of the Marihuana and Health Reports, we at NIDA are proud to publish our first major report describing what is known and not known about cocaine and its implications for health. We hope that this book will serve not only as a useful reference work for clinicians and scientists interested in the area, but also that it will become a useful document for those interested in applying modern scientific knowledge to the serious social policy questions associated with cocaine use in America today.

Robert L. DuPont, M.D.
Director
National Institute on Drug Abuse

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INTRODUCTION

The marked rise in interest in the use of illicit drugs in the past decade has brought with it renewed interest in a drug with a long and romantic history. As with other "recreational" drugs, cocaine has elicited uncritical enthusiasm in some while others better acquainted with its earlier history have viewed it with alarm. Cocaine today is perceived by many users as being a physically and psychologically safe recreational drug. It is also an extremely well liked drug. In one recent survey of 100 drug-using college students (Stillman, pers. comn.), cocaine was the recreational drug of choice of all but 2 of the 29 students who had tried it. From their standpoint the only limitations on its use were its high cost and lack of availability. Yet if cocaine becomes cheaper and more readily available dosages will undoubtedly rise and the more unpleasant and dangerous aspects of the drug may become more apparent. Although the data presented in this volume show that cocaine as typically used in the United States at present poses only a limited hazard, these same data also demonstrate that it can be physically dangerous in ways that marihuana, for example, is not.

The present volume represents an attempt to summarize our admittedly limited knowledge of cocaine through a series of reports by leading workers in the cocaine area. They range from animal behaviorists conducting research at the preclinical level to clinicians contending with the problems of the street user. The emphasis is on developing a picture of our current knowledge with special attention to its limitations. The authors have not tried to gloss over the areas of ignorance that exist nor to substitute unsubstantiated opinion for authoritative data. It is our belief that the needs of all readers - from the interested layman to the practicing clinician -- are better served by as objective an assessment as is now possible rather than by more dogmatic assertions.

Although the present volume cannot be totally comprehensive, we hope that it will serve as a useful "map" of the larger domain. To that end a brief description of the contents of the various sections may be helpful:

- An overview of what is presently known about cocaine is primarily intended to provide a non-technical review of our present knowledge about the drug and to provide some overall perspective.

- The chapter on the history of coca and cocaine provides a brief historical review which may be useful in placing present use in a larger time perspective.

- Ms. Eleanor Carroll, in her chapter on coca use and its health implications, examines briefly what is known about various aspects of the use of the plant material from which cocaine is derived. While coca chewing is not part of the U.S. drug scene, there has been considerable interest and some confusion concerning the differing implications of use of the plant material from that of the pure drug.

- The chapter on the material itself by Dr. Richard Hawks describes the chemistry of cocaine with particular attention to newer analytic methods for the detection of the drug and its metabolites.

- Dr. James Woods in his chapter on animal behavioral research summarizes the effects of cocaine on a wide range of behavior and critically evaluates the evidence for and against several proposed mechanisms of action of the drug.

- Drs. Robert Byck and Craig Van Dyke provide a succinct review of the known effects of cocaine in man. A meticulously constructed table of source material accompanies their discussion and gives a clear indication of the adequacy and limitations of the reports on which our knowledge is based.

- Dr. Ronald Siegel describes a detailed survey of a sample of cocaine users providing a quantitative assessment of the styles of use and reactions to the drug on the part of some 85 users. He also describes a type of hallucinatory phenomenon reported by users which appears to be more common than previously believed.

- Drs. David Smith and Donald Wesson contribute their insights into street use of cocaine from the vantage point of a "free clinic" in the Haight-Ashbury area of San Francisco, their association with the San Francisco Polydrug Research Project and from their extensive clinical experience with drug users. They document their concern that cocaine use may be significantly more hazardous than marihuana use and that the psychological dangers of sustained heavier use are not to be dismissed lightly.

- Drs. Bryan Finkle and Kevin McCloskey -- based on an intensive study of cocaine-related deaths in the United States and Canada -- analyze mortality connected with use.

While the number of deaths that were documented was small (26 due to cocaine alone in a population of 63,000,000 over a 5-year period), their findings suggest that cocaine use, even by "snorting", can be occasionally and unpredictably fatal.

- Dr. Paul Barash in his chapter on current uses of cocaine in clinical. medicine provides a review of the present status of the drug as an anesthetic possessing some uniquely desirable properties. He also describes hospital treatment for cocaine overdoses.

- Finally, in a brief chapter based on a nationwide Federal drug abuse treatment monitoring system (CODAP), Dr. Eduardo Siguel describes the characteristics of patients seeking treatment for whom cocaine abuse is a prominent feature.

A modest degree of overlap of content has been retained in sane of the chapters in order to facilitate understanding should each be read in isolation.

Although cocaine use and abuse has many broader implications related to the problems of social policy and drug abuse control, those aspects seem more appropriately dealt with in a different context from that of the health implications. Nevertheless, it is our hope that this compendium will provide up-to-date information that contributes usefully to better informed discussion of the broader social issues that cocaine use entails.

Robert C. Petersen, Ph.D. and Richard C. Stillman, M.D., Editors

National Institute on Drug Abuse

COCAINE: AN OVERVIEW

Robert C. Petersen, Ph.D.

WHAT IS IT?

Cocaine is a naturally occurring stimulant drug which is extracted from the leaves of the coca plant (Erythroxylon coca). The leaves of this Western South American shrub have been chewed by Bolivian and Peruvian Indians since antiquity for a variety of religious, medicinal and work-related reasons (cf., Petersen, Chapter 1; Carroll, Chapter 2, this volume). Allegedly, the chewing of coca leaves has enabled the Indians to work under extremely arduous conditions of high altitude and inadequate diet. This chewing of the coca leaf which continues to the present day should not, however, be confused with the use of the extracted drug, cocaine. Coca leaves contain only about ½-1 percent cocaine; the cocaine contained within them is released more slowly and the route of administration is different (oral) from that of most cocaine use.

Because reports of native coca use had generated considerable interest in Europe, efforts were made in the 19th century to isolate the purified psychoactive ingredient in coca leaves. When success in isolating cocaine was achieved in the 1880's, its potential value as a tonic, its general stimulant properties, its possible value for specific ailments and its local anesthetic properties were explored. Its use as an anesthetic was particularly important because it could be used in eye surgery for which no previous drug had been suitable. A second desirable property of cocaine when used as a local anesthetic was (and is) its ability to constrict blood vessels and thus limit bleeding in the anesthetized area. This made it especially valuable for surgery involving the nose and throat, areas richly supplied with blood. Although many of cocaine's uses as a therapeutic drug have been abandoned, its use as a local anesthetic for specific medical purposes continues (cf. Barash, Chapter 9).

Illicit cocaine is sold as a white translucent crystalline powder frequently adulterated to about half its volume by a variety of other ingredients. The most common adulterants are various sugars (especially, lactose and glucose) and other local anesthetics (lidocaine, procaine and tetracaine) with similar appearance and taste to cocaine. The amphetamines, other drugs with stimulant properties, are also sometimes used. Given the very high cost of the drug, the temptation to adulterate at each level of sale is great. The current street price (1977) may range from $60-$100 a gram (about 1/30 of an ounce). The combination of the very high price and the exotic properties attributed to it have contributed to cocaine's street reputation as the status drug.

WHO USES COCAINE?

Determining the nature and extent of illicit drug use poses formidable problems. This is particularly true when assessing present patterns and trends in cocaine use, which is thought to be used only by certain segments of the population. Because the street drug is typically adulterated to varying degrees, even self-reports of use offered in good faith may be inadequate. The more naive experimenter may believe s/he is using cocaine when, in fact, s/he is actually consuming an amphetamine or cocaine adulterated extensively by other substances.

While cocaine and coca extracts were widely used in patent medicine, wines and soft drinks at the turn of the century, it is virtually impossible to get any reliable estimates of who was using them and in what quantities. And, aside from clinical reports, there are no statistics indicating the number and kinds of adverse reactions occurring among those users.

Figures dealing with Federal seizures of cocaine are of limited value. The amounts confiscated are small compared to the total imported and fluctuations in success in intercepting shipments can result in substantial variations in quantities seized from year to year which may not reflect levels of actual use.

Data from the several national interview surveys that have been conducted in 1972, 1974 and 1975/76 have some value, but because they are household surveys they are unlikely to include transient street populations or to accurately reflect use in high status professional, artistic or creative circles in which there are anecdotal reports of widespread use. The honesty of respondents will also determine the levels of use reported, and this candor may vary from year to year. Despite these obvious limitations, the last several years of uniformly collected nationwide data are still of considerable interest. Among adults (those over 18) the percentage reporting ever having tried cocaine'in all three surveys has been 3-4 percent. The percentage of adults reporting having used in the month preceding each of the surveys has been consistently just under 1 percent. The figures for youth -- those 12-17 -- have been approximately the same as for adults. While there have been minor fluctuations from year to year, the numbers involved are too small to know whether the differences are real or simply variations to be expected from sampling differences.

In the 18-25-year-old group, the peak age group for all illicit drug use, nearly one in eight (13.4 percent) report having ever used cocaine and of those who have, nearly one in six (2 percent of the entire group) had done so in the month preceding the most recent (1975/76) survey. Comparable figures for marihuana use in 1975/76 are much higher -- nearly four times as many young adults 18-25 (52.9 percent) have tried marihuana, almost half of those within the past month.

A nationwide study of young men and drugs conducted in 1974 with a random national sample of men between 20 and 30 provides additional confirming evidence of use by young adults. Of this group 14 percent reported having ever used cocaine, half within the year preceding the survey. At least in this sample it is also clear that the likelihood of having used cocaine is much greater if one has used other licit and illicit drugs (though not necessarily implying a causal sense). Of those who had ever used cocaine, all had used alcohol and marihuana and nearly all (96 percent) tobacco. More than 7 out of 10 had also used sedatives, opiates (excluding heroin), psychedelics or other stimulants. Almost two out of five (38 percent) of those who had used cocaine had also tried heroin (O'Donnell et al., 1976).

A nationwide study specifically aimed at high school seniors is of interest because of their transitional status between adolescence and adulthood. In this group, 9 percent of the 1975 senior class reported having tried cocaine in 1975 and 9.8 percent in 1976 -- the increase is too small to be certain it is not simply a result of sampling variation. About 1 in 100 seniors in each of the 2 classes reported having used cocaine 20 or more times. Most seniors reported relatively conservative attitudes toward cocaine (and other regular drug use) -- nearly 19 out of 20 disapproved of the regular use of cocaine and more than 4 out of 5 disapproved of even trying the substance (Johnston, 1976).

Another measure that has sometimes proven useful in indicating trends in drug use, especially as reflected in medical emergencies resulting from such use, is the DAWN system (a Drug Abuse Warning Network operated by the Federal government). DAWN receives reports of drug related emergencies from 24 standard metropolitan statistical areas, each of which transmits data from such facilities as crisis centers, emergency rooms and medical examiners. Although the number of cocaine-related emergencies is presently too small to provide a reliable indicator of cocaine use trends, the most recently available figures are still of some interest. During the one year period from May, 1975 to April, 1976, cocaine alone or in combination with other drugs was mentioned in connection with less than 1 percent of emergency roan episodes involving drug use (958 of 118,311 drug mentions). In crisis centers (facilities established to provide "walk in" or "phone in" help to those experiencing personal crisis) 3.6 percent of the drug related crises involved cocaine alone or in combination with other drugs (1,802 of 49,633 drug mentions). In both emergency roan and crisis center episodes involving cocaine, half involved cocaine alone, the other half cocaine in caubination with other drugs. Thus, cocaine, contrary to some beliefs, played a role in drug-related problems although less commonly than other drugs. Unfortunately, there is no way of knowing how the number involved in such emergencies compares to the number using the drug during the period involved. It may well be that present typical patterns of American use -- sporadic use of relatively small quantities of the drug -- make cocaine related emergencies less likely to occur than other drug-related emergencies.

Overall, most evidence suggests that there is a trend toward increasing use of cocaine, although the exact dimensions of the increase are not known.

While a few other studies have been done of users (cf. Siegel, Chapter 7, this volume), there is little detailed information about typical patterns of use.

HOW IS IT USED?

Cocaine is most commonly inhaled or "snorted" through the nose. As a result, the drug is deposited on the mucous linings of the nose from which it is readily absorbed into the blood stream of the user. Repeated use in this way often results in an irritation to the nostrils and nasal mucous membranes. Symptoms may resemble those of a common cold, i.e., congestion or a "runny nose."

In attempting to cope with these secondary symptoms of their cocaine use, users often resort to a variety of "cold remedies" such as nasal sprays to relieve their chronic nasal congestion. While their has been no systematic study of this, some users have reported that the chronic use of nasal sprays brings with it further difficulties -- the user may find he or she is unable to breathe comfortably through the nose without habitually using a spray to keep the nasal passages open.

A less common route of administration for cocaine is intravenous injection directly into the blood stream. The solution injected may be cocaine alone or sometimes a combination of heroin and cocaine. This alternative route of administration, of course, is more dangerous because of the hazards of hepatitis and other infections transmitted by the use of non-sterile needles and syringes. Furthermore, it introduces unknown quantities of cocaine or cocaine and heroin directly and suddenly into the blood stream, leaving body organs wholly unprotected from the toxic effects of the drug. Cocaine deaths from intravenous self-administration are more numerous than from snorting despite the greater prevalence of the latter method (Cf., Finkle and McCloskey, Chapter 8 this volume).

WHY IS IT USED?

While it is difficult to give an altogether satisfactory explanation of why people use any drug, we can talk about what they say about their drug use. As other chapters in this volume illustrate (Cf., Smith and Wesson, Chapter 6; Siegel, Chapter 7) cocaine is ranked first among recreational drugs of choice by many experienced users because it produces a euphoria, a sense of intense stimulation and of psychic and physical well-being accompanied by reduced fatigue. Users ranging from Sigmund Freud to William

Burroughs, have waxed lyrical over cocaine's positive attributes; occasionally these descriptions are tempered by descriptions of more negative implications of heavier, prolonged use.

Unlike such drugs as LSD and heroin, which are frequently viewed as leading to a greater orientation toward self and one's internal processes, cocaine is considered by users as a social drug -- one which facilitates social interaction. It is also ranked high in desirability because of its convenience of use, rapid onset of action and its exotic qualities. At least part of its appeal is its rarity, high price and use by celebrities, musicians and other folk heroes. Users also believe that cocaine is relatively free from markedly undesirable side effects and is generally safe. Its reputation for safety may be overstated since it is based on low doses taken relatively infrequently. Under conditions of heavier, more frequent use, adverse consequences may be considerably more common than generally believed.

It should be emphasized that with cocaine, as with other psychoactive drugs, the subjective effects of the drug are modified by the circumstances under which the individual takes the drug; these include the physical surroundings and the overall "atmosphere" of those surroundings (both may be summarized as the "setting" of use). A second equally important factor is the totality of the user's expectations molded by personality, previous drug experiences, attitude, etc. (his or her "set"). In addition to set and setting a variety of other properties of cocaine may be important, including dose, route of drug administration, chronic vs. acute use and possible interactive effects with other drugs used (including alcohol and heroin). For example, if a normally somewhat apprehensive person takes cocaine among relative strangers, which may contribute to a feeling of insecurity, it is likely that s/he will react with more heightened anxiety and suspiciousness than with close friends, in the relaxed circumstances of his/her own home.

WHAT ARE THE ACUTE AND CHRONIC EFFECTS OF COCAINE?

As the various authors of this monograph emphasize (especially Byck and Van Dyke, Chapter 5 this volume), there has been a range of effects attributed to cocaine. Some, which are individual and subjective, can never be adequately confirmed simply because they are idiosyncratic and atypical of most users. To the extent the experience is shared with others, despite its subjectivity, it may yield a common description either offered spontaneously or in response to various rating scales. Other responses (e.g., blood pressure, body temperature) can be objectively measured under carefully controlled conditions of the laboratory with known drug doses and a specified schedule of drug administration. Some responses which occur in other species as well as in humans -- the effects on general activity or appetite are examples -- can be examined under

very tightly controlled conditions in which such variables as the biological history of the organism is known and its learning history can also be specified with precision. Others -- often among the most fascinating effects of a drug -- may involve complex behavior not easily measured. Distinguishing the drug's effect from other elements of expectation and the situation can be difficult -- the effect of cocaine on sexuality is an example.

Other aspects of a drug, previously alluded to, which are important include: length of drug use -- acute vs. chronic effects; the dosage received -- the effects of a drug may be quite different at low doses from those at higher doses, even opposite; and the route of administration -- intravenous effects may differ from those of snorted cocaine and both may be different from oral administration.

A final caveat should be stressed. Cocaine, like other drugs of abuse, has both fascinated and repelled man throughout its history. It is little wonder, then, that a bewildering array of "effects," which may have little to do with the pharmacological action of the drug itself, have been attributed to it. Reassertion of often repeated fictions does not, however, make them well verified facts. Cur need for certainty is not necessarily matched by equally adequate evidence to allay our doubts. Unfortunately, a lack of adequate information is sometimes interpreted as indicating that a drug is "safe" when it would be more accurate to admit that our knowledge is simply inadequate to specify the parameters of risk. Moreover, a substance which when used under conditions of relatively infrequent, low dosage may pose few hazards, may present quite a different picture when widely available and regularly used in larger amounts.

An important, verified effect when used medically is cocaine's local anesthetic action as well as its ability to constrict blood vessels in the area to which it is applied. (Cf., Barash, Chapter 9 this volume) One consequence of this property when cocaine is used illicitly and snorted repeatedly is a tendency to cause a chronic inflammation of the nasal membranes, ulceration, local tissue death and sloughing off of the injured tissue. While perforation of the nasal septum (the wall dividing the two halves of the nose) is often mentioned, it is noteworthy that in the United States, at least, this consequence appears to be rare (Cf. Barash, Chapter 9; Smith & Wesson, Chapter 6 this volume).

There is good evidence that cocaine in moderate doses (10-25 mg i.v. and 100 mg intranasally) significantly increases both heart rate and blood pressure. Increases following lower doses occurred more rapidly when the drug was administered directly into the vein than when snorted. Heart rate increased from about 30 to 50 percent above normal non-drug levels. Increases in blood pressure when the heart was in its contracting phase (systolic pressure) were oh the order of 10-15 percent. (See Byck & Van Dyke, Chapter 5 this volume).

In addition to the street reputation of the drug and historical accounts, even under conditions of carefully controlled laboratory administration, a sense of well-being -- euphoria -- subjectively characterizes cocaine use. Interestingly enough, however, when the drug was administered intravenously under laboratory conditions the subjective effects were not easily distinguished from those of amphetamines (synthetic stimulants having more prolonged activity). A feeling of calmness and/or relaxation is described by most of the subjects who have participated in controlled laboratory studies; they also report diminished appetite. The observed and reported effects of several laboratory studies are generally consistent with anecdotal accounts based on street use. However, there is much street lore and some clinical evidence emphasizing other effects that have not been systematically verified by controlled experimentation.

Clinical reports dating back to the 1880's have described a range of response to heavier, more prolonged use of cocaine. Early reports by Freud and others also emphasized that there was wide individual variation in the physiological and psychological responses to cocaine. Von Fleischl (Cf. Petersen, Chapter 1 this volume), who was encouraged to use cocaine by Freud to alleviate symptoms of nerve pain, rapidly progressed to heavy, intravenous use (up to a gram per day). With heavier use, Fleischl's condition deteriorated to the point of a chronic intoxication characterized by hallucinations of white snakes creeping over his skin and insects that had to be dug out of his skin. A cocaine psychosis very similar to paranoid schizophrenia has been described in the scientific literature. One common aspect of this disorder has been tactile hallucinations similar to those experienced by Fleischl. The hallucinations have been described as sufficiently real to the victim that s/he frequently injures the skin in a futile attempt to remove the offending parasites (Woods & Downs, 1973). Other paranoid delusions which have been reported as characteristic of chronic cocaine intoxication include fears of imaginary police, beliefs one is being watched, etc.

Apart from clinical description and case reports, however, there have still been no systematic controlled studies to determine the level and frequency of cocaine use which leads to serious, adverse psychic effects such as those described. It is not known how common such paranoid symptoms are at various levels of use, the degree to which individual personality differences contribute to their development or whether they are a consequence of use if large enough quantities are used over a sufficiently extended period. Because present American use patterns are characterized by relatively infrequent use of small quantities of the drug, serious adverse effects of use may be quite rare (Cf. Smith & Wesson, Chapter 5 this volume) . In one recent study of recreational users (Siegel, Chapter 5) 85 regular users (1 gram per month or more) recruited by means of newspaper ads were studied. None of these subjects were compulsive users in the sense described in the earlier literature. Although their self-reported experiences were generally positive (e.g., all

reported euphoria in connection with use), negative effects were also indicated, such as restlessness, anxiety, hyperirritability and for some (5 percent) paranoia. In this study, positive effects were reported on all occasions of use with negative consequences experienced in from 3-5 percent of them.

COCAINE MORTALITY

Unlike marihuana, there is little question that cocaine can cause death as a direct effect of the pharmacological action of the drug. By 1891 some 13 deaths had been attributed to the drug (Woods & Downs, 1973) and in 1924, a report was published of 26 deaths attributed to cocaine (Mayer, 1924). These deaths were results of errors of medical administration when the drug was used therapeutically or as an anesthetic. They were virtually always rapid in onset and characterized by respiratory depression and cardiovascular collapse. Because there has been little systematic study of cocaine death in recent years aside from a few isolated case studies, the National Institute on Drug Abuse recently commissioned a study of cocaine-related deaths between 1971 and 1976 in 27 U.S. and Canadian locations. (Cf., Finkle and McCloskey, Chapter 8 this volume).

The geographical area covered by this study included nearly 30 percent of the population of the United States. The records of a total of Ill deaths in which cocaine was in some way involved were studied. While drugs were causative in 86 cases, only 26 involved cocaine alone and of those 6 were suicides.

Another source of data on cocaine-related deaths is the Federal Drug Abuse Warning Network (DAWN). During the one year period from May, 1975 through April, 1976, some 57 cocaine-related deaths were reported to DAWN by the medical examiners of the 24 standard metropolitan statistical areas monitored by the system. Of these, 6 of a total of 4,668 drug-related deaths reported involved cocaine alone. These figures are roughly comparable to those in the more intensive study discussed above. Both studies indicate that accidental deaths due to cocaine, while uncommon, do occur. This is in contrast with the widespread street belief that cocaine is without significant hazard. Moreover, the first of these studies found that two deaths due to cocaine occurred in those who had "snorted" the drug. This, too, is in some contrast to the widespread belief that snorting is completely safe.

TREATMENT OF COCAINE ABUSE

Aside from some specific suggestions for the treatment of acute anxiety, drug-induced depression and cocaine psychosis (cf., Smith

& Wesson, Chapter 6 this volume for treatment of medical toxicity see Barash, Chapter 9), there has been little reported, systematic information on the treatment of cocaine abuse. Because of the lack of evidence for a physical dependence on the drug, it has been suggested that using cocaine to "maintain" a patient in a manner analogous to methadone maintenance of the heroin addict is inappropriate (Woods & Downs, 1973). Since many patients use both heroin and cocaine simultaneously, physical addiction to the heroin involved may be the primary problem.

Reports based on CODAP (the Federal Client-Oriented Data Acquisition Process), a reporting system designed to monitor Federally supported or assisted drug treatment programs, rarely indicate cocaine as the primary drug of abuse (i.e., as the reason for seeking treatment). Only 1.2 percent of the 202,000 admissions in the latest report (cf., Siguel Chapter 10 this volume) were for cocaine abuse. An additional 5.5 percent of clients treated reported that cocaine was a secondary or tertiary drug problem to other drugs of abuse.

Although cocaine users apparently seek treatment rather infrequently, it is not known if this is the result of the limited availability and high cost which, in turn, limits its use and reduces the likelihood of more serious consequences.

FUTURE DIRECTIONS

As this and other monographs on cocaine illustrate, our present knowledge of cocaine remains fragmentary. The areas of certainty, when closely examined, are quite modest. Much of the anecdotally based information about the drug has never been subjected to systematic investigation.

While cocaine-containing coca, as well as the extracted drug are alleged to enhance endurance and physical strength under conditions of adversity, this has not been adequately explored. Aside from Freud's early attempt to examine cocaine's effect on physical strength in himself (Freud, 1885), there have been few experimental studies of the effects of cocaine on physical performance and endurance.

When we turn to the question of psychological effects (e.g., the widely cited effect of cocaine on intellectual performance and creativity), the "hard" evidence for such effects is non-existent. While the drug has frequently been anecdotally linked with aggression and criminality, adequate evidence to assess cocaine's possible impact in these areas is again lacking.

There is much controversy about cocaine's toxicity, especially its psychotoxicity, and there is little adequate evidence to resolve the uncertainty. As early as the late 19th century, there were

clinical reports that cocaine could cause paranoid thinking and hallucinations resembling the alcoholicls delirium tremens. Despite the numerous clinical reports and individual case histories documenting this, little is known on the basis of controlled experimentation of the extent to which such symptoms are related to personality or the doses and patterns of use likely to precipitate them.

Depression subsequent to extended use ("crashing") has been reported. Again, the correlates and patterns of use associated with this symptom are inadequately specified.

Even the trends and patterns of typical use in the United States remain a matter of speculation. The statistically low level of use in the general population makes tracing trends in use difficult. Although there are several converging lines of evidence suggesting that use is increasing, the small numbers involved and the likelihood of variability from year to year make their interpretation difficult. Thus it is hard to be certain whether the increased attention cocaine is currently receiving reflects general patterns of markedly increased use or renewed media interest because of the prominence of some of cocaine's users. Whatever the ultimate realities or the imperfect relationship between interest in the drug and actual levels of use, it is likely that use will increase in response to the publicity of cocaine effects. This argues persuasively for expanded research efforts in the following areas:

- Incidence, prevalence and patterns of cocaine abuse;
- Factors in popularity of the drug and the characteristics of the cocaine "high."
- The role of personality factors in determining who uses, the patterns of use and the likelihood of adverse consequences;
- The pharmacology of cocaine including the possible development of dependence;
- Effects of cocaine on human performance;
- Types of cocaine toxicity, the relation to dose and user predisposition.

Robert C. Petersen, Ph.D.
Division of Research
Rational Institute on Drug Abuse

REFERENCES

Cocaine -- An Overview

Freud, S. A contribution to the knowledge of the effect of cocaine, Vienna Medical Weekly, January, 1885. In Byck, R. (ed.), Cocaine Papers: Sigmund Freud. New York, NY: Stonehill Publishing Co., 1974.

Johnston, L.D. Monitoring the future: Continuing study of life styles and values of youth. University of Michigan, Ann Arbor, 1976. Personal comunication.

Mayer, E. The toxic effects following the use of local anesthetics. Journal of the American Medical Association, 82: 876-885 (1924).

O'Donnell, J.A., Voss H.L., Clayton, R.R., Slatin, G.T. and Roan, R.G.W. Young men and drugs -- A nationwide survey. Research Monograph No. 5, National Institute on Drug Abuse, Rockville, MD, 1976.

Woods, J.H. and Downs, D.A. The psychopharmacology of cocaine. In Drug Use in America: Problem in Perspective, Appendix Volume 1: Patterns and Consequences of Drug Use, Washington, DC: U.S. Government Printing Office, 1973, pp. 116-139.

Chapter I HISTORY OF COCAINE

Robert C. Petersen, Ph.D.

The purpose of this brief history of coca and its pure alkaloid derivative, cocaine, is to place the present day scientific assessment of cocaine's properties and possible health implications in some cultural and historical perspective. The reader should recognize that cocaine, like other mind-altering drugs, has always evoked emotions ranging from great optimism to fearful dread regarding its societal implications. Even today, because fact and myth about its use and properties are not always easily separated, a concern about its hazards coexists with an optimism on the part of others about its desirability for use as a recreational drug.

A history such as this can hope to do little more than convey some of the highlights of the plant's and drug's background, barely addressing the cultural and historical complexity of its origins and earlier use. For the interested reader, recent interest in cocaine has resulted is the publication of several more detailed sources of information.

EARLY COCA USE

Although the history of the pure drug substance, cocaine, covers little more than a hundred years, use of coca can be traced to prehistoric times. While it is impossible to date precisely the point at which chewing of the leaves of the coca plant, Erythroxylon coca, began, the sixth century A.D. if not earlier is generally agreed upon. Archeological evidence of this practice is found in unearthed Indian mummies which had been buried with supplies of coca leaves as well as in a variety of pottery portraying the characteristic cheek bulge of the coca chewer.

In contrast with later European and American consumption in the form of an infusion of extract of the coca leaves, early (and present-day) use in South America involves chewing a wad of leaves along with a quantity of a lime substance typically derived from the ashes remaining after burning plants, shells or limestone. The exact purpose of the lime is in some dispute; it may improve the flavor of the leaves, potentiate the action, release the cocaine from the coca leaves or it may simply promote salivation.

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[1] Ashley, 1975; Byck, 1974; Mortimer, 1974; Grinspoon & Bakalar, 1976; Andrews & Solomon, 1975.

Because the wild species of the plant produces smaller leaves that are regarded as inferior in flavor, cultivation of the plant took place early in history. Although coca use antedated the Incan civilization, it is most commonly associated with this empire which became the dominant influence in what is now Peru, Bolivia, Ecuador and Columbia during the 11th century. Whatever its earlier status, coca use achieved great symbolic importance under Incan rule. The plant was carefully cultivated on its own plantations, had central religious significance and became identified with the politically powerful as one of the prerogatives of rank.

Several Incan myths that account for its origins are reviewed by Gagliano (1960) in his detailed social history of coca in Peru. In one account, before coca was a shrub it was a beautiful woman who was executed for adultery, cut in half and buried. Prom one part of her remains, the coca plant grew and blossomed to be consumed, only by men, in her memory.

A second myth describes coca as an herb created by the god, Inti. Having instructed the moon mother, Mama Quilla, to plant coca in humid valleys, he also ordered that only the descendants of the gods were to eat of it. The drug was provided to mitigate the hunger and thirst of the Incas, the descendants of the gods, so that they might endure to meet earthly demands.

Less romantically, the use of coca may have become important in Incan life as a result of their contact with coca chewing Indians from the Eastern Andean slopes during the reign of the Inca Roca (ca. 1250-1315 A.D.).

Since the drug was believed to be of divine origin even prior to the Incas, its use was a privilege reserved for members of the highest classes. By the end of the 15th century under the rule of Topa Inca (ca. 1471-1493) coca plantations had become a state monopoly and coca use was quite restricted. Indiscriminate chewing was viewed as a sacrilege. Although use was originally confined to the members of the ruling class, it was sometimes extended as a sign of special merit to soldiers during military campaigns, workers engaged in public works projects and others judged especially deserving.

Throughout the period of Incan rule and afterwards, coca had religious significance. It was a magical offering to the gods for such purposes as insuring safe passage through the Andes and good -- or restored -- health.

Learning the full range of coca's uses by the Incas is hampered by their lack of a written language. However, there is reason to believe the drug may have been used as an analgesic in skull trephining. In these early attempts at neurosurgery, openings were cut in the skull presumably to permit evil spirits to escape from their victims. Despite the crude procedures involved, there is archeological evidence that the operation was sometimes a success in that the victim survived.

With the decline of the Incan empire during the 15th century, many of the rules and taboos concerning the use and cultivation of coca became less restrictive. Coca growing, which had been a state monopoly, now became a privilege granted to deserving followers of the Incan emperor, Huayana Capes (ca. 1493-1527), concomitant with the granting of noble status for their loyal service. By the time of Francisco Pizarro's advance on Cuzco, which completed his conquest of Peru (1536)) coca had lost much of its earlier significance and was no longer a symbol of exclusive political rank or of social status.

The attitude of the Spanish conquerors toward coca was decidedly mixed. On the one hand there was great opposition to it by some of the missionaries (and some of the conquistadores as well) who saw in it a symbol of persistent idolatry and a barrier to religious conversion. At the same time it was recognized that the coca habit was important to the health and motivation of the Andean Indian. Phillip II of Spain in a crown law of 1569 declared the coca habit essential to the well-being of Andean Indians while concurrently urging the missionaries to end the idolatrous use of the plant.

The Spanish became increasingly aware that coca chewing was needed to recruit the Indians to work in the mines and similar settings where conditions were brutal, labor arduous and food limited. It was inevitable therefore that coca cultivation, distribution and use would be permitted -- and even encouraged -- as a tool for the economic exploitation of a subjugated people.

Aside from the contribution of coca to the Indians' production in the mines under arduous conditions, the Spaniards soon recognized coca's euphorogenic properties as well. Nicholas Monardes, writing in 1569, described the Indian practice of chewing a mixture of tobacco and coca leaves to make themselves drunk and to induce "great contentment."

> . . .(When the Indians wished to) make themselves drunk and . . . out of judgment (they chewed a mixture of tobacco and coca leaves which) . . . make them go as they were out of their wittes . . .
>
> -- from Joyful1 Newes out of the Newe Founde Worlde (a 1596 translation of an essay which appeared in 1569, Monardes, 1925)

During the 16th and 17th centuries there was also recognition of the role of coca as an Indian folk remedy for such diverse medical problems as stomach disorders, skin ulcerations, venereal diseases, headache and muscular pains. Spanish physicians also began advocating its therapeutic use for skin disorders, colds, asthma, rheumatism, laryngitis and toothaches.

In the 18th century Antonio Julian, a former Jesuit, urged the use of coca by the laboring classes of Spain, believing that it would improve both their health and productivity. He also felt its use

should be encouraged as the preferred stimulant drink in Spain, thus reducing the economic drain resulting from the import of coffee and tea. Moreover, he reasoned, should coca come to replace stimulant drinks used elsewhere in Europe, this would be to the benefit of Spain, which could then serve as a coca supplier for the remainder of the continent.

While it has been suggested by some historians that the Spanish colonialists in South America used coca as a conscious instrument for suppressing the Andean Indians, such assertions seem questionable. It is doubtful that the Spanish were pharmacologically sophisticated enough to recognize such a role for coca. Use was extensive before the Spanish conquest, suggesting well entrenched patterns needing little encouragement from the conquerors. There were also abortive attempts by the Spanish to curb the use of coca as an impediment to the religious conversion of the Indians. It is possible that there was an increase in use following the fall of the Incan Empire, but this may most readily be attributed to such factors as a decline in food production, an increase in forced labor, the profits involved in the exchange of coca for precious metals and an increased desire to use the drug corresponding to increased hardship following the conquest.

COCA IN EUROPE

When Pizarro returned from Peru to the Court of Spain it is likely that he brought back coca. As Mortimer suggests, the plant's obvious importance to the Incas, as evidenced by the gold replicas found in their edifices, must surely have excited admiration and comment (Mortimer, 1901; reprinted, 1974). But whatever the informal status of coca's introduction into Europe, it was not until two centuries later (in 1750) that the botanist Joseph de Jussieu, then accompanying a scientific expedition to Peru, sent specimens of the shrub to his brother Antoine in Paris for study. These plants, which were preserved in the herbarium of the Museum of Natural History, became the basis for much subsequent study. Members of this expedition were aware of at least some of the pharmacological properties of the plant. Captain Don Antonio d'Ulloa wrote:

> This herb is so nutritious and invigorating that the Indians labor whole days without anything else, and on the want of it they find a decay in their strength (Mortimer, 1901; reprinted, 1974).

Despite the many contemporary accounts describing coca and even advocating its substitution for tea and coffee by such figures as Antonio Julian in the 18th century, it attracted little European attention for over three centuries. The authenticity of its attributed characteristics was even questioned.

How is the paradoxical lack of impact on Europe by this drug which had been so glowingly described by so many travelers to South America to be explained? Guttmacher writing in 1885 (Byck, 1974) and Mortimer in 1901 offer a similar rationale: The pharmacologic inertness of the poorly preserved leaves that were available early in the drug's European history. In addition to the probable deterioration of the imported leaves during a long sea voyage, growing it locally was difficult since the plant was ill suited to a European climate (Guttmacher, 1885).

Several individuals played a role in the ultimate isolation and extraction of cocaine as the principal psychoactive ingredient of the coca plant. Mortimer traces the history as follows: As early as 1850 a Dr. Weddell, following his personal experiences with coca in the Andes, suggested that its stimulant properties might be the result of having the same active ingredient as tea. Following an analysis of coca leaves, a very bitter substance, soluble in alcohol, but insoluble in ether, was found. Still later, in 1885, Friedrich Gaedcke was able to separate an oily substance along with a sublimate of small needlelike crystals from a distillate of the dry residue of an aqueous coca extract. This substance he named "Erythroxyline." Although several others contributed to the isolation of cocaine, ultimate success is usually attributed to Albert Nieiuann of the University of Gottingen, who also characterized it chemically and named it cocaine. William Lossen, also from Gottingen, built on Niemann's work and established cocaine's formula in keeping with the then new chemical notation.

About the same time that Niemann was achieving his successful isolation of cocaine, an Italian neurologist, Dr. Paolo Mantegazza, made a significant contribution to the psychopharmacology of coca. His lyrical observations of effects on a single subject, himself, provide one of the more colorful descriptions of the drug's subjective impact. He recounted in detail the physiological effects and, especially, the "deeply joyful and intensely alive" feelings coca engendered in him. Fart of his description is particularly communicative of the experience:

> Some of the images I tried to describe in the first part of my delirium were full of poetry. I sneered at the poor mortals condemned to live in this valley of tears while I, carried on the winds of two leaves of coca, went flying through the spaces of 77,438 worlds, each more splendid than the one before.
>
> An hour later I was sufficiently calm to write these words in a steady hand: "God is unjust because he made man incapable of sustaining the effect of coca all life long. I would rather have a life span of ten years with coca than one of 1000000 . . . (and here I had inserted a line of zeros) centuries without coca." (in Andrews & Solomon, 1975)

Mantegazza's early monograph based on his subjective and therapeutic impressions of coca, "On the Hygienic and Medicinal Virtues of Coca" undoubtedly influenced a number of physicians and researchers, including Sigmund Freud. Cocaine initially inspired Sigmund Freud's uncritical endorsement, which bordered on the lyrical, of both its therapeutic potential and contribution to creativity. And in the process of touting cocaine's virtues young Freud nearly destroyed his career as a promising researcher. Earlier in this century in the United States, dread of cocaine's putative powers to evoke superhuman aggression both fueled and was fueled by rampant racist attitudes.

The obvious interest in coca and cocaine that was increasing in Europe had its counterpart in the United States, where great enthusiasm was developing for the therapeutic potential of this promising new drug. By 1883, for example, the Index-Catalogue of the Library of the U.S. Surgeon-General's Office listed well over 50 scientific papers concerned with the therapeutic potential of coca. Two reports from the Therapeutic Gazette, (in Byck, 1974) an American medical journal devoted primarily to new therapeutic agents which advocated coca use in the treatment of the "opium habit," were to prove especially influential on the work of a young and ambitious Viennese physician -- Sigmund Freud.

FREUD AND COCAINE

Early in 1884 Freud was casting about for an area of research in which he could both make a contribution and attain some success permitting him to marry. He had become interested in coca and cocaine from a variety of reports which had appeared in the literature including those from the Detroit Therapeutic Gazette. Another report which especially impressed him was by a Bavarian army surgeon, Dr. Theodor Aschenbrandt. Aschenbrandt had become interested in the effects of cocaine on humans while at the Wurzburg Pharmacological Institute. Unfortunately, the unavailability of a suitable subject population -- "strong and healthy people, exposed to the greatest exertion, hunger, thirst and the like" -- precluded this work. Later, while on maneuvers with a unit of the artillery, Aschenbrandt seized the opportunity to treat soldiers suffering primarily with exhaustion and diarrhea with cocaine. He found that the stimulating effects of cocaine both on himself and these patients permitted effective functioning despite physical adversity (Aschenbrandt, 1883).

Freud ordered a supply of the new drug, determined to try it on patients suffering from heart disease, "nervous exhaustion" and morphine withdrawal. The latter intent was based both on the favorable reports emanating from America and Freud's concern over the plight of a colleague, Ernst von Fleischl-Marxow. Fleischl, whom Freud greatly admired, had become morphine-dependent as a

result of the use of the drug to treat nerve pain from the stump of an amputated thumb. Upon receiving the drug, Freud tried it on himself and was impressed with its effects both on his mood and his capacity for work. He also offered the drug to von Fleischl whom he later described in a letter (May 7, 1884) to his future wife, Martha Bernays, as having clutched at the drug "like a drowning man" (Jones, 1961).

By July of 1884, Freud's famous paper, "On Coca," had appeared. In it he briefly described the plant, its history and manner of use in Peru citing several authorities who attested to its effects on the Indians, enabling them to withstand great hardship without eating. While mentioning in passing reports that coca's immoderate use was reported to cause "physical and intellectual decadence" together with weakness, emaciation and "moral depravity," he concluded, "but all other observers affirm that the use of coca in moderation is more likely to promote health than to impair it..." (in Byck, 1974).

In his highly acclaimed review of cocaine's history up until that time, Freud cited the work and observations of most of the leading figures including Monardes, Julian, de Jussieu and Niemann. He wrote approvingly of the observations of Paolo Mantegazza as "an enthusiastic eulogist of coca" whose observations struck Freud as essentially accurate. He also reported the drug's effects in warding off hunger, sleep, fatigue and "steeling one to intellectual effort" which he observed in himself and others.

In discussing therapeutic uses he cited the "promise of widespread (therapeutic) recognition and use of coca preparations in North America, while in Europe doctors scarcely know their name." This he attributed to the "doubtful quality" of the preparations available on the Continent, their high price and the initially unfavorable (while in Freud's opinion, unmerited) reports of adverse consequences of use. He went on to list the following therapeutic uses:

a) as a stimulant;

b) for digestive disorders of the stomach;

c) in cachexia (wasting diseases);

d) in the treatment of alcohol and morphine addiction;

e) in treating asthma;

f) as an aphrodisiac; and

g) as a local anesthetic.

The last of these -- cocaine's usefulness as a local anesthetic -- proved to be the only persistently medically useful property of the drug. Ironically, it was with respect to this persistent use of

cocaine that whatever enduring fame Freud sought in his cocaine research was to elude him.

Among Freud's colleagues was a young ophthalmologist, Karl Koller. His particular interest was in a possible local anesthetic for eye Surgery. Such a substance was vital because in much of eye surgery the patient's cooperation is needed, precluding the use of general anesthesia. Moreover, the'general anesthesia used at that time was known to induce post-operative nausea and vomiting, the strain of which could cause damage to the operated eye.

As Freud later related it, he was with a group of colleagues when an intern passed by obviously in pain. Freud offered to help him, explaining to the others that the drug cocaine with which he had been working seemed to have impressive pain relieving qualities. This may have jogged the thinking of Koller, who was in the group and later read Freud's paper. About three months later Koller experimented with a cocaine solution and found it capable of anesthetizing not only the eyes of experimental animals, but his own as well.

Shortly thereafter, another ophthalmologist friend to whom Freud had more directly suggested the possible use of cocaine as an ocular analgesic and anesthetic, independently performed an experiment somewhat similar to Koller's. With Freud's assistance, Leopold Konigstein removed a dog's eye using cocaine as the local anesthetic. His work was reported at a meeting at which Keller's research was also described. It was only later upon learning of Keller's "Preliminary Communication" the preceding month that Konigstein was persuaded with some reluctance to acknowledge the primacy of Karl Keller's contribution (Bernfeld in Byck, 1974).

While others, such as Mantegazza, DeMarles, Moreno y Maiz and Von Anrep, may have anticipated the potential of cocaine as a local anesthetic in eye surgery, it was Karl Koller who is credited with the decisive experimentation leading to this important medical use. Freud apparently took the news well, at least initially, reporting to his fiancee in a letter:

> My second piece of news is pleasanter. A colleague has found a striking application for coca in ophthalmology and communicated it to the Heidelberg Congress where it caused great excitement. . .in any event it is to the credit of coca, and my work retains its reputation of having successfully recommended it to the Viennese. (in Byck, 1974)

Whatever his ultimate lack of credit for a contribution Freud might as easily have made, he and Koller had the satisfaction of assisting when Konigstein operated on Freud's father for glaucoma six months

later using the new anesthetic technique the three had helped develop (Bernfeld in Byck, 1974).

Meanwhile, Fleischl, whom Freud greatly respected, was rapidly transforming himself from the "first morphine addict in Europe to be cured by cocaine" into "the first cocaine addict in Europe" (Bernfeld in Byck, 1974). Whatever the accuracy of that description (it is questionable whether cocaine can be described as "addictive" in the same sense as opiates, for example), Fleischl, who had been using increasing quantities of cocaine by injection, had undergone serious psychological deterioration. He was troubled by paranoid hallucinations very like those of the alcoholic with delirium tremens. Other examples of cases of chronic intoxication were also reported. They, too, were often characterized by hallucinations of animals crawling on, under or digging into the skin.

Freud, who had hoped to achieve a reputation based on his work with cocaine, found himself accused of irresponsibility and recklessness three years after that work began. Erlenmeyer, an authority on addiction, even charged Freud with unleashing "the third scourge of humanity" (after alcohol and opiates) (Jones, 1961). In reply to these charges, Freud indicated that he believed that cocaine was not inherently addictive. He explained that for those already addicted to morphine, their "weakened will power and need for stimulus" led to the abuse of all stimulants. Whatever the ultimate reality, the criticisms stung; he was later to describe that year as "(the least successful and darkest year" of his life (Bernfeld in Byck, 1974).

Following the revelation that some people had become seriously cocaine dependent, increasing anxiety about cocaine's use naturally set in. Among his other optimistic assertions, Freud had indicated in his "Addenda to 'On Coca'" that, "For humans the toxic dose (of cocaine) is very high, and there seems to be no lethal dose." Contrary to this belief, one of Freud's patients died from an overdose prescribed by Freud. By 1891 some 200 reports of systemic cocaine intoxication had appeared, including 13 deaths attributable to the drug (Woods & Downs, 1973).

While the European enthusiasm regarding the therapeutic potential of cocaine was being eroded by reports of adverse effects, interest in America remained high. The work of William A. Hammond, a former Surgeon General of the United States, is of particular interest not only because Freud regarded it as significant enough to cite in his last paper on cocaine, but also because his was among the earliest attempts to determine a dose-response curve for cocaine. Hammond reported favorably on the therapeutic use of the drug in overcoming morphine addiction. He also commended it as a treatment for "nervous prostration, and neurasthenia, general debility, etc." and for treating mental depression (Byck, 1974). Interestingly enough, in reporting on his own response to increasing doses of injected cocaine, he spoke of having "lost consciousness of all my acts within, I think, half an hour after administration of the dose" at higher doses. He also admitted he "came very near taking a fatal

dose and I would not advise anybody to repeat the experiment." Based on his own subjective experience and that of patients he had treated, Dr. Hammond concluded that there was no such thing as a cocaine habit; an individual could readily give up the drug of his own volition (Hammond in Byck, 1974).

William Golden Mortimer, a New York physician, was the Editor of the Pharmaceutical Journal and of the New York Journal of Medicine. A man of impressively wide ranging interests, he published an extensive History of Coca in 1901 (reprinted 1974). This volume summarized the existing knowledge about coca and cocaine. While it must be viewed as the product of an advocate more than a skeptic (the book is dedicated to Angelo Mariani of Vin Mariani fame -- see next page Patent Medicine Era), it is an impressively wide-ranging book and a classic work on the subject. Its topics include not only coca's history, the botany of the plant, its products, chemistry, physiological and therapeutic effects, but also its role in music and in the singer's voice production!

Mortimer (1901; reprinted, 1974) also has the distinction of being among the first clinical investigators to systematically query his colleagues on a large scale regarding the effects of a drug. In 18% he wrote to 5,000 fellow physicians principally teaching in the medical schools of the day, inquiring about their "personal observations upon the uses of Coca." Almost 25 percent responded (1,206). Mortimer's tabulation of these responses provided a systematic resume of the physiological action of the drug, its therapeutic applications and its "food value," as reported by his physician sample. The results were included as an appendix of his book subtitled, "A Collective Investigation Upon the Physiological Action and Therapeutic Application of Coca, Among Several Hundred Physicians."

Perhaps the most significant American medical figure of the late 19th century to become involved with cocaine was the "father of modern surgery," William Stewart Halsted. While Koller was demonstrating the use of cocaine as an ocular local anesthetic, Halsted was developing a technique for using the drug as a "neural block." By injecting cocaine into nerve centers, he was able to produce a regional anesthesia of the area served' by the chemically blocked nerves. In 1884 he began publishing reports of his work, eventually reporting on the results of 1,000 operations of many types using the technique.

Unfortunately, there was one adverse consequence of this work. As a result of his own experimental use, Halsted and several of his assistants became heavily dependent on cocaine. Halsted's habit in particular became sufficiently disturbing to his friends that they spirited him away on a ocean voyage to the Windward Islands in hope of weaning him from his habit. This treatment failed, as did a subsequent period of several months' hospitalization. In a reversal of the usual sequence, Halsted apparently used morphine as a way of "curing" his cocaine dependency. He continued to be morphine dependent until his death in 1922 (Byck, 1974).

COCA, COCAINE AND THE PATENT MEDICINE ERA

The last two decades of the 19th century spawned both a serious interest in coca and cocaine and a relatively uncritical promotion and advocacy of cocaine-containing patent medicines and tonics. In a relatively unrestricted age with modern pharmacology in its infancy, there were few restraints governing the production and sale of remedies containing a variety of what are now regarded as abusable substances.

Given the enthusiasm that cocaine generated in scientists such as Sigmund Freud, it is not surprising that it was actively promoted by commercial interests. It must, of course, be remembered that the prevailing standards did nothing to discourage such comercial exploitation. Such international authorities as Dr. William Martindale -- later president of the Pharmaceutical Society of Great Britain -- were early advocates of the use of coca and cocaine for a variety of specific medical problems as well as in tonics and stimulant drinks. In a widely circulated book, he suggested substituting an infusion of coca for coffee and tea as a means of strengthening the nervous system (Martindale, 1886 in Ahdrews & Solomon, 1975).

Manufacturers of patent medicines, tonics and soft drinks produced a plethora of cocaine-containing products, ranging from ointments, nose powders, suppositories, throat lozenges and sprays to wines and coca cigarettes. They allegedly cured an equally wide range of disorders, including alcoholism, asthma, colds, corns, eczema, neuralgia, opiate addiction and venereal disease (Ashley, 1975).

Internationally, perhaps the most successful advocate and producer of a coca-containing product was Angelo Mariani, a Corsican chemist whose life's work was the development and promotion of coca wine. Of him the physician W. Golden Mortimer, a turn of the century coca authority, was moved to say:

> . . .the wonderful qualities of Coca remained locked as a scientific mystery unsolvable by the multitude, until it was finally released from its enchanting spell as through some magic touch of a modern Merlin." Mortimer, 1901; reprinted, 1974)

Allegedly, in 1863 Mariani, unlike some of his competitors, very carefully experimented with a variety of coca leaves, choosing for his purpose only those which combined the finest flavor with the desired stimulant effect. Whatever his success in developing a better tasting wine, he was clearly successful in its promotion. He published some 13 volumes of testimonials by some of the greatest luminaries of his day attesting to the value of his product. Among

these endorsers were two popes, reigning monarchs of a host of countries, many physicians of prominence and such figures as Anatole France, Henrik Ibsen, H. G. Wells, Jules Verne, Thomas A. Edison and Auguste Rodin (The Mariani Album: 1884-1913; excerpted in Andrews & Solomon, 1975).

Another coca-containing product ultimately destined to become internationally famous was the soft drink, Coca Cola. Along with many other cola drinks of the period (1886-1903), it used the cocaine-containing extract of coca leaves together with other ingredients for flavoring. Originally advertised as a patent medicine when introduced in 1886 -- "a valuable Brain tonic and cure for all nervous affections – SICK HEADACHE, NEURALGIA, HYSTERIA, MELANCHOLY, etc." -- it was later promoted simply as a soft drink. By 1903, the manufacturer abandoned the use of cocaine-containing syrup, resorting instead to a flavoring derived from decocainized coca leaves (Musto, 1973).

An indication of the popularity of cocaine and cocaine-containing products is given by Sir Arthur Conan Doyle's attribution of its use to his famed literary character Sherlock Holmes, who used it as a stimulant when bored by the lack of challenging cases.

THE END OF AN ERA

In view of the uncritical enthusiasm with which coca, cocaine and their products were initially embraced by some physicians and laymen, a reaction was probably inevitable. As with more recent "wonder drugs," initial widespread acceptance was increasingly tempered by the recognition that cocaine had undesirable side effects and could pose a serious health hazard. While originally considered relatively safe, it became apparent that cocaine created dependence in susceptible individuals, and that toxic psychosis and death could result from heavy injudicious use. Fleischl, who was among the first to manifest symptoms of cocaine abuse like those of alcoholic delirium tremens, was not the last; while deaths through self-administration were rare, there was an increasing frequency of deaths from medically administered overdoses and/or unusual susceptibility to the drug's effects. As Freud had observed earlier, there were marked individual differences in response to varying doses of the drug and this appeared to be true of its toxic effects as well.

Another important factor in the restriction of cocaine use was a reaction to the excesses of the patent medicine era. One has only to peruse an early edition of a Sears, Roebuck catalog to realize that patent medicines promised cures to diseases that have yet to be conquered. . .and Sears was relatively conservative in its advertisements! (Sears, Roebuck and Company, 1902; reprinted 1969) It was becoming clear that some degree of government control was necessary to curtail the indiscriminate inclusion of opiates and cocaine in over-the-counter medicines and tonics.

The beginning of the 20th century marked another important trend. American medicine, characterized by relatively lenient professional standards until that time, was coming of age. Prior to the 20th century, a medical degree was easily obtained, even in the best medical schools. While still in its infancy, the American Medical Association became increasingly concerned with establishing and maintaining higher standards of medical training and practice. Pharmacists were also becoming more professional. While it has been argued that physicians and pharmacists had an economic interest in curbing patent medicine sales (Ashley, 1975), ethical concern over the dangers of self-administration -- including the use of dependency-producing proprietary medicines -- was also a factor.

"Muckraking" writers and journalists, bent on social reform, included the patent medicine manufacturers in their targets, labeling them as irresponsible.

One of the reprehensible factors in curbing the use of cocaine and of cocaine-containing preparations in the period from 1900 to 1920 was the spector raised by the mass media of cocaine-crazed blacks committing heinous crimes. Even such "respectable[n] sources as the Journal of the American Medical Association published accounts of blacks becoming addicted to "a new form of vice" and indulging in a "coke drunk" (The cocain (sic) habit, JAMA, 1900). Articles in the popular press, including the New York Times were less restrained. Thev reported that cocaine resulted in mass murders by "crazed (black) cocaine takers" whose marksmanship was markedly improved by the drug. It was also alleged that use of cocaine imparted "temporary immunity to shock -- a resistance to the 'knock down' effects of fatal wounds." The drug was accused of being a "potent incentive in driving the humbler negroes all over the country to abnormal crimes (Williams, 1914 in Ashley, 1975). The same article asserted that "Most attacks upon white women of the South...are the direct result of coke-crazed negro brain." Whatever the incidence of cocaine use among convicted felons -- and an examination of objective evidence suggests there was little -- myths of this type were potent in swaying public opinion.

State after state passed laws prohibiting or restricting the distribution of cocaine in some manner. By the time the Federal Harrison Narcotics Act of 1914 was passed, 46 of the 48 states had passed similar legislation. Obviously cocaine was viewed as a greater threat than the opiates; only 29 states had laws regulating the latter (Ashley, 1975)

In a detailed review of the legislative history of cocaine regulation, McLaughlin traced a trend started by many states which required manufacturers, distributors, physicians and dentists to keep records of their cocaine dispensing. These early laws typically made unauthorized possession of cocaine a misdemeanor. Under these laws, patent medicine manufacturers were usually permitted to include limited amounts of opiates or cocaine in their products McLaughlin, 1973).

On the Federal level, legislative inroads were also being made into the unrestricted use of cocaine. The Pure Food and Drug Act of 1906 had some impact on the marketing of proprietary remedies containing cocaine by requiring that such ingredients be listed on the product label. In practice this legal requirement was sometimes ignored, since the penalties for non-compliance were modest, but it increased the likelihood that the wary consumer could avoid cocaine-containing products.

The Harrison Narcotics Act of 1914 was the first major Federal legislation to significantly restrict the availability of coca and cocaine and sounded the death knell for its inclusion in patent medicines. The Act required registration with the Internal Revenue Service of those involved in the importation, manufacture, distribution or dispensing of opium, coca or their derivatives and that careful records of their transfers be kept. Use of cocaine in proprietary medicines was specifically forbidden.

This act was important not only as a precedent, but also because it invoked sufficiently strong penalties (fines of up to $2,000 and prison sentences of up to five years for violators) to discourage violation.

Subsequent legislation (in 1922) amended the Harrison Act to increase the penalties for violation (up to a $5,000 fine and 10 years imprisonment) and to define (erroneously, from a pharmacological standpoint) cocaine as a narcotic. Nevertheless, the pattern had been set; henceforth, cocaine was legal only for restricted medical uses.

Additional legislative amendments (in 1951 and 1956) to the Harrison Act and to a companion piece of legislation, the Narcotic Drugs Import and Export Act (which prohibited export of cocaine to countries lacking import regulations)' further increased penalties and established increasingly severe mandatory minimum sentences for violations.

Later state laws were based on the Uniform Narcotic Drug Act -- originally promulgated by the Commissioners on Uniform State Laws in 1932 -- which, in turn, followed Federal precedent. This act was adopted by almost all the states, with the exceptions of Pennsylvania and California (New Hampshire and Montana repealed their versions in 1967).

Earlier legislation on the Federal level was replaced in 1970 by the Comprehensive Drug Abuse Prevention and Control Act which categorized drugs in schedules according to their uses and potential for abuse, required registration of those involved in the production and distribution of controlled substances, and established import, export and production limitations on these substances. A new model, the Uniform Controlled Substances Act, was drafted by the Commissioners on Uniform State Laws to replace the earlier Uniform Narcotic Drug Act on the state level. Like the earlier act, it was patterned after the Federal legislation.

In both the Federal and model state legislation, cocaine was placed in Schedule II, the category for drugs with an acceptable medical use, but with high potential for abuse. (Schedule I consists of drugs with no recognized medical use, such as heroin; the other schedules include drugs with progressively lower potential for abuse.)

POST-REGULATORY COCAINE USE

With the passage of the various Federal and State laws making all but restricted medical use of cocaine illegal, use patterns markedly changed. Unfortunately, even before the introduction of regulation, it was difficult to determine what proportion of the population used the drug. Many used it inadvertently in patent medicines. During one two-year period late in the patent medicine era there was a five-fold increase in the amount of cocaine or coca leaf imported. (In 1904, a cocaine yield of 4,125 pounds could be obtained from the amount of cocaine and coca leaf imported. By 1906 the cocaine yield from the increased amount of coca leaf imported had jumped to 21,000 pounds.) To what extent this increase represented an increased number of users, increased use by a relatively constant number of users, or some combination, is unknown.

The combination of increasingly adverse publicity regarding the use of cocaine and specific legislation making it illegal effectively removed it from respectability. Widespread use by a broad spectrum of society became use by a more "bohemian" set, such as jazz musicians, actors, actresses and other members of the cultural "avant garde." Use also continued among affluent drug dealers in the ghetto.

As with other periods, it is difficult to describe with any precision the extent of cocaine use between the time of World War I and its present re-emerging popularity. With the change in its legal status, cocaine became quite expensive, making it affordable to only an affluent minority. The drug's prevalence among popular musicians is indicated by the number of songs in which it figures prominently. Perhaps the best known of these is the original lyric from the Cole Porter musical of 1934, Anything Goes, for the song "I Get a Kick Gut of You":

I get no kick from cocaine
I'm sure that if
I took even one sniff
It would bore me terrifically too
But I get a kick out of you.

Use in the movie colony in Hollywood is indicated by a number of contemporary accounts although, again, the extent of such use is in some doubt. It has been widely reported that during the Nazi period in Germany, some of the prominent members of the party, including Field Marshal Herman Goering, were users of cocaine (Ashley, 1975).

By the early 30's, the availability of amphetamines together with the continued high cost of illicit cocaine reduced its popularity even further. Although legal seizures of a drug are but imperfect indicators of its use, it is noteworthy that only six pounds of cocaine were seized by the Federal Bureau of Narcotics in 1960. By 1968 seizures by its successor agency had climbed to 63 pounds and by 1971 to 436 pounds.

The combination of a new affluence and a greatly increased interest in drug use in the late 1960's and early 1970's resulted in a renascence of interest in cocaine as the status drug. Evidence for this is provided by accounts of the drug use in the mass media, its importance in such films as Easy Rider (released in 1969) and Superfly (1972), a spate of books and articles dealing with cocaine, and the re-emergence of cocaine-related songs.

By the 1970's a variety of local and national surveys (cf. Overview) provided somewhat more data on the extent of cocaine use.

Robert C. Petersen, Ph.D.
Division of Research
Rational Institute on Drug Abuse

REFERENCES

History of Cocaine

Andrews, G. and Solomon, D. (eds.) The Coca Leaf and Cocaine Papers. New York, NY: Harcourt Brace Jovanovich, 1975.

Aschenbrandt, T. Die Physiologische Wirkung und Bedeutung des Cocain auf den Mehschlichen Organisms. Deutsche Medizinische Wochenschrift, 50:730-732 (1883), reprinted in Byck, R. (ed.), Cocaine Papers: Sigmund Freud. New York, NY: Stonehill Publishing Co., 1974.

Ashley, R. Cocaine: Its History, Uses and Effects. New York, NY: St. Martin's Press, 1975.

Bentley, W.H. Erythroxylon coca in the opium and alcohol habits. In Byck, R. (ed.), Cocaine Papers: Sigmund Freud. New York, NY: Stonehill Publishing Co., 1974, pp. 15-19.

Bernfeld, S. Freud's studies on cocaine. In Byck, R. (ed.), Cocaine Papers: Sigmund Freud. New York, NY: Stonehill Publishing Co., 1974, pp. 321-352.

Byck, R. (ed.) Cocaine Papers: Sigmund Freud. New York, NY: Stonehill Publishing Co., 1974.

The cocain (sic) habit. Journal of the American Medical Association, 34:1637 (1900).

Gagliano, J. A social history of coca in Peru. Unpublished doctoral dissertation, Georgetown University, Washington, DC, 1960.

Grinspoon, L. and Bakalar, J.B. Cocaine: A Drug and Its Social Evolution. New York, NY: Basic Books, 1976.

Guttmacher, H. New medications and therapeutic techniques. Concerning the different cocaine preparations and their effect. In Byck, R. (ed.), Cocaine Papers: Sigmund Freud. New York, NY: Stonehill Publishing Co., 1974, pp.120-125.

Hammond, W.A. Coca: Its preparations and their therapeutical qualities with some remarks on the so-called "cocaine habit." In Byck, R. (ed.), Cocaine Papers: Sigmund Freud. New York, NY: Stonehill Publishing Co., 1974, pp. 177-193.

Jones, E. The Life and Work of Sigmund Freud. Volume I. New York, NY: Basic Books, 1961.

Mantegazza, P. On the hygienic and medicinal virtues of coca. In Andrews, G. and Solomon, D. (eds.), The Coca Leaf and Cocaine Papers. New York, NY: Harcourt Brace Jovanovich, 1975, pp. 38-42.

Martindale, W. Coca, cocaine and its salts. In Andrews, G. and Solomon, D. (eds.), The Coca Leaf and Cocaine Papers. New York, NY: Harcourt Brace Jovanovich, 1975, pp. 43-49.

McLaughlin, G.T. Cocaine: The history and regulation of a dangerous drug. Cornell Law Review, 58:537-573 (1973).

Monardes, N. Joyful1 Newes out of the Newe Founde Worlde. Translated into English by J. Frampton. New York, NY: Alfred Knopf, 1925.

Mortimer, W.G. History of Coca The Divine Plant of the Incas. 1901, reprinted, San Francisco, CA: And/Or Press, 1974.

Musto, D. The American Disease--Origins of Narcotic Control. New Haven, CT: Yale University Press, 1973.

Sears, Roebuck and Company. The 1902 Edition of the Sears Roebuck Catalogue (Facsimile). New York, NY: Bounty Books, 1969.

Williams, E.H. Negro cocaine "fiends" are a new southern menace. In Ashley, R., Cocaine: Its History, Uses and Effects. New York, NY: St. Martin's Press, 1975.

Woods, J.H. and Downs, D.A. The psychopharmacology of cocaine. In Drug Use in America: Problem in Perspective. Appendix Volume 1: Patterns and Consequences of Drug Use. Washington, DC: U.S. Government Printing Office, 1973, pp. 116-139.

Chapter II
COCA: THE PLANT AND ITS USE

Eleanor Carroll, M.A.

COCA AND HEALTH

Extent of Use -- Past and Present

At the time of the Inca, use of coca was confined, according to many historians, to the royal family, and to certain favored others -- for example, courtiers, court orators, and members of the army during battles. It is impossible to say how much coca was produced or consumed during this time, but there is abundant evidence from many sources, that it was considered to be an extremely important, even precious crop.

Contemporary observers, at the time of the Conquest, commented on the gold representations of the coca plant in the special gardens of the Inca in Cuzco. From the same Inca period (AD 800-1000) come numerous examples of small spoons or spatulas for extracting the lime added to coca leaves) made of bronze, silver or gold, with miniature figures of men or animals on the handles. Even before the time of the Inca the quality of the grave goods from various archaeological sites attest to the supreme value placed on coca by higher classes of society. The Moche period (AD 200-700) has yielded up valuable figured gold bags for coca leaves, and containers for lime made of precious metals come from the coastal Tiahuanaco period (AD 800-1000).

The Spanish conquerors made an early, and unsuccessful attempt to eliminate the use of coca, because of its prominence in native religious ceremonies. They soon became not only reconciled to its use but even exploiters of the plant. Use was no longer confined to the nobility; as soon as the stimulating effects of coca on work production were recognized, hacienda owners took full advantage of the fact and put more and more land into the production of coca. Sixteenth Century chroniclers report that many Spaniards became extremely wealthy simply from the yields of their coca plantations. To meet the need of more land for coca production, the Spaniards extended their subjugation efforts even to primitive forest Indians who had not succumbed to Inca domination. Even the Church, which had initially been so opposed to coca production and use, saw its economic value, and initiated and maintained coca plantations of its own.

It was also, shortly after the time of the Conquest that the custom of giving workers coca as part of their wage began. This custom persists to this day, both on the part of major employers (for example mining companies and major hacienda owners) and on the part of small farmers who have assembled a group of their neighbors for cooperative farming activities.

At the time of the Inca, production of coca had spread as far north as the Isthmus of Panama and the Caribbean, and as far south as Chile. During the latter half of the 19th century, when the use of cocaine for various therapeutic purposes had come to be recognized, production of coca was introduced into Java, Ceylon and even the island of Jamaica.

Today, most of the coca which is legally produced comes from Peru and Bolivia, although there is still extensive illegal cultivation and use in Colombia, parts of Argentina, Brazil and some parts of Ecuador. Concern about illegal channeling into the production of cocaine is centered in Peru, Colombia, Bolivia and Ecuador. Neither Peru nor Bolivia has ever outlawed the production of coca, although in Peru efforts have been made to confine its production to certain departments. In Bolivia the abolition of large estates after the Bolivian agricultural reform of 1953 led to a temporary reduction in coca production because of neglect of the estates during the transition and because the government forbade the planting of new coca fields. However, the agricultural workers who had become independent ignored the government decree and extended the area of cultivation in order to keep up with increasing demand.

According to figures submitted by the Peruvian Government to the United Nations Fund for Drug Abuse Control in December, 1975, production of coca is authorized in 11 of the 24 Peruvian Departments. These departments are Amazones, La Libertad, Cajamarca, San Martin, Ancash, Junin, Cuzco, Puno, Ayacucho, Apurimac and Arequipa. Approximately 17,500 authorized growers of coca are distributed over 16,000 hectares of territory. These growers produce almost 10,000,000 kilos of coca annually. About 57 percent of production comes from the Department of Cuzco. The government estimates that about 6,000,000 kilos of coca are consumed locally by approximately 900,000 persons.

In Peru, as well as Bolivia, the primary coca producing and consuming countries, comparatively little is known about the ways coca is ingested or its distribution of use across racial, ethnic, social class and occupational categories. The bulk of Indian users continue to employ coca as a masticatory, while most of the mestizo and criollo users ingest coca in the form of a tea, as either a refreshing beverage or as a treatment for a variety of ailments. For a long time, the conventional wisdom asserted that coca chewing was confined to Andean Quechua-speaking Indians, and that Indians living in a tropical environment did not use it. There is now increasing evidence that even lowland Indians chew coca. In addition, of course, an unknown amount of coca is used by the Indians in teas, or for poultices, etc. Current findings indicate that mestizo farmers in the Peruvian coastal areas below Arequipa

chew coca, as do truck drivers, fishermen, and stevedores in various parts of the country. In Cuzco, coca is chewed by some mestizo and criollo intellectuals and artists. Coca tea is dispensed in many tourist hotels in Cuzco to help guests cope with the difficulties of altitude sickness ("soroche"). Coca is currently being packaged in tea bags in Lima and simply marked as "refreshing tea."

Bolivia is another principal producer of coca. For a while, during the latter part of the 19th century, when cocaine was extensively used in various therapeutic preparations, the coca leaf of Bolivia was prized above that of Peru because of the higher cocaine alkaloid content.

There are no exact figures on the overall amount of coca being produced in Bolivia nor on the number of acres under cultivation, according to Bolivia's December, 1975 statement to the United Nations Fund for Drug Abuse Control. Coca production is legal in all department of Bolivia, but most of the production is confined to the subtropical, humid valleys of the Yungas (north of La Paz), to Chapara in the Department of Cochabamba, and to Yepecani in Santa Cruz.

According to estimates produced for the U.S. Embassy in Bolivia in 1975, more than half of the native population of about 5 million are coca consumers -- in other words at least 2-3 million persons. About 7,000 metric tons are consumed legally within the country each year, and at least 2,000 metric tons are exported legally each year.

The actual number of consumers of coca in Bolivia is a matter of more than purely academic interest, since the Bolivian Government is on record as having no intention of doing away with the indigenous consumption of coca. However, it is firmly committed, with the aid of United States agricultural experts, to reducing the overall coca production to levels consonant with traditional use and to experimenting with substitute crops to determine the potential contribution of these crops to the overall economic well-being of the country.

There is almost no material in the literature about the process of socialization into the use of coca, particularly in the case of children. We do not know at exactly what age a child is socialized into the use of coca; whether male and female children are socialized at the same, or different, ages, in the same ways; or, indeed, whether and how many females use coca at all. The differential use of coca by the sexes varies not only from one country to another, but even from one region to another within the same country.

It is safe to assume that there is postponement of the use of coca as a masticatory until adolescence or later, a time which will correspond to the assumption of adult role and occupational responsibilities. Among the variety of uses to which coca, in various forms, is put, certainly one of the preeminent is its use as a work adjunct (as a stimulant) and this fact would dictate that full use would coincide with the beginning of mature work patterns.

Not enough work has been done so far on the crucial distinctions between the varying types of role allocations and role responsibilities, and the amount of coca which might be consumed in carrying out one's duties. It is especially necessary to break down any occupational role into the component parts tied to specific functions, and to determine -- both from observation and from interviews with users themselves -- what they consider the appropriate amounts of coca to be used by members of both sexes, by persons with varying degrees of responsibility and so on. Similarly, it is also necessary to ask such questions as what kinds of coca are to be used and how the respondent chooses the leaves he/she is going to buy. some initial efforts have been made to account for the differences in the way volume is conceived and measured by the Indian population and by official investigators.

In any consideration of drug use (whether natural or synthetic) it is essential that the fullest possible description be given both of the material and of the method of ingestion. It is not necessary to go into a botanical description of the coca shrub and of its many species (estimated to be about 250) here. About 24 of these 250 are known to grow in Peru. The two domesticated species most widely cultivated in Peru are Erythoxylon coca and Erythoxylon novogranatense var truxillense, usually called Truxillo coca. Huanaco coca, from Bolivia, was preferred by 19th century manufacturers of cocaine-based products because it is much richer in cocaine alkaloids.

It is interesting to note, however, that from the 18th century onward, travelers have commented on the fact that the Indians, given a choice of leaves for chewing, always rejected those leaves with the heaviest concentration of the cocaine alkaloid, since those leaves have a bitter taste. They much preferred leaves which are richer in aromatic alkaloids. Unfortunately, some modern studies do not distinguish between the various types of coca, and almost all research to date has concentrated solely on the cocaine alkaloid; the other 13 known alkaloids in the leaf have been neglected almost completely.

Martin (1975) has noted that the process of masticating coca -- termed "chaccar[n]" or "acullicar" in Peru and Bolivia -- is essentially the same now as it was in the time of the Incas. The Indian carries the coca leaves (in a woven sack) with him carefully choosing several leaves to chew until they form a sort of quid (the acullico), which is held between the mouth and gums. Then an alkaline mixture is inserted into the wad of leaves. This alkaline mixture -- known as, "llipta," "tocra," or "mambe" --varies from one region to another, depending on the materials available. It can be made up of quick lime, ashes obtained from burning the stalks of the quinoa plant, or bark from certain trees. This alkaline mixture is carried in a separate container, quite frequently a gourd ("ishcupuru" in Peru; "poporo" in Colunbia), an ancient method represented in the grave goods at pre-Incan burial sites. The present day Indians usually use a moistened stick to dip into the alkaline mixture and moisten the coca quid with it; in earlier times, these

spatulas were themselves often made of precious materials and extensively decorated. Great care must be exercised to prevent this caustic material from touching the lips or gums, as some novices have learned to their sorrow. Apparently this alkaline mixture facilitates the release of the active alkaloid principles of the coca. The leaves and alkaline mixture is kept in the mouth, and the juice trickles into the stomach. Although the term masticate is used to describe the process, it is not strictly accurate to say that the Indians chew the leaves. It might be added that this admixture of a lime substance to a plant drug is not confined solely to the use of coca -- it is also the practice of many betel nut chewers.

There are some variations on this method of preparing and using coca leaves. Some small Indian groups in Colombia (in the areas bordering on Brazil), as well as some Brazilian Amazonian Indians, do not use the leaves until they have been pounded into a fine powder. The ashes of burned alkaline substances are then added to this powder before putting it into one's mouth.

The supposedly noxious effects of coca chewing attributed to it by some observers, have succeeded in giving the coca leaf a reputation only slightly less abhorrent than that of cocaine. However, even cocaine does not produce withdrawal symptoms similar to those produced by narcotics. Coca leaves were employed by the Indians for over 2,000 years prior to cocaine's discovery without any notable toxic effects. The reports of overindulgence in coca leaves are few and far between in the literature. No clinical disease is directly attributable to coca chewing; even the withdrawal syndrome is relatively mild. Indians of the Sierra, when drafted into military service, where use of coca is forbidden, give it up without any noticeable ill effects.

In the last several decades, an increasing number of authors have asserted that a variety of pathological defects can be attributed to coca chewing, including hyponutrition, ocular disturbance, enlarged thyroid glands and lymph nodes; yet, for each of these assertions, an equally well-trained observer has claimed just the opposite.

From the standpoint of health, we lack research which will fit the coca shrub into the overall folk pharmacopoeia of the country. (It is estimated that in Bolivia alone there are more than 5,000 different plants, each with its assigned role in the folk medicine of the country.) We need an investigation of medical folklore -- the reasons assigned to various kinds of illnesses, and the way in which the Spanish notions of hot and cold (in relationship to both the origin and the treatment of various ailments) have been tied into the pre-Conquest beliefs of the Indian populations. Further, there have been no studies, in either Peru or Boliva which examine the beliefs and attitudes toward coca and coca chewers of a cross-section of the populations of these countries.

Coca is only one of the many indigenous psychoactive drugs presently used by large portions of the population in various Latin American countries, particularly Mexico, Ecuador, Peru and Brazil. Although use of such drugs is most characteristic of the rural, primarily

Indian, sections of the countries, use is spreading to the more urbanized areas. This extension of use is due in great part to the fact that many of these drugs (for example, ayahuasca and San Pedro cactus) are used by native curers (curanderos) in their healing ceremonies. Curanderos are patronized in the towns not only by Indians, but by mestizos (i.e. those of mixed Indian-Spanish origins) as well.

There are tremendous difficulties attendant upon the initiation of research in this area, beginning with the choice of sample and control subjects to be studied. If the study is to be undertaken in the high Andes region, traditionally the area of greatest coca consumption, it may be difficult to find control subjects who are not users. Extreme poverty, malnutrition, and inadequate health care are characteristics of the inhospitable ecological regions where these heavy coca chewers live. These conditions make it difficult to factor out the possible causal effects of coca chewing on poor physical health. Further, most ethnographic evidence indicates that coca chewing increases with age, so this is another confounding factor. Possibly the most difficult correlative factor to control for is alcohol use. Heavy users of coca also tend to be heavy users of alcohol (usually an indigenous type of beverage, fermented rather than distilled). Alcohol, as well as coca, is consumed at major and minor fiestas. There is, indeed, some slight indication that as Indians become acculturated to the meztizo way of life, particularly in cities, that they may increasingly turn to alcohol as a substitute, rather than as a supplement to coca use.

COCA AS A THERAPEUTIC

Coca is one of the most important, if not the most important of all drugs in the folk pharmacopeia of the Altipano. The Indians use the term "mamita kukita" (little mother coca) to describe the coca plant, and this sobriquet gives eloquent expression to the essentially protective and comforting role they assign to the drug. The role, of course, has many facets.

The most widely publicized function of the drug is its energizing capacity; that is, its ability to reduce muscular exhaustion and alleviate hunger and thirst. The Incas recognized this quality, and distributed coca leaves to their "chasquis" (relay messengers) as well as to soldiers.

The Incas believed that coca could stimulate mental as well as physical activity, and the "varavecsw (court orators), who served as the repositories of Incan history in the absence of written records, were among the privileged few allowed to chew coca. Some present day Peruvian commentators, however, not only completely reject the idea of coca as a spur to mental production, but go so far as to say that it impedes cerebral activity.

from the 16th century onward, foreigners have commented extensively on the incredible ability of the Peruvian Indians of the Sierra to

travel along narrow mountain paths while bearing heavy burdens, sustained only by an occasional "acullico," or chew of coca. These Indians are even accustomed to measuring the length of a journey by the hours that one chew of coca will sustain them -- a period of time called the "cocada" (about 45 minutes).

Coca is equally important to the routine work of the Indians either on the farm or in the mines. The Spanish conquerors recognized the stimulating quality of the drug soon after the Conquest and, devil or not, they began to employ it extensively and brutally. They sometimes forced the Indians to work unbelievably long hours -- up to 48 hours at one stretch -- without any food or rest. Work in the Potosi mines of Bolivia was so terrible that many Indians committed suicide when told they were being sent to work there.

An insightful article about the miners and their lives underground by June Nash (1972), an anthropologist, explains that coca is used not only as an energizer, but also as an important ingredient in religious and magic rituals. According to the article, coca use is inextricably intertwined in the daily lives of these Aymara Indians.

The miners believe that a pre-Christian ogre "Huari," lives in the hills where the mines are located, and he is venerated in the form of the devil, or Tio. They are convinced that Huari alone knows the location of rich veins of ore and that he will lead persons who sacrifice to him to those veins. Not only can the Tio reveal, or withhold, the knowledge of rich veins; he can also cause accidents to those who fail to placate him with proper offerings.

Miners make images of the Tio (the features may differ, but the body is always made of ore) and place them in niches cut into the walls of the mine, where the miners rest. Hands, face, arms and legs are shaped of clay from the walls of the mine, and the main feature of the figure is always an enormous mouth into which offerings are placed. Coca remains are placed there; his hands grasp bottles of alcohol and his nose is burnt black by lighted cigarettes. Every Friday the workers make a ceremonial offering, a "ch'alla," to the Tio, composed of coca, cigarettes and alcohol. Here, too, the beneficial effects of coca are also recognized because the miners say that coca is a gift of the Pachamama (a deity who precedes the Incas) to help them in their work.

In the rituals of the ch'alla and the even more elaborate "k'araku" (involving the sacrifice of llamas in addition to the offerings of coca and "chicha") after deaths caused by mine accidents, Tie's power to destroy is transformed into the socially useful function of increasing mineral yield, giving at least some peace of mind to the miners.

Coca is very important to the Indian farmer who also practices special rituals involving the use of coca for the specific tasks of farming (e.g., sowing, weeding, harvesting, house building). The Indians almost universally regard coca as a food, although this does not mean that they choose to subsist exclusively on coca, as has sometimes been alleged.

Some modern observers have condemned the use of coca, alleging that it simply anesthetizes the feelings of hunger without contributing in any way to nutrition. In fact, some of these observers attribute malnutrition to the use of coca. Other observers, however, point out that chemical analysis of coca leaves has shown that they are relatively rich in vitamins, particularly vitamin B1, riboflavin and vitamin C. Approximately 2 ounces of coca leaves (an average daily amount) contains almost the minimum daily vitamin requirement, an important point, they have argued, in view of the great shortage of fruits and vegetables (particularly fresh vegetables) in the Sierra. Many Indian farmers in the Altiplano subsist today, as they have for centuries, on a diet consisting primarily of varieties of dried and frozen potatoes, very small amounts of dried meat (something like jerky), and roasted maize and barley.

Some 19th century observers stated that coca assisted in the assimilation of other foods, by increasing the flow of saliva and gastric secretions and giving strength to the muscles of the gastro-intestinal tract. Whatever the validity of this observation, it is noteworthy that even today, throughout a great part of South America, an infusion of coca leaves is regarded as a sovereign remedy for indigestion and stomach complaints. A decoction of the leaves, drunk regularly, allegedly guards against bowel laxity, while a powder of the leaves, drunk with salt and egg white, is used in the treatment of ulcers.

Coca continues to be used to relieve the pain of rheumatism and external sores. In the 16th century, indigenous practitioners employed coca to reduce the swelling of wounds and to strengthen broken bones. It is widely believed that coca served as a local anesthetic in skull trephining in pre-Conquest times. Coca seeds employed in vapors are used to stem nose bleeds, while powdered coca taken in tea' with sugar is used for asthma. One 19th century scientist pointed out that Bolivian Indians, employed in collecting cinchona bark in the forests of Bolivia, were inclined to rely more heavily on coca for the treatment of malaria than on the malaria-specific antidote, quinine-containing cinchona bark.

Coca is also employed by the Indians not only to prevent but also to treat disease of the teeth and gums -- an effect attested to by many European observers. Masticated coca leaves are used as a poultice for the treatment of sore eyes. For headache, in addition to the tea made of an infusion of coca leaves, a poultice of chewed leaves is placed on the patient's forehead. Coca ia also used to ease uterine contractions in childbirth.

Coca is esteemed by the Indians as an aphrodisiac, and is reputed to insure longevity with unimpaired sexual powers. Nineteenth century observers commented on the incredible longevity of some Ecuadorean Indians, with life spans stretching up to 100 years or more.

One aspect of health in relation to coca which has rarely been mentioned is psychic. health; that is, what is the contribution of coca to the psychic well-being of the Andean populations? Coca is used to diagnose disease, to divine the future, to placate irate

spirits; in other words, to give an individual some sense of control in a hostile and threatening world. Only now are the importance of studies which would delineate the role of coca in the maintenance of mental health beginning to be appreciated, and there have been some small beginnings in this area.

During the latter part of the 19th century, U.S. physicians experimented widely with many coca preparations, as they had with cannabis preparations. Coca was used in the treatment of a variety of ailments, including neurasthenia (nervous exhaustion), depression, nervous disorders, stomach disorders and throat infections. Then, all coca preparations fell under a cloud, not only because of the growing reluctance to depend on herbal remedies, but also because coca was increasingly identified with cocaine and that substance's toxic effects.

The history of coca is, in many ways, strikingly similar to that of cannabis. Although, of course, the provenance of the shrub Erythoxylon coca is more circumscribed than that of cannabis, and coca history -- so far as is known at the present time --is of much shorter duration, coca is, in many ways, a multi-purpose drug as is cannabis. It is a plant deemed by its indigenous users to be of divine origin because of its miraculous properties, which is the way cannabis was regarded both in India and China. It is a plant which has been used, and continues to be used, in religious rituals, just as cannabis is in many parts of India and Pakistan; it is a basic ingredient in fiestas, as cannabis was, for example, in celebrations of the harvest in Poland, Hungary and parts of Russia well into this century. It is the basic ingredient in the folk pharmacopeia -- a sort of all-purpose drug -- similar to the role of cannabis in India, parts of Pakistan and Jamiaca, to name but a few countries. Coca has always been employed as an energizer, as a work adjunct, as a motivator for undertaking and continuing arduous types of jobs, which is, indeed, the way ganja is used today in Jamaica, bhang in India and cannabis among some Brazilian Indians.

Coca also resembles cannabis in the variety of methods of ingestion which can be employed in its use, with the sole exception of smoking. Coca is ordinarily used as a masticatory, and the user keeps coca leaves, along with "llipta," in his mouth. However, in some parts of Colombia, for example, the coca leaves and the ingredients of the llipta are ground together into a very fine powder, and it is the powder which is placed in the mouth. In some parts of Brazil, coca is mixed with "cassava," (a bread), which is strongly reminiscent of cannabis' traditional use for food preparation in, to cite only one example, Nepal. In several parts of the world, coca is used externally in the form of poultices, as is cannabis for example, to treat aching teeth.

Less is known about the chemical properties of coca than about cannabis. Of the 14 alkaloids known to be contained in the plant, almost all the research to date has concentrated only on the cocaine alkaloid, despite the fact that as early as the late 19th century, there were calls to investigate the alkaloid cuskohygrine.

There are other ways, of course, in which coca and cannabis resemble each other, as there are ways in which coca resembles other widely used indigenous drugs. For example, coca still serves as a medium of exchange, as does opium in many parts of the Golden Triangle; it is like khat, from Yemen, in that it is always a part of celebrations; it is like peyote from Mexico in that it is still widely used as a method of divination. from the standpoint of the Indians who use it, it is not accident that the coca plant has been given a divine origin and attributes, since it is used for so many purposes -- therapeutic, religious, recreational, occupational, and economic.

Eleanor Carroll, M.A.
Division of Research
Rational Institute on Drug Abuse

REFERENCES

Coca: The Plant and Its Use

Grinspoon, L. and Bakalar, J.B. Cocaine, A Drug and Its Social Evolution. New York, NY: Basic Books, Inc., 1976.

Gutierrez-Noriega, C. and Zapata Ortiz, V. Estudios sobre la Coca y la Cocaina en el Peru. Lima, Ministero de Education Publica, 1947.

Hanna, J.M. Coca Leaf Use in Southern Peru: Some Biosocial Aspects. American Anthropoligist, 76:281-296 (1974).

Martin, R.T. The role of coca in the history, religion and medicine of South American Indians. Economic Botany, 24, (1970). In Andrews, G. and Solomon, D. (eds), The Coca Leaf and Cocaine Papers. New York, NY: Harcourt Brace Jovanovich, 1975.

Metzger, D. Personal communications. (5 ROl DAO1257. Quechua Use of Erythoxylon Coca in Southern Peru).

Murphy, H.B.M., Rios, O. and Negrete, J.C. The Effects of Abstinence and Retraining on the Chewer of Coca Leaf. Bulletin on Narcotics 21(2):41-47 (1969).

Nash, J. Devils, Witches and sudden death. Natural History, 71(3):52-60 (1972).

Chapter III COCAINE: THE MATERIAL

Richard Hawks, Ph.D.

Cocaine and its companion alkaloids are found in the leaves of the shrub Erythroxylon coca, a plant whose principal habitat is western South America. Trace amounts of the alkaloid have been isolated from other species of 'the Erythroxylon genus (Willaman & Schubert, 1961), but the major source is the E. Coca species, principally found in Bolivia and Peru.

The cocaine alkaloid itself makes up about 0.5-1.0 percent of the dry weight of the plant material (DeJong, 1974; Aynilian et al., 1974). Several other related alkaloids are also present in the coca leaf and may contribute to the leaf's pharmacological properties (Martin, 1975). These constituents apparently do determine the quality of the leaf for the chewing consumer. Leaf choice is made on the basis of smell and taste, but these factors do not correlate with the actual cocaine concentration in the leaves (Martin, 1975; Mortimer, 1901, reprinted 1974). Plants cultivated for harvest are kept pruned to a height of 3-6 feet, convenient for picking. The elliptical leaves, which vary from 1 to 4 inches in length, can be harvested several times a year since the plant is an evergreen.

Although estimates vary significantly, it seems that approximately one-half of the harvest is consumed by inhabitants of coca growing countries. The role coca plays in the life and health of these users is a matter of some controversy Martin, 1975; Mortimer, 1901, reprinted 1974; Burchard, 1975). The rest of the crop is exported to the United States and Europe for the production of cocaine for pharmaceutical use. In Peru a portion of the harvest is used in legally sanctioned laboratories to produce cocaine for export but no legitimate laboratories for cocaine production exist in Bolivia.

Only one company in the U.S. is licensed to import coca leaves. This company produces all the pharmaceutical cocaine used in the U.S. (approximately 410 kg in 1976 Streit et al., 1976) while at the same time producing the "decocainized" resin extract from the leaf which is used in the production of Coca Cola(R). This extension process, instituted in 1910, removes all detectable amounts of cocaine from the leaf. Prior to 1910, cocaine-based cola drinks were both popular and readily available in this country and in Europe.

A portion of the coca harvest is diverted to illicit laboratories in producing countries for the preparation of cocaine for illegal

exportation. The production process in these labs involves: 1) extraction of the total base from the leaf material with a solvent (often kerosene); 2) portioning the alkaloids into an aqueous acid solution with subsequent solvent extraction to remove non-alkaloid impurities; and, finally 3) neutralization of the acidic solution to allow extraction and isolation of the partially purified cocaine. The final stages of purification involve one or two recrystallizations of the hydrochloride salt form of cocaine. If the purity of the salt is good (90-100 percent), the crystals will appear as fine white flakes having a powdery consistency. Some illicit laboratories use less sophisticated extraction processes which usually involve only the crude crystallization of the initial extract without extraction of non-alkaloid impurities. These processes yield material of 70-85 percent purity.

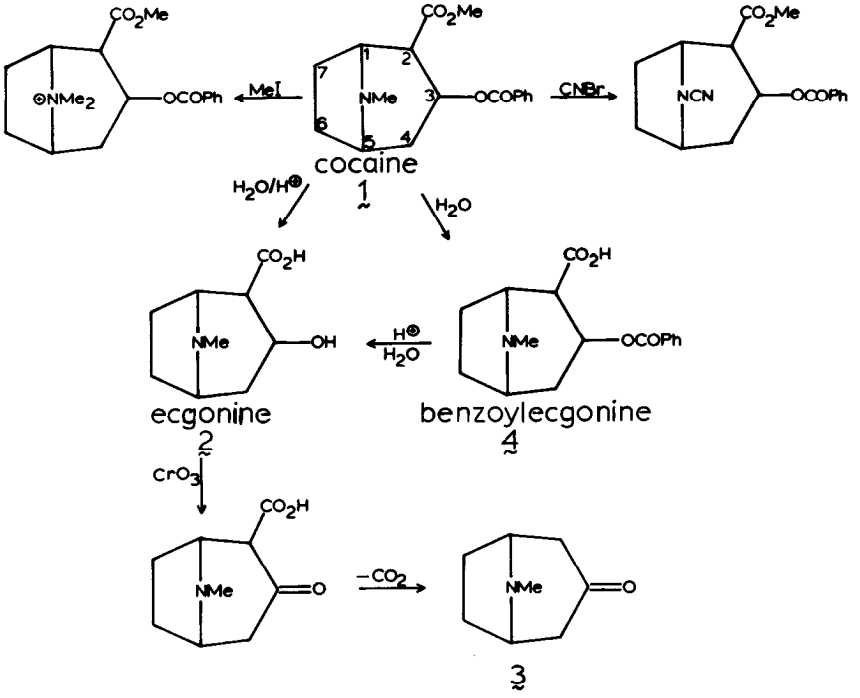
STRUCTURE ELUCIDATION AND SYNTHESIS

Due to great academic interest in its stimulant properties, cocaine was one of the most intensively studied natural products of the late 19th century. The first extraction of cocaine is generally credited to Gaedcke in 1855 who distilled a portion of a residue from an aqueous extraction of coca leaves. from this distillation, crystals formed, mixed with an oily residue. These crystals were given the name "Erythroxyline" after the family of which coca is a species.

Coca leaves eventually came into the hands of professor V. Wohler of Gottingen for analysis (Mortimer, 1901, reprinted, 1974). Professor Wohler, who is often referred to as the father of synthetic organic chemistry, had synthesized urea, the first synthesis of a compound of biological origin. The leaves were turned over to his assistant, Dr. Albert Niemann, who proceeded to extract and purify a crystalline compound, which was named cocaine (Wohler, 1862).

The first structural studies involved the acid hydrolysis of cocaine, from which benzoic acid, methanol and a basic compound were isolated (Mortimer, 1901, reprinted, 1974). This result indicated that cocaine must contain a carbomethoxy and benzolyloxy group. Other studies showed cocaine to be a monomethyl tertiary base, due to its action with methyl iodine (Einhorn, 1888) and cyanogen bromide (Braun & Muller, 1918) (see Figure 3-1). The basic compound resulting from the hydrolysis of cocaine was isolated in salt form and given the name "ecgonine" a word derived from the Greek word meaning "son" or "descendant" (Mortimer, 1901, reprinted, 1974). Ecgonine (2 in Figure 3-1) was later shown to yield tropinone when subjected to chemical oxidation (Willstatter & Muller, 1898), thus providing the link between a known organic compound, tropinone (3), and cocaine (1) itself. By considering the sequence of chemical degradation steps between cocaine (1) and tropinone (3), the chemical structure of cocaine was secured. The proposed structure of cocaine resulting from these studies was confirmed in 1923 by total synthesis (Willstatter et al., 1923). By the application of a

FIGURE 3-1


CO2Me
⊙NMe2
OCOPh
MeI
NMe
CNBr
NCN
cocaine
1
H2O/H⊕
H2O
CO2H
OH
ecgonine
2
H⊕
H2O
benzoylecgonine
4
CrO3
−CO2
O
3

four-step chemical synthesis, Wilstatter crystallized a pure material which was chemically identical to naturally occurring cocaine. The synthetic approach used by Willstatter in 1923 is still the preferred method of cocaine synthesis today, with only minor modification (Archer & Hawks, 1976).

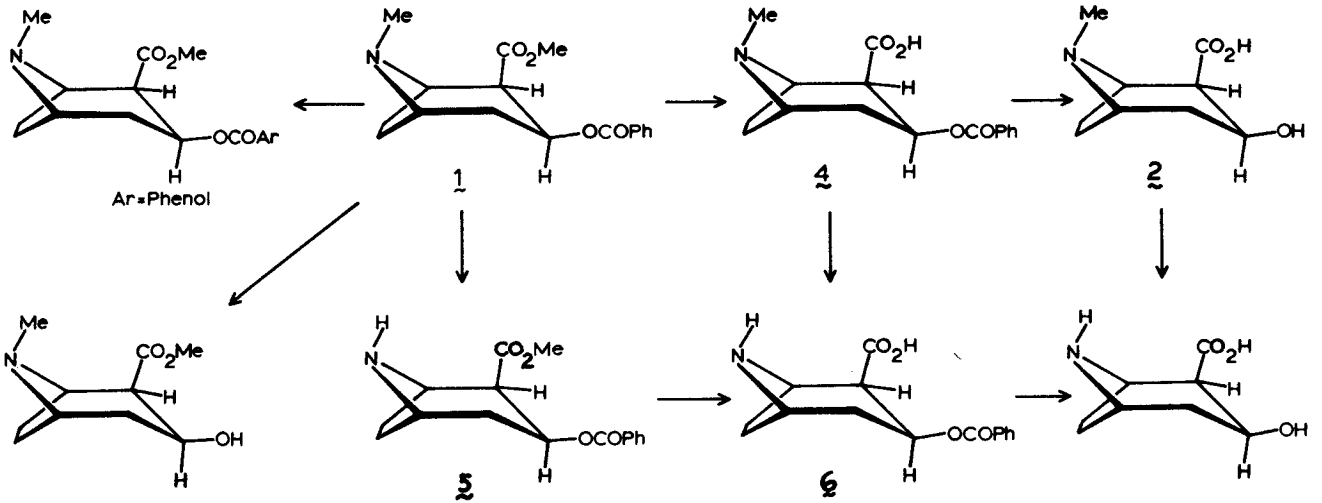
The stereochemical nature of the molecule, that is, the orientation of its substituent groups in three-dimensional space and the stereochemical characteristics of the molecule which enables a solution of cocaine to rotate plane polarized light remained undetermined until the mid 1950s. This latter ability is shared by nearly all molecules of biological origin and the source of this ability is a particular structural characteristic of the individual molecule. This stereochemical determination was made by the chemical degradation of cocaine through specific reactions to yield a compound of known structure and stereochemistry. However simple this process now sounds, the feat was not achieved until 1955 (Hardeggar & Ott, 1955) after much work by a number of skillful investigators. These studies determined that cocaine had the stereochemical characteristics depicted in Figure 3-2. Thus, cocaine was established as 3S-benzoyloxy-2R-methoxycarbonyl tropane. (The symbols R and S refer to accepted designations of absolute stereochemistry.) For a detailed account of the chemistry involved in this investigation, the reader is referred to several reviews of the subject (Archer & Hawks, 1976; Fodor, 1970).

METABOLIC PATHWAYS OF COCAINE

Cocaine is rapidly metabolized in animals to yield benzoylecgonine (4 in Figure 3-1) and ecgonine (2) as the principal products along with the several other metabolites listed in Figure 3-2.

These metabolic products are inactive when administered to animals with the exception of norcocaine (5) which is reported to be equipotent to cocaine (Hawks et al., 1974; Misra et al., 1975). The absence of activity of these metabolites may be due to the fact that they are very polar, a characteristic which causes them to be eliminated rapidly by excretion and to be relatively ineffective in crossing the blood/brain barrier, which is critical to eliciting a central nervous system effect. In vitro experiments have shown that these metabolites show little activity in influencing the concentration of catechol neurotransmitters at nerve endings (Hawks et al., 1974). The catechol neurotransmitters make up the biological system in animals which is thought to be involved in the regulation of mental processes affected by drugs such as cocaine. Roth cocaine and norcocaine show significant activity on this system. It has been reported, however, that the metabolites norbenzoylecgonine (6) and to a lesser extent benzoylecgonine (4), show pharmacological activity in rats after intracisternal injection (Misra et al., 1975). Since the material was administered directly to the brain, there was no need to cross the blood/brain barrier.

FIGURE 3-2



The mechanism by which cocaine causes its central nervous system effects is not clear. The implication of the two experiments mentioned above seem to be that there is more involved than simply cocaine's effect on the neurotransmitter system. A more complicated mechanism is necessary to explain why norbenzoylecgonine has no effect on the concentration of neurotransmitters at nerve junctions in in vitro experiments, but elicits a pharmacological effect when administered directly to the brain of the animal. More research in this area is indicated.

STREET PREPARATIONS

Cocaine illicitly prepared in South America for export to the United States street market is for the most part relatively pure -- and usually prepared as the hydrochloride salt. The purity generally ranges from 80-95 percent. The substance usually appears as a translucent crystalline material ("flake") or as small, somewhat transparent chunks ("rock"). These forms are the most desirable to the street purchaser, but are rare since the material is usually adulterated for economic reasons as it passes through the chains of middlemen. Typically, cocaine is purchased in one or two kilogram quantities (although larger shipments are frequent) in Bolivia, Peru or Colombia by users/dealers. Upon arrival in this country, it is divided into lots of several ounces each and sold quickly. These ounces are then cut into lots of single ounces or multigram sizes before resale. Eventually, the quantities are reduced to single grams or to "spoons." "Spoons" are in the half-gram category and are so-called because of the often used method of measuring the material by the quarter teaspoon. Since each division into smaller portions for further resale lends a tempting opportunity to either add an adulterant or, in the case of the smaller doses, to weigh short, it would be a rare case if material which started at 90 percent purity ended up at that level. For this reason the user who can afford to buy the larger quantity gets the purer product (Lee, 1976).

Street cocaine is adulterated with a variety of substances. The most common ones are mannitol, lactose and glucose. These substances are all of the carbohydrate family and are relatively innocuous. Mannitol, which crystallizes in a form similar to cocaine, is useful as an adulterant when cocaine is to be dissolved and recrystallized. lactose and glucose are common sugars which cause no adverse effects. Among the other compounds sometimes used as active substitutes for cocaine are lidocaine, procaine and tetracaine. These are local anesthetics which have an appearance, taste and local anesthetic effect similar to cocaine. They may be added to or, in some cases, substituted entirely for cocaine. The effects of these compounds on the central nervous system are different from cocaine and allergic reaction to them is not uncommon. Street cocaine is also sometimes sold mixed with heroin. It can probably be assumed that such a mixture is sold as the mixture rather than as a subterfuge.

Caffeine and the amphetamines have also been used as stimulant adulterants in street cocaine, particularly where the original material has been so diluted that its lack of stimulant activity makes it unsalable. Occasionally quinine is used in the cut due to its availability and, perhaps, to the dealer's experience in using it to adulterate heroin. Allergic reactions to quinine can lead to pulmonary edema and death in some individuals; in fact, quinine has been implicated as a possible factor in heroin "sudden death syndrome" (Fodor, 1960, 1970).

ANALYTICAL METHODOLOGY

Various methods for analyzing cocaine and its metabolites have been developed for forensic or research applications. Less rigorous methods have even been devised for analyzing street samples by the illicit user (Lee, 1976).

In forensic chemistry, post-mortem samples are analyzed to determine if cocaine can be implicated in death. Law enforcement organizations employ assays to determine the content of street samples confiscated during drug-related arrests. Other forensic applications include urine screening methods, which are used to detect drug use in methadone maintenance programs and in various "drug free" treatment programs. Analytic methods used in post-mortem assays are often qualitative or semi-quantitative. A qualitative assay provides information oh the presence of the drug, but does not actually indicate the amount of the drug in the sample being tested. In some cases this information is sufficient for the post-mortem test. However, in many situations it is useful to knew the actual quantity of cocaine (or metabolite) present in the sample of blood or urine to determine, for example, the time of ingestion of the drug or whether cocaine could be considered the principal cause of death (e.g., where it is determined that other drugs are also present in the body). In cases of confiscation of illicit cocaine, quantitative analysis of the sample might indicate the extent to which it has been cut with adulterants and whether a given sample (due to its quantitative composition) matches other samples in the same geographic area, perhaps indicating that they came from a common source. For purposes for which urinalysis is done, it is sufficient to determine the presence of cocaine; quantitative assays are usually unnecessary.

In research, a quantitative assay is usually used, since most research involves the determination of a time course of drug action in the body making it necessary to determine an accurate concentration of the drug at each sample (blood, urine, etc.) collection time.

Basic differences, therefore, exist between the forensic requirements for an assay and research needs. Even if a quantitative assay is used for both purposes, there will be cost and time constraints on the forensic assay, not necessarily factors in an assay used by

researchers. A description of four types of analytical methodology follows. The choice of which analysis to use depends oh such factors as cost per sample, the number of samples to be analyzed in a given period of time, the limits of sensitivity and specificity required in the assay and, in some cases, the scientific sophistication required of the person actually performing the assay.

Thin Layer Chromatography (TLC)

Thin layer chranatography (TLC) is the most widely used method for the qualitative-analysis of cocaine. This method employs the use of plates made of glass, metal or plastic which are coated with an absorbent substance -- usually silica gel or alumina. The drug sample in a very small amount of solvent is spotted on the bottom of the plate and the plate is then placed upright in a closed container with a shallow layer of solvent on the bottom. As the solvent moves up the plate due to the action of the absorbent, the drug is carried along because of its solubility in the solvent. A second factor impedes this progress, however: The drug also has atendency to be absorbed by the material on the plate. This competition between the drugs tendency to be absorbed by the plate and its tendency to move with the solvent provides the essence of chranatography. Due to structural differences among molecules, drugs will respond differently to this competition between solvent and absorbent with the net effect that the various drugs will appear at different distances from the bottom of the plate by the time the solvent reaches the top. Since each drug has its characteristic distance, a qualitative assay is provided. TLC methods for detecting cocaine and its metabolites differ in the solvents employed and the reagents used for spraying the plate after solvent development, which reveal the spots where the drug is located.

Thin-layer chranatography (TLC) requires a minimal investment in equipment and supplies. Correspondingly, it is also the least sensitive technique, being capable of detecting, usually 5-10 µg of compound which is in the samples applied to the plate, although sensitivity to 0.5 µg has been reported for behzoylecgonine (Wallace et al., 1975). TLC is also the least specific in that more compounds can potentially interfere with the analysis. Interference results when some other material in the sample has a coincidental migration characteristic on the plate, thus producing a spot in the same vicinity as cocaine's (or a metabolite's). TLC is relatively rapid because several samples can be applied to the same plate and run simultaneously.

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[1]Misra et al., 1973, 1975; Bastos et al., 1974; Meola & Brown, 1975; Valanju et al., 1973; Wallace et al., 1975.

Gas Liquid Chromatography (GLC)

Another method for analyzing cocaine and its metabolites is gas-liquid chromatography (GLC). This method is theoretically similar to that of TLC. In this method, the absorbent phase analogous to the coating on the TLC plate occurs in a long tube of glass or metal. The tube is usually 2-4 mm internal diameter and 4-6 feet in length and is referred to as the chromatographic "co1umn." The absorbent material is actually a high boiling point viscous liquid coated on an inert solid support. Rather than a liquid phase like the solvent in TLC, GLC employs a gas. The drug is applied to the end of the column which is enclosed in an oven. An inert gas is passed through the column continuously. The drug, again, has the tendency to equilibrate between the phase coated on the solid support and the hot gas phase in which it is soluble. A detection device, which is located at the end of the tube, measures material passing through it, recording the results on a strip chart. (A peak appears on the chart when a compound makes contact with the detector.) Since different molecules equilibrate between the two phases to a different extent, a means of characterization is provided by measuring the time it takes for a given drug to get through the tube. GLC provides the added potential for quantitative analysis as well as qualitative analysis since the height of the peak is proportional to the amount of material passing through the detector. It is employed both in forensic chemistry[1] and in research[2].

Gas chromatography requires the purchase of an instrument costing several thousand dollars and requiring more sophistication of the operator. It is slower than TLC since samples have to be run individually and the usual time for each compound to pass through the column (tube) is on the order of several minutes. However, it is more specific than TLC and considerably more sensitive, depending on the type of detector employed. Another advantage is its versatility in that it can be applied to many types of drugs and can be used both qualitatively and quantitatively.

The EMIT(R) System

The EMIT(R) (Bastos et al, 1974) system is another approach used by many forensic laboratories for the analysis of cocaine. It is generally employed as a qualitative assay system for determining the presence of the major cocaine metabolite, benzoylecgonine, in biological specimens. The extent to which this reaction occurs is mediated by an immunological reaction involving a competition

[1]Blake et al., 1974; Hammer et al., 1974; Koontz et al., 1973; Moore, 1974.

[2]As discussed in Jatlow & Bailey, 1975; Javaid et al., 1975; Wallace et al., 1976.

between benzoylecgonine in the sample to be analyzed and the assay reagent material. Therefore, if a large amount of drug (benzoylecgonine) is present in the unknown sample, the reaction monitored will achieve a maximum response; but if little or no benzoylecgonine is present, inhibition of the reaction will be maximized. By calibrating the system with known amounts of benzoylecgonine, a means of predicting the presence of the metabolite is provided by the extent to which the measurable reaction is inhibited.

EMIT(R) assays require the purchase of a comercial system which costs several thousand dollars as well as the purchase of reagent materials from the commercial source on a per assay basis. In terms of cost per sample it is the second least expensive technique to TLC. Samples have to be run individually but each takes less than two minutes. The sensitivity is on the order of 1 µg/ml of urine and is relatively specific for the cocaine metabolite. To be more specific, a sample giving a positive response will often be subjected to a subsequent confirmatory analysis by gas-chramtography. EMIT(R) requires relatively little training of its operators.

Gas chromatography - Mass Spectrometry (GC-MS)

Another method of cocaine analysis used by researchers is that of gas chrauatography-mass spectrometry (Archer & Hawks, 1976; Hawks, 1974). In this technique a gas chromatograph discussed above is connected to a mass spectrometer which acts as the detector. The mass spectrometer is an instrument capable of detecting very small amounts of material caning through the column of the GC and specifically detecting those compounds of a specific molecular weight, thus providing a means of excluding many compounds which might interfere with the assay. This technique is too cmbersome and expensive to be used in most situations other than research projects.

The technique of gas chranatography-mass spectrometry is the most expensive, specific and sensitive of the methods mentioned. The initial investment will usually exceed $60,000 and the sophistication required of the operator is significantly higher than for the other techniques. This technique is, therefore, generally employed for research purposes only.

A Comment on Methods

At the present time, the technique of gas chromatography is probably the most generally useful for both forensic and research purposes, considering its cost and versatility. The analytical situation with cocaine is changing rapidly, however, with the advent of more sensitive techniques for TLC, better detectors for GLC and, particularly, new advances with high performance liquid chromatography, which will have considerable application to the analysis of cocaine metabolites.

Cocaine has a high clearance rate in vitro. It is metabolized and excreted rapidly from the kidney. When cocaine is added to blood plasma outside the body, (in vitro), it manifests a half-life (the time for its concentration to decrease by half) of approximately 0.5-1.0 hour. This is reportedly due to pseudocholinesterase activity in the plasma (and is reported to be inhibited by the addition of a fluoride ion) (Jatlow et al., 1976). Since this half-life is comparable to that of cocaine's in vivo half-life (Hawks, unpublished), it is possible that the majority of cocaine's in vivo metabolism occurs in the blood rather than in the liver. These considerations have implications to forensic scientists who may be analyzing samples taken from a corpse which is several hours old. It is important to consider in these situations that the cocaine present may be only a small part of that which was present at the time of death. This rapid enzymatic breakdown of cocaine in blood complicates the investigation of post-mortem cases, particularly in determining whether cocaine itself was the principal factor in the death. This ability to hydrolyze also makes quantitative analysis of cocaine more difficult in the work-up stages of the analysis. Care must be exercised in the design and execution of extraction and chromatographic steps in the work-up in order to minimize loss of cocaine.

SUMMARY

Coca and cocaine have been subjects of fascination to historians, anthropologists and chemists for many years. The use of coca has had a great influence on many South American cultures as far back as recorded history. It was one of the first of the "natural" organic compounds to be chemically investigated. It seems that these various interests in cocaine and coca waned somewhat during the first two-thirds of the 20th century, perhaps due to restrictions on its use which came about in the early 1900's.

At the present, however, this interest has revived and the number of chemical, anthropological and pharmacological studies of cocaine has mushroomed. Analytical chemical techniques for cocaine still have much room for improvement in the areas of sensitivity and simplicity. At present much information remains to be gathered concerning the use of coca by populations of South America. The biomedical considerations underlying the habitual and cultural use of the coca leaf is an area of research which will require extremely sensitive assays.

Much is still not known about cocaine use in this country -- its toxicity during chronic use, its basic mode of action after different types of administration, and the basic ethnography of use. In all of these areas of study, cocaine's chemistry plays an essential role. Analytical techniques are needed for studying plasma and tissue levels in humans and animals under many conditions. Fast and reliable qualitative analyses are necessary for forensic purposes. Sufficient historical evidence exists to

warrant an examination of the volatile constituents of the coca leaf using modern techniques for new biologically active compounds. Even though much new information about coca and cocaine has appeared in recent years, the dearth of basic knowledge concerning the plant and the chemical leaves much room for investigation.

Richard Hawks, Ph.D.
Division of Research
National Institute on Drug Abuse

REFERENCES

Cocaine: The Material

Archer, S. and Hawks, R.L. The chemistry of cocaine and its derivatives. In Mule, S.J. (ed.) Cocaine: Chemical, Biological, Social, and Treatment Aspects. Cleveland, OH: CRC Press, 1977, pp. 13-32.

Aynilian, G.H., Duke, J.A., Genter, W.A. and Farnsworth, N.R. Cocaine content of Erythroxylon species. Journal of Pharmaceutical Sciences, 63:1938 (1974).

Bastos, M.L., Jukofsky, D. and Mule, S.J. Routine identification of cocaine metabolites in human urine. Journal of Chromatography, 89:335-342 (1974).

Blake, J.W., Ray, R.S., Noonan, J.S. and Murdick, P.W. Rapid, sensitive gas-liquid chromatographic screening procedure for cocaine. Analytical Chemistry, 46:288 (1974).

Braun, J. and Muller, E. Umwandlung des cocains in neue, physiologisch wirdsame substanzen. Deutsche Chemische Gesellschaft, Berlin, 51:235 (1918).

Brecher, E.M. and the Editors of Consumer Reports. Licit and Illicit Drugs. The Consumers Union Report on Narcotics, Stimulants, Depressants, Inhalants, Hallucinogens, and Marijuana -- including Caffeine, Nicotine and Alcohol. Boston, MA: Little, Brown & Co., 1972.

Burchard, R.E. Coca chewing: A new prospective. In Rubin, V. (ed.) Cannabis and Culture. The Hague: Mouton & Co., 1975, p. 463.

Byck, R. Personal comunication.

DeJong, A.W.K. The alkaloids of coca. Recueil des Travaux Chimiques des Pays-Bas, 25:233, 1938 (1974).

Einhorn, A. Weitere uhtersuchungen uber das cocain. Deutsche Chemische Gesellschaft, 21:3029 (1888).

Fodor, G. The tropane alkaloids. In Manske, R.H.F. (ed.) The Alkaloids, Volume 6. New York, NY: Academic Press, 1960, pp. 145-177.

Fodor, G. Tropanealkaloids. In Pelletier, S.W. (ed.), Chemistry of the Alkaloids. New York, NY: Van Nostrand Reinhold, 1970, pp. 431-467.

Gaedcke, F. Uber das Erythroxylin, dargestellt aus den blattern des in Sudamerika cultiverten strauches erythroxylon coca lam. Archiv der Pharmacie, 132:141-150 (1855).

Hammer, R.H., Templeton, J.L. and Panzik, H.L. Definitive GLC method for the identification of cocaine. Journal of Pharmaceutical Sciences, 63:1963 (1974).

Hardegger, E. and Ott, H. Konfiguration des Cocains und Derivate der Ecgoninsaure. Helvetica Chimica Acta, 38:312 (1955).

Hawks, R.L. Gas chromatographic mass spectrometry in drug screening by immunoassay. In Mule, S.J., Sunshine, I., Braude, M. and Willette, R.E. (eds.), Immunoassays for Drugs Subject to Abuse. Cleveland, OH: CRC Press, 1974, pp. 73-85.

Hawks, R.L., Kopin, I.J., Colburn, R.W. and Thoa, N.B. Norcocaine: A pharmacologically active metabolite of cocaine found in brain. Life Sciences, 15:2189-2195 (1974).

Jatlow, P., Barash, P.G., Van Dyke, C. and Byck, R. Impaired hydrolysis of cocaine in plasma from succinylcholine sensitive individuals. Clinical Research, 23(3):255A (1976).

Jatlow, P.I. and Bailey, D.N. Gas chromatographic measurement of cocaine in plasma using a nitrogen detector. Clinical Chemistry, 21:946 (1975).

Javaid, J.L., Dekirmenjian, H., Brunngraber, E.G. and Davis, J.M. Quantitative determination of cocaine and its metabolites benzoylecgonine and ecgonine by gas-liquid chromatography. Journal of Chromatography, 110:141 (1975).

Koontz, S., Besemer, D., Mockey, N. and Phillips, R. Detection of benzoylecgonine (cocaine metabolite) in urine by gas chromatography. Journal of Chromatography, 85:75 (1973).

Lee, D. Cocaine Consumer's Handbook. Berkeley, CA: And/Or Press, 1976.

Lossen, W. Uber das Cocain. Justus Liebigs Annalen der Chemie, 133:351 (1865).

Martin, R.T. The role of coca in history, religion and medicine. In Andrews, G. and Solomon, D. (eds.), The Coca Leaf and Cocaine Papers. New York, NY: Harcourt Brace Jovanovich, 1975.

Meola, J.M. and Brown, H.H. Detection of benzoylecgonine (metabolite of cocaine) in urine; drug abuse screening by thin-layer chrauatography. Clinical Chemistry, 21:945 (1975).

Misra, A.L., Nayak, P.K., Block, R. and Mule, S.J. Estimation and disposition of (^{3}H)-benzoylecgonine and the pharmacological activity of some cocaine metabolites. Journal of Pharmacy and Pharmacology, 27:784-786 (1975).

Misra, A.L., Pontani, R.B. and Mule, S.J. Separation of cocaine, some of its metabolites and cogeners on glass fiber sheets. Journal of Chromatography, 81:167 (1973).

Moore, J.M. Gas chromatographic detection of ecgonine and benzoylecgonine in cocaine. Journal of Chromatography, 101:215 (1974).

Mortimer, W.G. History of Coca The Divine Plant of the Incas. 1901, reprinted, San Francisco, CA: And/Or Press, 1974.

Mule, S.J. (ed.) Cocaine: Chemical, Biological, Social, and Treatment Aspects. Cleveland, OH: CRC Press, 1977.

Streit, F., Nicolich, M.J. and Backenheimer, M.S. Purchase of Predictions of Schedule II Drugs under the Controlled Substances Act of 1970. Rockville, MD: National Institute on Drug Abuse, 1976.

Valanju, N.N., Baden, M.M., Valanju, S.M., Bulligan, D. and Verma, S.K. Detection of biotransformed cocaine in urine from drug abusers. Journal of Chromatography, 81:170 (1973).

Wallace, J.E., Hamilton, H.E., King, D.E., Bason, D.J., Schwertner, H.A. and Harris, S.C. Gas-liquid chromatographic determination of cocaine and benzoylecgonine in urine. Analytical Chemistry, 48(1):34-38 (1976).

Wallace, J.E., Hamilton, H.E., Schwertner, H. and King, D.E. Thin-layer chromatographic analysis of cocaine and benzoylecgonine in urine. Journal of Chranatography, 114:433 (1975).

Willaman, J.J. and Schubert, B.G. Alkaloid bearing plants and their contained alkaloids. Technical Bulletin No. 4234. Washington, DC: Agricultural Research Service, U.S. Department of Agriculture, 1961.

Willstatter, R. and Muller, W. Uber die Constitution des Ecgonins. Deutsche Chemische Gesellschaft (Berlin), 31:2655 (1898).

Willstatter, R., Wolfes, 0. and Mader, H. Syntheses des Naturlichen Cocaines. Justus Liebigs Annalen der Chemie, 434:111 (1923).

Wohler, V. Fortsetzung der Untersuchungen uber die Coca und das Cocain. Justus Liebigs Annalen der Chemie, 121:372 (1862).

Chapter IV BEHAVIORAL EFFECTS OF COCAINE IN ANIMALS

James Woods, Ph.D.

The inclusion of a paper on the behavioral effects of cocaine in animals in a set of papers that deals primarily with cocaine's effects in man may seem peculiar at the outset. Yet, there are a variety of reasons for covering this subject. Often we are faced with such complex problems concerning the behavioral effects of cocaine in man and it is more straightforward to approach the problems by involving animals. Often we will want to examine questions associated with cocaine self-administration, but the ethical issues associated with human experimentation may dictate severe restrictions, if not total prohibition. Animals, however, can provide much useful information about cocaine self-administration. Further, we often face the problem of the need for control of behavioral history as it influences drug effect. Such histories can be better controlled using animals in laboratory settings e.g., where the amount and kind of drugs previously taken can be specified.

This paper is intended to be a review of experimental work on the effects of cocaine on the behavior of non-human animals. It is not intended to be a critical review of this literature, but rather a rapid way of providing the interested reader with a general awareness of what has been done in this area.

Early descriptions of the behavioral effects of cocaine in a variety of animal species (e.g., Tatum & Seevers, 1929) established some of the general reactions to cocaine that occur in animals and may also occur in man. Later descriptions of the effects of cocaine included changes in conditioned behavior as well as elaborations of descriptions of the drug's actions on unconditioned behaviors. Still later, animals were shown to self-administer cocaine, showing another parallel to man's behavior with respect to cocaine (e.g., Deneau et al., 1969) These are some of the effects of cocaine in animals that may resemble its effects in man and which will be described in greater detail in this chapter.

To introduce the effects of cocaine on behavior, a brief outline of the effects of cocaine on a variety of physiological systems is provided. These occur in concert with behavioral effects and while the reader should be mindful of their occurrence, physiological effects will not be mentioned subsequently.

In rodents or primates, the physiological effects of the smallest doses of cocaine that can be reliably measured are pupil dilation, heart rate and respiratory rate increases. Blood pressure increases at slightly higher doses. At still larger doses, body temperature increases significantly; in addition, the previously described effects are exacerbated. Electrical activity of the brain is characterized by patterns of activity of an aroused state; still larger doses may lead to grand mal convulsions. At the stage of imminent death, the physical signs may be a mixture of stimulation of the central nervous system, respiratory depression and cardiovascular collapse. Death may be due primarily to either cardiovascular collapse or respiratory depression, or a complex joint action of these effects. (For a more detailed discussion, see Woods & Downs, 1973.)

Many of the effects of cocaine depend to an important extent on environmental factors that exaggerate or diminish the physiological and behavioral effects of cocaine. Even the lethal dose of cocaine may be modified 'by the environment in which the animal is placed. Cocaine will produce a greater proportion of deaths in mice if they are grouped together rather than if they are isolated. Likewise, if mice are given electric shocks after having been administered cocaine, many more will die even though the electric shock alone is not strong enough to induce lethal effects (La1 & Chessick, 1965). Still other factors (e.g., environmental temperature and exercise) may decrease the dose of cocaine necessary to produce death. It is thought that these effects may be exerted through the exaggerated hyperpyrexia induced by these environmental manipulations (Peterson & Bardinge, 1967).

There are a variety of other determinants of cocaine's actions on behavior. The magnitude and quality of every effect of cocaine will critically depend on the dose of cocaine and the route of administration. Species differences in effect are marked; a dose of cocaine that would produce a modest increase in locomotion in a mouse would kill a rhesus monkey. It is difficult to appreciate the importance of these differential effects until one has a sample of them.

Cocaine may alter behavior in a variety of ways; it may change both unconditioned and conditioned behaviors. We shall first examine the varieties of behavior that are changedby cocaine in situations that do not explicitly depend on prior experience. Cocaine alters the gross behavioral activity of animals: it induces specific kinds of behaviors and it alters certain reflexive responses to aversive stimuli. In addition, a number of experiments have examined the biological systems utilized for the mediation of these effects.

LOCOMOTOR ACTIVITY: The amount of locomotor activity an animal engages in may be measured by the rate at which it interrupts a beam of light that crosses an enclosed space occupied by the animal. For example, a mouse may be placed in an enclosed circular chamber with

an 18-inch diameter; the chamber is divided by two perpendicular light beams. The mouse may, in its normal meanderings, interrupt a beam of light at a rate of 300 times per hour. Cocaine will increase the number of interruptions five-fold at its maximal doses (30-56 mg/kg , intraperitoneal); lower, and higher doses produce smaller increases or none at all (Dews, 1953; Villarreal et al., 1973). Similar results have been reported by other investigators in the mouse (e.g., Costa et al., 1972; van Rossum & Simons, 1969). Locomotor activity increases have also been obtained in rats (e.g., Fog, 1969; Wilson & Holbrook, 1974; Post & Rose, 1976) and the dog (Tatum & Seevers, 1929). In the latter species, 3 mg/kg induces a small increase in activity, an increase in reaction to slight environmental changes (apprehension) and quick head movements. The rhesus monkey reacts at this dose of cocaine with restlessness, heightened activity, and an increased sensitivity 'to environmental change (e.g., Tatum & Seevers, 1929; Wilson et al., 1976).

STEREOTYPY: At very large doses in rats (250-600 mg/kg, subcutaneous), cocaine induces a form of invariant repetition of responses, e.g., grooming a portion of the body. This stereotyped behavior, which occurs to the exclusion of normal variations in behavior, emerges slowly with high doses and may continue for more than a day (Fog, 1969). Similar activities have been observed in a variety of animal species, including man, with amphetamines and other related drugs (Randrup & Munkvad, 1967). The occurrence of these behaviors, at doses usually larger than those required to produce increases in general activity, has been observed in cats (Wallach & Gershon, 1971), in dogs (Tatum & Seevers, 1929; Hatch & Fischer, 1972; Hatch, 1973) and in monkeys (Tatum & Seevers, 1929; Wilson et al., 1976).

AGGRESSION: Cocaine changes aggressive behavior in the situations and species in which it has been studied (Hutchinson & Emley, in press). Reflexive fighting can be produced by the delivery of electric shock to pairs of members of the same species, providing they are housed in chambers in which the chance for bodily contact is relatively high and there is no opportunity for escape from the shock. Aggression may also be indicated by biting attacks toward inanimate, soft objects when shocks are administered or when positive reinforcement is terminated; in addition, these biting responses may be reinforced by delivering a reinforcing stimulus when the biting response has occurred, or the biting response may be reinforced by postponement of electric shock (e.g., Hutchinson, 1973). In each of these situations, some aspect of aggression is investigated and the relation of cocaine to aggression may be established.

In the squirrel monkey, cocaine at intermediate doses (0.1 to 1.0 mg/kg, subcutaneous) increases responding that is elicited by electric shock. It increases biting responses maintained by avoidance of electric shock over a similar dose range; it produces only a very modest increase in biting responses that are reinforced by food. At higher doses, cocaine reduces responding in each of these situations (Hutchinson & Emley, in press).

Pigeons have been studied in situations in which a hungry bird attacks a restrained bird or a stuffed model if food delivery to the "free" bird is momentarily terminated. In another behavioral situation similar to those described above with the squirrel monkey, biting responses are obtained from mice when they are shocked. With both these animals, cocaine reduced aggressive responses (Hutchinson & Emley, in press). It is clear that aggressive behaviors may be increased or decreased by cocaine depending upon conditions under which they are studied. Cocaine does not appear to induce an enhanced aggressiveness at doses that do not affect a variety of other behaviors (e.g., behaviors controlled by food reinforcement as discussed in a subsequent section). In the studies noted above, cocaine does not by itself induce aggression; however, when aggression has been elicited by environmental events, cocaine may increase or decrease this aggression.

INTERACTIONS WITH OTHER DRUGS: In attempts to understand more fully the biological mechanisms for some of the direct behavioral effects of cocaine, a number of studies have investigated the ability of other drugs to alter cocaine's effects. Frequently, these drugs alter the activity of putative neurotransmitters. Through studies of this kind, it is hoped that those of cocaine's effects which are accomplished through changes in neurotransmission will be better understood. In most of the experiments that have been done on this topic, locomotor activity in rats or mice has been modified by cocaine administration. For example, van Rossum et al. (1962) and Smith (1963) showed that cocaine-induced increases in activity were less in mice pretreated with reserpine. Reserpine reduces the brain content of three neurotransmitters in the mouse: norepinephrine, dopamine and serotonin. Villarreal et al. (1973) showed that alpha-methyl-para-tyrosine, a drug which depletes the brain of norepinephrine and dopamine, had no effect upon cocaine-induced increases in locomotion. Drugs that prolong the actions of dopamine, norepinephrine and serotonin by a variety of mechanisms have not had uniform effects upon cocaine-induced hyperactivity. Smith (1964) found that iproniazid, a drug which slows the metabolism of the transmitters noted above, did not alter the response of mice to a variety of doses of cocaine; other drugs, which have actions similar to those of iproniazid, increased cocaine's locomotor effects (Christie & Crow, 1973; Scheel-Kruger, 1972). Atropine, a drug which blocks some of the central and peripheral actions of the neurotransmitter, acetylcholine, potentiates cocaine's effects on locomotor activity (Galambos et al., 1967).

There are a vast number of centrally acting drugs that may modify cocaine's actions in a way that may be relatively obscure at the cellular level of description; it is surprising that a larger number of experiments have not been done on the topic. There is an interesting report of the potentiation of toxic actions of cocaine by phenytoin in dogs (Hatch & Fischer, 1972; Hatch, 1973). Blumberg and Ikeda (1975a; 1975b) have reported that morphine in large doses will reduce cocaine hyperactivity, and naltrexone, a narcotic antagonist, did not alter the locomotor stimulation produced by cocaine in mice or rats.

Taken together, these data suggest that cocaine's locomotor stimulant effect may be altered by a variety of drugs but the experiments have not pointed to a single neurochemical mechanism even for cocaine's locomotor stimulant effect in rodents.

BEHAVIORAL ACTIONS OF COCAINE METABOLITES: It is generally believed that cocaine acts directly to bring about its effects; in other words, it need not be converted metabolically to some other active compound in order to achieve its action in the body. However, in a variety of species it is de-esterified and N-demethylated, although as Nayak et al. (1976) point out, its metabolism is not well characterized in any species other than the rat. The N-demethylation product, norcocaine, has been identified in both the monkey brain (Hawks et al., 1974) and rat brain (Misra et al., 1974a) following the administration of cocaine. Hawks et al. (1974) demonstrated that norcocaine is equipotent with cocaine in blocking the uptake of norepinephrine in rat brain synaptosomes, and norcocaine has been shown to have convulsant actions similar to cocaine in the rat (Misra et al., 1975). Apart from this report, there is as yet very little characterization of norcocaine's actions on behavior. Cocaine may also be hydrolyzed at the ester in the 2 position (see Hawks, Chapter 3, this volume) to form benzoylecgonine or, at the equivalent position, to form benzoylnorecgonine from norcocaine. Both have been identified as urinary metabolites of cocaine in the rat (Nayak et al., 1976). Neither of these compounds has locomotor stimulant activity in rats even in very high doses by systemic administration (Misra et al., 1975). Probably due to their polar characteristics, they achieve only relatively small concentrations in brain tissue. By injection into cerebral spinal fluid, however, both compounds have strong stimulant characteristics that appear to be qualitatively different from cocaine or norcocaine (Misra et al., 1975). However, if either of the compounds is formed in the brain in significant concentrations, it may play a role in the behavioral effects of cocaine.

Benzoylecgonine may be further hydrolyzed to form ecgonine. Due to its polar nature, it is thought to be relatively unimportant in the behavioral effects of cocaine. Misra et al. (1974b) reported a sensitive technique for its identification; apparently it is not further metabolized in the rat. Thus, while a number of metabolites of cocaine have been identified, it is not clear as yet whether any of these metabolites are involved in the behavioral effects of cocaine.

Just as the variety of metabolites of cocaine must be studied further for their contribution to the behavioral pharmacology of cocaine, the study of structural relatives should yield important insights into the mechanisms of cocaine's actions. Spealman et al. (1976) have recently reported that elimination of the ester link between the phenyl and tropane portions of the cocaine molecule prolongs its action but does not change the qualitative effects on operant behavior in squirrel monkeys. There are also stereoisomers and epimers of cocaine whose effects on behavior need to be examined in considerable detail.

CHANCES IN COCAINE'S DIRECT EFFECTS WITH CHRONIC ADMINISTRATION: Some of the effects of cocaine have been shown to decrease or increase following repeated administration. These changes, regardless of their direction, should not be viewed as changes in the character of the drug; rather, they are changes in the dose required to bring about the same cocaine effect.

Tolerance to cocaine's action is inferred when the dose required to bring about an effect is increased, or when there is a shift to the right in the dose-effect relation for cocaine. In examining increases in heart and respiratory rates of rhesus monkeys administered 4 mg/kg of intravenous cocaine during a three-day period, Matsuzaki et al. (1976) demonstrated a reduction in the increases by the second and third day. Likewise, the dose required to induce changes in the electroencephalographic record, predictive of convulsions, is increased following the initial administration of the drug. It appears that the reduced effect is obtained very quickly, i.e., within 3-5 administrations of cocaine. This reduced sensitivity is not lost with a 2-3 day interruption of drug administration, but recovery does occur following 30-40 days of abstinence (see Figure 4, Matsuzaki et al., 1976). It is not likely that similar reduced effects are encountered with behavioral endpoints with the rhesus monkey since they have not been noted in the behavioral literature; however, the effect described is an initial drug administration effect and may reflect the novelty of the first experience with cocaine. Protocols that are designed to detect novelty effects must be applied to this phenomenon for further elucidation.

Woolverton et al. (in press) described an experiment which suggests that the behavioral context of cocaine's administration may be important to the prediction of its chronic behavioral effects. They measured in rats the suppression of drinking sweetened milk by cocaine administration. Acute cocaine administration suppressed the consumption of the milk in a dose-dependent manner. Tolerance to daily cocaine (16 mg/kg, intraperitoneal administration) was observed in a group of rats'given the drug prior to milk exposure, but not in a group receiving cocaine after milk exposure. If the tolerance had been the same in the two groups, then it could have been due to the common effect of the drug; e.g., enhanced elimination which has been shown to occur in rats (Nayak et al., 1976). However, the difference in effect suggests that some aspect of the milk exposure in the presence of cocaine was important for the development of tolerance. Similar findings have been reported for amphetamine in rats (e.g., Schuster et al., 1966).

Tatum and Seevers (1929) noted an increased behavioral reaction to cocaine with repeated administration in both dogs and rhesus monkeys. They also noted conditioned changes that could be elicited by the stimuli that preceded drug administration. Downs and Eddy (1932a; 1932b) found increased responsiveness to cocain in the form of convulsions and death in the rat, and an increased reaction

to a fixed dose in the dog as well. Post and Rose (1976) have shown an increasing effect of daily 10 mg/kg doses of cocaine on locomotor activity in the rat.

Finally, in a study using extremely large doses of cocaine in rhesus monkeys (10-17 mg/kg intraperitoneal; twice per 24 hours), Post et al. (1976) observed complex progressive changes in cocaine-induced patterns of behavior. Severe stereotyped behaviors occurred during a six-week period of administration; in some of their monkeys, this pattern of behavior subsided and was replaced by dyskinesias and inhibition of locomotor activity. In accordance with the results of previous studies, convulsions tended to occur more often with chronic administration.

These studies show that a complex set of changes in cocaine's behavioral effects may occur with the chronic administration of cocaine. There is no easy guide for predicting the direction of the changes that might occur following chronic cocaine administration. Behavioral changes associated with chronic administration need to be studied in situations in which the contribution of factors that usually influence behavioral tolerance development may be more fully examined (e.g., Thompson & Schuster, 1968). It is only then that a full characterization can be made of these interesting initial observations.

Direct Effects on Operant Behavior

Operant behavior can be described as behavior controlled by its consequences: it is increased and maintained by the presentation or termination of environmental events. If responding is maintained by stimulus presentation, then we refer to the stimulus as a positive reinforcer. If an event maintains behavior by its termination, then the event is a negative reinforcer. If the future probability of a response is reduced by the presentation of a consequence, the consequence is referred to as a punisher. The administration of cocaine has been studied in situations in which these different consequences control behavior and generalizations have been drawn with respect to these drug-behavior interactions. The organization of empirical effects will focus on these generalizations.

Profound alterations in operant behavior can also be produced by the particular arrangement of the consequent event with respect to responding. The same event may maintain behavior or suppress it, depending on its schedule of presentation (Morse & Kelleher, 1970). The schedule of presentation of reinforcers or punishers may also affect the rate and pattern of behavior. There are a variety of ways to arrange events to affect changes in behavior through their schedules of delivery. These are basically derived from arrangements where responses bring about reinforcers on the basis of a temporal requirement, a number requirement or some combination of these two. In a fixed-interval schedule, for example, reinforce-

ment is delivered following the first response after a fixed interval of time since the last reinforcement delivery. After this schedule has been in effect for some period of time, it produces low rates of responding that accelerate positively between deliveries of the contingent stimulus. The final highest rate is sustained until the next reinforcer is delivered. In fixed-ratio schedules, reinforcement is delivered following the occurrence of a given number of responses, regardless of the time since the last reinforcement. In the latter case, if the response requirement is reasonably small, a short pause occurs following reinforcement delivery, after which responding resumes at a high sustained rate. These patterns of responding occur with great regularity with these schedules in rodents, pigeons and primates. The evidence below provides numerous examples of these patterns.

Schedule-controlled performances may be used to examine the effect of cocaine on a variety of rates and patterns of responding. Smith (1964) examined the effects of cocaine on patterns of key-peck responding under the schedules mentioned above when short periods of food access were used as reinforcements for food-deprived pigeons. He found that 0.3-3.0 mg/kg doses of cocaine increased responding in the fixed-interval schedule while they decreased responding in the fixed-ratio schedule. A similar range of doses (0.1-1.0 mg/kg) of cocaine increased responding under fixed-interval schedules of food reinforcement in squirrel monkeys (Barrett, 1976; Gonzalez & Goldberg, in press). Dose-related decreases have been found in fixed-ratio responding maintained by food reinforcement over a 0.3-3.0 mg/kg dose range in squirrel monkeys (Gonzalez & Goldberg, in press) and rhesus monkeys (Woods & Tessel, 1974; Johanson, in press a).

Gonzalez and Goldberg (in press) noted that cocaine and amphetamine have similar qualitative and quantitative effects on these and other schedule-controlled performances maintained by food delivery, although d-amphetamine has a slightly longer duration of action. Dews (1958) has formulated a general framework for the description of drug effects on schedule-controlled responding, noting that many drug effects depend upon the rate of ongoing responding. A typical result is that of amphetamine which increases the lower rates of responding controlled by fixed interval schedules while leaving unchanged or decreasing the high rates associated with fixed-ratio schedules of food delivery. The examples given above of cocaine-induced rate changes conform well to this rate-dependent analysis of drug effects.

Barrett (1976) compared the effects of cocaine on fixed-interval responding maintained by food to similar behavior maintained by presentation of electric shock in squirrel monkeys. He found that the effects of cocaine were similar for the two reinforcers. Intermediate doses increased responding; higher doses reduced the frequency of behavior maintained by shock and food by about the same amount. Other drugs (e.g., pentobarbital) had markedly different effects on behavior maintained by these reinforcers. Herling et al.

(1975) reported that under some circumstances, food- and cocaine-maintained fixed- interval responding in rhesus monkeys may be affected similarly by cocaine administration; in both situations, rate of response was increased by moderate doses and decreased by higher doses of cocaine.

Hutchinson and Emley (in press) found that 0.3-3.0 mg/kg of cocaine increased responding that postponed the delivery of electric shock in the squirrel monkey. The response used in this situation was biting, a response elicited by electric shock in this species, as described above. Spealman et al. (personal communication) compared fixed-interval and fixed ratio schedules of negative reinforcement based on electric shock delivery to similar schedules of food delivery in squirrel monkeys. They found similar effects of cocaine on the two types of reinforcement. These effects depended on control rate of responding as determined by the schedules of reinforcement.

The results of the experiments on schedule-controlled performances suggest that cocaine may affect rates of responding maintained by different reinforcers in the same way. Johanson (in press: a), however, found that cocaine decreased food-reinforced fixed-ratio responding at doses that did not affect fixed-ratio responding maintained by the termination of stimuli associated with electric shock. On the other hand, perphenazine in some situations reduced responding controlled by the two reinforcers to a comparable extent. Clearly, further experimentation is needed to clarify the conditions under which these reinforcer-dependent differences will be obtained with cocaine.

Large doses of cocaine (2.5-10 mg/kg), relative to those used in primates, increase low rates of responding maintained by electrical brain stimulation in rats. High rates of brain self-stimulation may be unaffected at these doses (Crow, 1970; Wauquier & Niegemeers, 1974).

Behavior suppressed by punishment was increased by cocaine in rodents over a 10-30 mg/kg dose range (Morpurgo, 1965) while behavior maintained by negative reinforcement was decreased. Smaller doses were ineffective in increasing behavior suppressed by stimuli associated with electric shock (Hill et al., 1967). A similar dose range was found to reduce the frequency of behavior maintained by water reinforcement (MacPhail & Seiden, 1975). Taken together, the experiments with rodents using these operant techniques are consistent with experiments in primates in suggesting that low rate behavior may be increased by moderate doses of cocaine, while higher doses may reduce high-rate behavior regardless of the nature of the reinforcer. Indeed, these cocaine-induced effects indicate a strong dependence of the drug's effect on the rate of occurrence of operant behavior. With the exceptions noted, it seems that cocaine affects behavior controlled by different reinforcers in a similar manner as long as comparable rates of behavior are involved.

INDIRECT BEHAVIORAL EFFECTS OF COCAINE

The following sections deal with situations in which cocaine is used as a stimulus to bring about behavioral changes that are specific products of conditioning history. We shall first examine the interesting evidence that animals can recognize the 'effects of cocaine and can be taught to perform a response differentially in the presence or absence of the drug. Within this procedure, questions such as the following may be answered: What is the lowest dose of cocaine that can be differentiated from saline? What drugs are sufficiently similar to cocaine to be confused with it?

Another interesting use of cocaine is as a reward. In studies of this kind, delivery of a dose of cocaine is contingent on the performance of a response. The delivery of drug is said to be reinforcing (rewarding) if the response that precedes drug administration increases in frequency. As we will see, this procedure can answer questions such as: How strong a reinforcer is cocaine relative to other drug and non-drug reinforcers? How can other drugs affect cocaine-reinforced responding? and, equally important, How is cocaine different from other reinforcers?

Cocaine as an Unconditioned Stimulus

Still another use of cocaine in conditioning is that of establishing classically conditioned responses. Many drugs can serve as unconditioned stimuli for the formation of classically conditioned responses. Cappell and LeBlanc (in press) compared the effectiveness of amphetamine, cocaine and morphine as unconditioned stimuli producing conditioned suppression of the drinking of sweetened water in rats. While both morphine and amphetamine produced conditioned suppression of drinking, cocaine, even in doses that have been shown to decrease drinking directly (Woolverton et al., in press), did not produce conditioned decreases in fluid intake. Clearly, further experiments are necessary to examine the ability of cocaine to serve as a stimulus for classically conditioned responses in these and other contexts.

Cocaine as a Discriminative Stimulus

A discriminative stimulus is a feature of the environment which is correlated with the presentation of a reinforcer. To determine whether differences between environmental features can be used as discriminative stimuli, behavior is reinforced in the presence of one set of features and not reinforced in the presence of another. When a difference in behavior occurs under the two conditions, one may assume that the specified feature has become conditioned and that the features have been discriminated. This "feature of the environment" may be simply the presence or absence of a light in an animal's chamber, or a difference in wavelength of two lights.

Similarly, a discrimination may be based on differences in internal cues, such as those produced by food or water deprivation.

Researchers have shown that a variety of drugs can serve as discriminative stimuli (e.g., Overton, 1971; Barry, 1974). Barry and Kubena (1972) trained rats to press a lever for food reinforcement following the injection of 4 mg/kg of tetrahydrocannabinol (THC); following saline injections (in the absence of THC) responding was punished with electric shock. Another group of rats was trained in the same situation with the contingencies reversed. When cocaine (10 or 20 mg/kg, intraperitoneal) was substituted for THC, both groups of rats responded to cocaine as they did to saline. However, this may be due either to differences between the attributes of THC and cocaine, or to the use of inactive doses of cocaine.

Winter (1975) trained a group of rats to bar-press with mescaline (10 mg/kg, intraperitoneal) and saline as the cues to the presentation of either food reinforcement or shock. Cocaine was assessed for its stimulus equivalence to mescaline; if cocaine has effects similar to mescaline, the group punished following mescaline should also stop responding in the presence of cocaine, and the group conditioned to respond following mescaline should, similarly, respond following cocaine. Cocaine (3, 10 and 30 mg/kg, intraperitoneal) failed to engender responding in the group trained to respond following mescaline. The possibility that the doses of cocaine were too small is discredited by the fact that rats trained to respond in the presence of saline and refrain from responding following mescaline, showed dose-dependent decreases in responding over the range of cocaine doses administered. These results are consistent with a direct rate-decreasing effect of cocaine and the dosages were in the range found by MacPhail and Seiden (1975) to reduce responding maintained by similar schedules of reinforcement. Thus, behaviorally active doses were used by Winter, and we may conclude that cocaine is not functionally similar to mescaline in this behavioral situation.

Ando (1975) trained rats, catheterized for intravenous injection, to respond for food following a 0.2 mg/kg injection of amphetamine. Responding was reinforced for five minutes after the amphetamine injection and was not reinforced following saline injections. Periods of amphetamine and saline alternated, with injections given every half hour. Responding occurred rapidly after amphetamine but not after saline. Cocaine (0.2 mg/kg) acted like amphetamine in that it induced responding in the five-minute period following an injection. Ando's procedure provides more rapid testing of different doses and drugs, and may allow the recognition of smaller doses compared to other routes of administration. Unfortunately, the technical aspects of intravenous catheterization of rats and other small animals has not yet been developed sufficiently to permit long-term catheter patency in a large proportion of subjects.

The literature associated with the discriminative properties of cocaine is quite sparse, but the limited results are interesting. from the studies noted above, cocaine appears to have stimulus attributes more similar to amphetamine than to mescaline or THC. These studies have used drugs other than cocaine as discriminative cues and cocaine's similarity to these agents has been explored. No experiment using cocaine as the discriminative stimulus has been done although this approach is equally important. As a result, many questions remain unanswered. What are the dose and temporal dimensions under which cocaine and amphetamine are equivalent? Can animals be taught to discriminate cocaine from amphetamine, and, if so, under what circumstances? The relationship between the discriminative properties of the drug and the other behavioral actions of the drug (e.g., the many direct actions and the reinforcing action) should be explored. Finally, as noted previously, since tolerance is conferred to some behavioral actions of cocaine, do the discriminative properties of cocaine also change during chronic administration? These questions, which have yet to be analyzed in a systematic manner, might be explored using discriminative stimulus procedures such as those outlined here.

Cocaine as a Reinforcing Stimulus

If the frequency of a response increases when that response is followed by cocaine delivery, the cocaine is said to function as a reinforcer. A variety of species, routes of administration, doses and response requirements have been examined to determine the conditions under which cocaine acts as a reinforcer. Rats, guinea pigs (Dougherty, personal communication), pigeons (Wenger, personal communication), dogs (Risner, personal commnmication), squirrel and rhesus monkeys and baboons are among the species that have been tested. Indeed, the species generality has become sufficiently wide that a negative finding in a particular species would induce skepticism about the experimental conditions employed. However, the conditions of cocaine delivery that have been studied have been rather limited. The intravenous route is by far the most popular, probably because it is so effective in producing positive results. With the less popular routes of administration, we knew very little about cocaine's reinforcing effect.

In the most common experimental procedure, a simple response acts to deliver cocaine. The response is usually the depression of a lever that extends into the living space of the experimental subject. Depending on other experimental conditions, it may be important to examine whether the drug exerts direct behavioral effects on responding, so a second lever may be present that has no consequence with respect to drug delivery. Were the cocaine to have an important activity-increasing effect, for example, responding might increase equally on the two levers. This has not been the case in many experimental situations (e.g., Johanson et al., 1976a; Pickens & Thompson, 1968).

When intravenous routes of delivery of cocaine are employed, completion of the reinforcement contingency activates a pump that delivers drug directly into the blood through a chronic indwelling venous catheter. A variety of rather ingenious techniques have been devised to shield these catheters in monkeys (e.g., Deneau et al., 1969; Herd et al., 1969), dogs (Jones & Prada, 1973), baboons (Findley et al., 1972) and rats (Weeks, 1962). For intramuscular administration, rhesus monkeys can be trained to accept an intramuscular injection (apparently to avoid aversive handling) and subsequently can be taught to respond to turn on a light signaling to the experimenter the time for a cocaine injection (Goldberg et al., 1976). An oral route of administration has been examined in rhesus monkeys with the cocaine delivered in candy (Siegel et al., 1976), but it is not clear whether cocaine or the candy was the functional reinforcer in this situation. This result may have more to do with procedural detail than pervasive differences in results depending upon route of administration. Using a chronic intragastric cannula, cocaine injections have been found to reinforce lever-press responding in rhesus monkeys (Schuster, personal communication) . The oral and intragastric routes of administration bear further study because of the marked differences in various behavioral effects of cocaine by the oral as opposed to the intravenous route in man (e.g., Woods & Downs, 1973). The intranasal route of administration has not been examined in animals, although this appears to be the predominant mode of administration in man in this country. A single study approached this route in rhesus monkeys (Siegel et al., 1976) by encouraging the smoking of cocaine. Water-deprived rhesus monkeys were rewarded with water for puffing cocaine base in lettuce leaf cigarettes. When tested without the water contingency, two of the three monkeys continued to smoke the cocaine base cigarettes more than the cigarettes with lettuce alone. Subsequently, they appeared to prefer cocaine-containing cigarettes to plain cigarettes. Some cocaine was found to be absorbed under these conditions, since the cocaine metabolite, benzoylecgonine, appeared in the urine following cocaine intake.

Both the inhalation and intramuscular routes of administration have a tremendous practical advantage over the relatively short-term intravenous technique, due to the catheter problems mentioned previously. There are no reports of intraventricular or intracerebral cocaine self-injection.

Although our information on different species is far from complete, all animals that have been tested for reinforcing effects of cocaine show a positive response. Each of these situations has important behavioral parameters' that influence the expression of the reinforcing effects of cocaine. These parameters will be discussed with respect to the influence on the rate and pattern of the reinforcing effect of cocaine.

DOSE AS REINFORCER MAGNITUDE: As noted previously, most, if not all, of the behavioral effects of cocaine are dose-dependent. We have seen in previous sections, for example, that the effects of

cocaine on schedule-controlled performances may be an increase or a decrease depending on the dose. A moment's reflection should suggest that dose will be an important determinant of performance when cocaine itself is used as a reinforcer. Too small a dose, of course, will be totally ineffective; but as dose is increased, does the rate of responding indicate an increased effect due to increased reinforcing efficacy? The answer is yes, but this must be qualified by stating the specific experimental conditions. An example of experimental observation can be used to illustrate the point.

A monkey has been conditioned to self-inject cocaine. After each series of 30 responses, the monkey obtains an injection of cocaine. The rate of drug administration is entirely dependent on the speed of the monkey's responding. With experience, the monkey works at a rapid pace ($\geq$1 response per second) for a small intravenous dose (e.g., 0.01 mg/kg) that is used as the reinforcer. When the dose is decreased, the rate increases further but becomes more variable across sessions. If the dose is decreased further, the rate of responding drops considerably, indicating that the dose has been reduced to a level that either has no discernible effect or has too small an impact to maintain behavior. As the dose is increased again, rates of responding also increase to a maximal rate above which further dose increases lead to decreases in rates of responding (Downs & Woods, 1974). This type of relationship of dose to self-injection rate has been reported for fixed-ratio schedules of cocaine delivery in rodents and primates (e.g., Goldberg, 1973; Pickens & Thompson, 1968) and for fixed-interval schedules of cocaine delivery in primates (e.g., Balster & Schuster, 1973; Goldberg & Kelleher, 1976). The dose that maintains the maximum rate under these schedules depends on the parameters of the schedule and whether or not another opportunity for self-injection occurs immediately following the previous injection.

It is thought that the rate of cocaine-reinforced responding increases because the higher doses are stronger reinforcers. With further increases in dose, the appearance of direct rate-decreasing effects may in some way limit the rates of responding. Cocaine can decrease directly both fixed-interval and fixed-ratio schedule-controlled performances maintained by other reinforcers as noted previously. The use of schedules of reinforcement in which drug and other types of reinforcement alternate allows the determination of whether the rate-decreasing effects of the larger doses of Cocaine are behaviorally specific to particular reinforcers (e.g., Balster & Schuster, 1973; Tessel & Woods, 1975).

SCHEDULES OF COCAINE REINFORCEMENT: A schedule of reinforcement, as noted above, specifies the rule under which responses are followed by a consequence (e.g., Ferster & Skinner, 1957); in the cases to be discussed in this section, the reinforcing consequence is cocaine delivery. If responding is reinforced with intravenous cocaine on a fixed-interval schedule, responding -- as with food reinforcement -- shows a slowly accelerating rate of occurrence that rises to a final rate sustained until cocaine delivery. This

has been demonstrated for cocaine in both the rhesus monkey (Balster & Schuster, 1973; Goldberg & Kelleher, 1976; Pickens & Thompson, 1972) and in the rat (Dougherty & Pickens, 1973). A fixed-ratio schedule of intravenous cocaine delivery generates high sustained rates of responding if the requirement for cocaine delivery is a modest number of responses (e.g., 10-60) with no temporal restrictions. As when food is delivered under fixed-ratio schedules, the pattern of responding is a pause followed by a rapid sequence of responses terminated by delivery of cocaine. Responding may exceed one response per second under these schedules in rhesus and squirrel monkeys (Downs & Woods, 1974; Goldberg, 1973; Goldberg & Kelleher, 1976). Thus, the pattern of responding maintained by these schedules of cocaine delivery may be comparable to other reinforcing events. An excellent summary of schedules of cocaine injections in squirrel and rhesus monkeys will soon be available (Goldberg & Kelleher, 1977).

SCHEDULE-CONTROLLED PERFORMANCES OF PARTICULAR EKPERIMENTAL INTEREST: from the variety of ways in which cocaine is potentially useful as a reinforcer, experimenters interested in the examination of schedule-controlled performances have centered special interest on a few relatively complex procedures. The overall thrust of these experiments has been to measure the reinforcing strength of cocaine and to obtain a broad description of the variables that may interact with cocaine as a reinforcer. A brief description of the procedures will be given along with the concepts that have arisen from the studies.

A technique that has shown promise in ordering reinforcer magnitudes with reinforcers such as electrical brain stimulation or sweetened milk in rodents is to increase the number of responses required for each successive reinforcement delivery. The technique, which is called the progressive ratio schedule (Hodos, 1961; Hodos & Kalman, 1963), may require 100 responses for the initial reinforcer; then the requirement might double to 200, 400, 800, etc. The critical measure of behavior is the highest ratio completed in a given period of time, and this is used as an indicator of the strength of the reinforcer. It is thought that the application of this procedure will provide comparisons of the relative reinforcing strengths of different cocaine doses as well as comparisons among different drugs. Yanagita (1973) showed that rhesus monkeys completed larger ratios for larger doses of cocaine. Griffiths et al. (1975), however, found the largest completed ratio to be constant for baboons that were self-injecting cocaine in a variety of different doses. The procedures were slightly different in these studies, but as Brady and Griffiths (1977) point out, the major difference was that the doses studied by Griffiths et al. (1975) were larger than those used by Yanagita (1973).

Another technique used to measure the reinforcing strength of different cocaine doses involves behavioral situations in which a preference for or a choice between different doses of cocaine has been determined. Often these situations involve a set of levers,

each of which delivers a different consequence (e.g., different reinforcement magnitudes or different delays in reinforcement delivery). Preference is measured by the relative responding maintained by the different consequences; if the relative rate of responding increases on the lever that delivers reinforcement more often, a preference for that consequence is assumed. In a variety of circumstances with both the baboon Brady & Griffiths, 1977) and the rhesus monkey (Iglauer & Woods, 1974; Johanson & Schuster, 1975), a preference for the larger of two doses of intravenous cocaine has been demonstrated. At very large doses, however, lack of Preference has occasionally been noted (Johanson & Schuster, 1975; Llewellyn et al., 1976). These procedures and variations of them may also provide important data on preferences for different drug and non-drug reinforcers and may provide important ways of assessing behavioral procedures that may affect preferences for drug and non-drug reinforcers (e.g., Catania, 1975).

Another procedure that has been used for the assessment of cocaine as a reinforcer is a second-order schedule of reinforcement (e.g., Kelleher, 1966). This is a schedule that uses one schedule requirement as a building block -- a unitary response requirement -- for a second schedule. For example, a fixed ratio schedule could be used as a building block; it could be reinforced on a second schedule, perhaps a fixed interval. Continuing the example, a cocaine injection would be presented for the first completed fixed ratio after a fixed interval of time from the previous injection. Second-order schedules may be used to examine long sequences of behavior, which are largely maintained by stimuli which accompany the reinforcement. delivery. In the example, a stimulus which accompanies the drug injection when the ratio completed after the interval has passed would also occur with the completion of each fixed ratio within the fixed interval. Thus, it would be possible to examine the ability of stimuli associated with drug injections to maintain behavior that leads to these injections. Conditioned stimuli associated with cocaine and other drugs have been shown to have large effects in the maintenance of schedule-controlled performances in both rhesus and squirrel monkeys (Goldberg et al., 1975). This technique holds considerable promise for investigation of environmental factors affecting drug self-injection.

Recently, an international group convened under the auspices of the Committee on Problems of Drug Dependence to evaluate the above procedures in the preclinical assessment of the abuse potential of new drugs. It was the consensus of the group that the methods discussed in this section hold considerable promise in the evaluation of the abuse potential of both central stimulants and depressants (Unna & Thompson, in press). A full description of cocaine's effects in these procedures will provide a good basis for comparison with other drugs that may have different profiles of behavioral effects.

ACCESS CONDITIONS TO COCAINE: When animals are conditioned to self-inject cocaine, the self-injection behavior may be restricted to a

certain time of day or a specified total number of injections or some combination of these variables in order to limit the intake of cocaine. This limitation of intake has been found necessary for long-term experiments with intravenous cocaine self-injection, since rhesus monkeys will go through bouts of severe intoxication if their intake is not restricted (Deneau et al., 1969; Johanson et al., 1976a). The state of intoxication includes profound to complete anorexia, restlessness, stereotyped movement, piloerection, tremor, dysmetria, self-mutilation and mydriasis. During these periods, which may persist unabated for days, severe central stimulation may produce grand mal convulsions. heath can occur, presumably following either the convulsive episodes or cardiovascular complications. A bout may also be terminated in exhaustion and a period of abstinence, followed by another episode of cocaine self-injection. In the monkey, these cycles often produce death within one month, or, on occasion, in less than one week. Similar cocaine-induced forms of intoxication have been described in intravenous self-injection experiments in rats (Pickens & Thompson, 1971).

The particular parameters of chronic administration that induce these toxic effects are not known. The possibility of species differences exists: Pickens and Thompson (1971) suggested that in rats, amphetamine brings about gross toxicity more readily than cocaine, while Johanson et al. (1976a) suggested that the reverse holds true with the rhesus monkey. Regardless, in the latter species -- when intravenous cocaine is available in an unlimited fashion -- the drug kills with amazing speed and reliability. Yet, this form of intoxication is reversed by limiting the periods for cocaine administration. Most investigators have limited cocaine access to a dose far smaller than that necessary to produce convulsions. Opportunities for self-injection are spaced far enough apart to minimize cumulative drug effects. Quite limited access to the drug can be successfully used. For example, single intramuscular injections maintained responding in the rhesus monkey when access to the drug was limited to alternate days (Goldberg et al., 1976).

OTHER VARIABLES THAT AFFECT COCAINE-REINFORCED RESPONDING: Gollub and Ysnagita (1974) reported that the longer the delay imposed between the completion of a fixed-ratio requirement and its consequent intravenous injection, the slower the cocaine-reinforced responding. Johanson (1975) described a preference situation, however, in which rhesus monkeys chose a delayed injection over an immediate injection. Procedural details of these preliminary reports were not available to resolve these differences in effects. A better understanding of delay of reinforcement might help explain changes in quantitative effects with different routes of administration.

Grove and Schuster (1974) demonstrated that electric shock delivered inmediately following the reinforced response suppressed responding maintained by intravenous cocaine delivery in rhesus monkeys. Johanson (1975) showed that the shock-induced suppression

of a sequence of responses leading to cocaine delivery could be reversed by increasing the dose of cocaine available. These initial findings may lead to important generalizations about the punishment of drug-reinforced responding.

Only one experiment has been conducted on the influence of rate of cocaine injection on reinforced responding. Balster and Schuster (1973) showed that a given dose of intravenously injected cocaine was more effective in maintaining fixed-interval performance the more rapidly it was injected.

EFFECTS OF DRUGS ON RESPONDING MAINTAINED BY COCAINE REINFORCEMENT: A wide variety of drugs have been examined for their effects on cocaine-reinforced responding. These effects hold potential interest for a number of reasons: the pharmacology of cocaine's behavioral effects, including the reinforcing effect, may be described in part through analysis of the manner in which different drugs alter cocaine's reinforcing effects. Further, a drug that reduces the reinforcing effect of cocaine might be used to treat problems of excessive cocaine use. Similarly, a drug that alters the reinforcing effect of cocaine could be used to analyze the behavioral and pharmacological actions of cocaine. As has been mentioned, cocaine's locomotor stimulating effect is thought to be related to a potentiation of the effect of biogenic amines (e.g., norepinephrine, serotonin and dopamine).

Drugs which act to reduce the activity of catecholamine-containing neurons have been shown to alter cocaine-reinforced responding. For example, haloperidol is thought to act as an antagonist of dopamine's actions. It may increase cocaine-reinforced responding at small doses while reducing cocaine-maintained responding at larger doses (Gill et al., in press; Woods et al., in press). Other drugs which share haloperidol's property of blocking dopamine receptors (e.g., pimozide, chlorpromazine, perphenazine and trifluorperazine) also modify cocaine-reinforced responding.[1] Drugs that act to reduce adrenergic activity through different cellular mechanisms (e.g., alpha-methyl-para-tyrosine and reserpine) also bring about changes in cocaine-reinforced responding (Wilson & Schuster, 1973a; 1974). Because doses of haloperidol and chlorpromazine that affect behavior maintained by other reinforcers (e.g., food) also affect cocaine-reinforced responding, their behavioral specificity in changing cocaine-reinforced responding has to be examined in great detail.

Drugs that are known to potentiate the actions of biogenic amines by interfering with their termination of action (e.g., pargyline and imipramine) reduce cocaine-reinforced responding (Wilson &

[1]Gill et al., in press; Johanson et al., 1976b; Risner, 1977; Wilson & Schuster, 1972, 1973a; Woods et al., in press.

Schuster, 1973a; 1974). The specificity of this effect on cocaine-reinforced responding has not been assessed. Taken together, these results suggest that biogenic amines act as modulators of cocaine-reinforced responding. Further research is needed to delineate the pharmacological and behavioral actions of these drugs on cocaine-reinforced responding.

The schedule of cocaine reinforcement is an extremely important variable in determining the nature and magnitude of the effects of chlorpromazine and haloperidol on cocaine-reinforced responding (Woods et al., in press). It is likely that other variables (e.g., dose, pretreatment time and route of administration) interact in complex manners to determine the direction and magnitude of these drug effects.

Atropine, a drug which blocks some of the actions of the neurotransmitter, acetylcholine, has been shown to increase cocaine-reinforced responding in small doses. The quaternary form of the drug, which does not readily pass the blood-brain barrier, and consequently has little central action, did not increase cocaine self-injection (Wilson & Schuster, 1973b). The effect of atropine was similar to that described above for dopamine receptor blockers. However, atropine did not reverse cocaine-induced decreases in food-reinforced responding in rhesus monkeys whereas chlorpromazine did antagonize this effect of cocaine (Wilson & Schuster, 1975). This curious and interesting drug interaction deserves considerable further investigation.

Propranolol in the squirrel monkey reduces cocaine-reinforced responding in a manner similar to that brought about by increasing the cocaine dose. Moreover, doses of propranolol that decreased cocaine-reinforced responding had no effect on behavior maintained at comparable rates and patterns by food presentation (Goldberg & Gonzalez, in press). Propranolol has been shown to reduce cardiac output in the doses that reduced cocaine-reinforced responding and, thus, it may have slowed the delivery of cocaine to sites of inactivation or metabolism. This and other potential mechanisms of propranolol effects were entertained by the authors.

Dougherty and Pickens (1974) investigated two drugs that may influence metabolism of cocaine in a situation involving self-injection by rats. They found that phenobarbital, an agent that increases liver microsomal drug-metabolizing systems, increased cocaine self-injection. Another drug, SKF-525A, which blocks this same metabolism system in the liver, reduced cocaine self-injection. Since these effects are similar to those expected from changes in the cocaine dose, the authors suggest that the effects may have been due to altered metabolism of cocaine.

A variety of other drugs have been shown to reduce cocaine-reinforced responding, e.g., morphine, pentobarbital, d-amphetamine and phenmetrazine (Wilson & Schuster, 1973a). The interpretation of these findings will become clearer when the specificity of these

drugs has been assessed by comparing their effects on behavior comparably controlled by non-drug reinforcers. For instance, it may be that the doses of d-amphetamine required to reduce cocaine-reinforced responding are different than those needed to reduce food-reinforced responding occurring at the same rate.

This section of the paper has dealt with an important area of research which has not yet yielded its full potential. For example, in none of the research reported can one conclude that a drug interacts with the reinforcing effects of cocaine in a selective manner. Selective potentiation of its behavioral effects has been demonstrated with propranolol; yet, even in this case, the reinforcing effects of the drug may not have been altered selectively.

COMPARISON OF COCAINE'S REINFORCING EFFECT TO THAT OF OTHER REINFORCERS: Many individuals believe that cocaine is an inherently strong reinforcer; its reinforcing effect may in some way override the effects of other stimuli. By implication, for example, when pitted against cocaine, most stimuli would not be preferred. This impression of the strength of the reinforcing effect of cocaine has arisen from the observations of severely intoxicated states that have been induced as a consequence of self-injection by the intravenous route of administration rather than a more appropriate analysis compatible with the concept of a reinforcing effect of the drug. If we take the broader view, a variety of experimental conditions are important to a consideration of the strength of cocaine's reinforcing effect relative to other events. The comparison of cocaine's reinforcing effects with other drugs and non-drug reinforcers is both an important theoretical and empirical issue which has received little experimental attention. Thompson and Pickens pointed out in 1970 that there were no direct experimental comparisons of cocaine to other reinforcers. All experiments addressing the issue that have been done since that time have used intravenous routes of delivery and have drawn comparisons between drugs so delivered and food delivery. Ideally, a variety of events should be compared across different behavioral conditions in order to arrive at general conclusions. In addition, drugs and other interventions should be studied to determine whether they modify the reinforcing efficacy of cocaine and other events when they function as reinforcers. A multidimensional comparison of this kind is a complex undertaking and is by no means complete; nevertheless, there are a number of conditions under which comparisons have been drawn between cocaine and other events.

Unlimited Access: As mentioned previously, cocaine self-injection patterns under conditions of unlimited access are erratic with bouts of self-intoxication alternating with drug abstinence. Deneau et al. (1969) noted that this pattern occurred with amphetamine and ethanol but not with narcotics or pentobarbital. With cocaine, as with ethanol, this pattern of self-injection is probably terminated by the prolonged state of intoxication since it is not sustained under limited drug access with either drug (Winger & Woods, 1973; Woods & Schuster, 1970). Variables associated with the termination of these bouts of self-injection have not otherwise

been identified. It is possible that prolonged exposure to cocaine under limited but extensive access conditions may change the reinforcing value of cocaine.

Dose: A variety of procedures have been used to show that a larger cocaine dose is preferred to a smaller, as mentioned previously. Johanson and Schuster (1975) showed that cocaine was preferred to methylphenidate; however, ah increase in the dose of methylphenidate reversed the preference in favor of methylphenidate. Griffiths et al. (1975) found that cocaine could maintain higher-breaking points on progressive ratio schedules of drug delivery in baboons than either secobarbital or methylphenidate. A variety of doses and conditions for cocaine and comparison agents need to be evaluated to arrive at an assessment of the generality of these results.

Schedules of Reinforcement: Intravenous cocainemaintained fixed-ratio responding at higher maximal rates than codeine in the rhesus monkey (Dawns & Woods, 1974) and a similar finding has been shown with cocaine-pentobarbital comparisons in the rhesus monkey (Goldberg et al., 1971). Goldberg (1973) compared food and intravenous cocaine deliveries as reinforcers on both ratio schedules and second-order schedules of reinforcement in squirrel monkeys. He found that the reinforcers could be used to maintain comparable rates and patterns of responding on both types of schedules. Rut the degree of equivalence depended both on the history of exposure and, more importantly, on the magnitude of either food or cocaine delivered. More recently, Goldberg (1976) has suggested that the reinforcing effects of morphine and cocaine can be comparable under second-order schedules of drug delivery.

The continuing examination of important issues associated with the comparison of cocaine to other events as reinforcers is needed. Indeed, it is quite unfortunate that more experiments focusing on comparisons of this type have not been designed. Nevertheless, it is clear that other variables must be evaluated when reinforcers are compared; generalizations depend as much on conditions of cocaine delivery as on any general property of cocaine as a reinforcer.

GENERAL CONSIDERATIONS

Details of the patterns of human cocaine self-administration are essentially unknown. Anecdotal accounts suggest that the predominant route is intranasal, but there is virtually no reliable information on amounts taken over periods of cocaine use in any large group of individuals. (See Chapter 4, Byck & Van Dyke; Chapter 5, Smith & Wesson; and, Chapter 6, Siegel, this volume.) Consequently, it is impossible to evaluate the parallels between cocaine self-administration in animals and in humans. Even a full examination of cocaine self-administration in animals using the primary route of administration used by man would be informative; only a beginning has been made on that task.

Nevertheless, there are reasonable inductions from animal research that in principle are applicable to human self-administration. Severe cocaine intoxication is self-induced when the intravenous route of administration is used and access to the drug is unlimited. Limited access to the drug, routes of administration that delay onset of action, and low doses each contribute to reductions in the severity of self-induced intoxication.

It is important to examine in animals the conditions that induce patterns of behavior that, although initially characterized by insignificant drug-taking, may eventuate in severe self-intoxication. A much better description of factors that contribute to the progression of drug-taking from sampling to occasional use to severe chronic intoxication can be derived from such studies. Important clues to these factors can be gathered from studies exploring ways of potentiating the reinforcing potency of other drugs. For example, investigators have found a variety of ways to enhance the reinforcing properties of ethanol (e.g., Cotten, 1975). By comparing these factors, it may be possible to examine those that pertain generally to many drugs and those that are specific to cocaine.

Cocaine clearly functions as an effective stimulus to reinforce drug-taking behavior in animals. The conditions of cocaine delivery in relation to different behaviors are at least as important to how behavior is changed by cocaine as is any inherent property of cocaine. Studies of cocaine self-administration have shown repeatedly that either a great deal of behavior or very little can be maintained by cocaine depending on the conditions of delivery. It may be that cocaine will turn out to be an effective reinforcer of different behaviors under a much broader or different set of conditions than other drugs. This supposition will be borne out only by the systematic study of the drug as well as a reinforcer under a wide set of environmental conditions.

The mechanisms of cocaine's actions on behavior should be studied using the behavioral procedures described above. It is not clear whether any of the various behavioral actions of cocaine can be separated. For example, is it possible to alter the reinforcing effects of cocaine, leaving other effects of cocaine, e.g., the ability to change food-reinforced responding, unaltered? In principle, studies of this kind should allow answers to questions that have important clinical implications. For example, if drugs could be shown to alter the doses of cocaine that reinforce and maintain drug-taking behavior, these drugs could be used in a manner analogous to the use of narcotic antagonist therapy for heroin abuse. An important consideration in this type of therapy is whether other behaviors are also affected by doses of drugs that modify the reinforcing effects of the abused drug.

Though the question of whether cocaine's behavioral actions may be separated remains unanswered, questions about which of cocaine's specific physiological actions are most closely associated with its behavioral actions can be raised. Cocaine brings about some of its

physiological effects by two prominent actions: it stabilizes membranes, an action associated with its local anesthetic action; and it potentiates the actions of biogenic amines. It may so act by blocking uptake of these amines and it may release certain amines as well (e.g., Kalsner & Nickerson, 1969). Collier (1968) has speculated that the potentiation of the actions of norepinephrine by cocaine may be related to its reinforcing actions. A careful comparison of a variety of drugs, each of which has a different physiological property in common with cocaine, would be helpful in matching physiological mechanisms with behavioral effects.

The analysis of cocaine's behavioral actions in animals has led to a description of its effects in a variety of experimental contexts, increasing our understanding of the complex actions of the drug. The contribution of studies of this kind is especially important due to the paucity of information on human subjects.

James H. Woods, Ph.D.
Departments of Pharmacology and Psychology
University of Michigan
Ann Arbor, Michigan

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REFERENCES

The Behavioral Effects of Cocaine in Animals

Ando, K. The discriminative control of operant behavior by intravenous administration of drugs in rats. Psychopharmacologia, 45:47-50 (1975).

Balster, R. and Schuster, C.R. Fixed interval schedule of cocaine reinforcement: Effect of dose and infusion duration. Journal of the Experimental Analysis of Behavior, 20:119-129 (1973).

Barrett, J.E. Effects of alcohol, chlordiazepoxide, cocaine and pentobarbital on responding maintained under fixed-interval schedules of food or shock presentation. Journal of Pharmacology and Experimental Therapeutics, 196:605-615 (1976).

Barry, H. Classification of drugs according to their discriminable effects in rats. Federation Proceedings, 33:1814-1824 (1974).

Barry, H. and Kubena, R.K. Discriminative stimulus characteristics of alcohol, marihuana, and atropine. In Singh, J.M., Miller, L., and Lal, H. (eds.), Drug Addiction: Experimental Pharmacology. Mount Kisco, NY: Futura Press, 1972, pp. 3-16.

Blumberg, H. and Ikeda, C. Interactions between naltrexone, morphine, and cocaine in rats. Federation Proceedings, 34:714 (1975a).

Blumberg, H. and Ikeda, C. Naltrexone, morphine, and cocaine interactions in mice. Pharmacologist, 17:206 (1975b).

Brady, J.V. and Griffiths, R.R. Drug-maintained performance and the analysis of stimulant reinforcing effects. In Ellinwood, E.H. and Kilbey, M.M. (eds.), Cocaine and Other Stimulants. New York, NY: Plenum Press, 1977 pp. 599-614.

Cappell, H. and LeBlanc, A.E. Gustatory avoidance conditioning by drugs of abuse: Relationships to general issues in research on drug dependence. In: Pilgram, N.W., Krames, L. and Alloway, T.M. (eds.) Food Aversion Learning. New York, NY: Plenum Press, in press.

Catania, A.C. Drug effects and concurrent performances. Pharmacological Reviews, 27:385-394 (1975).

Christie, J.E. and Crow, T.J. Behavioural studies of the actions of cocaine, monoamine oxidase inhibitors, and iminodibenzyl compounds on central dopamine neurons. British Journal of Pharmacology, 47:39-47 (1973).

Collier, H.O.J. Supersensitivity and dependence on cocaine. Nature, 220:1327-1328 (1968).

Costa, E., Gropetti, A. and Naimzada, M.K. Effects of amphetamine on the turnover rate of brain catecholamines and motor activity. British Journal of Pharmacology, 44:742-751 (1972).

Cotten, M. de V. (ed.) Symposium on control of drug-taking behavior by schedules of reinforcement. Pharmacological Reviews 27:291-548 (1975).

Crow, T.J. Enhancement by cocaine of intracranial self-stimulation in the rat. Life Sciences, 9:375-381 (1970).

Deneau, G.W., Yanagita, T. and Seevers, M.H. Self-administration of psychoactive substances by the monkey: A measure of psychological dependence. Psychopharmacologia, 16:30-48 (1969).

Dews, P.B. The measurement of the influence of drugs on voluntary activity in mice. British Journal of Pharmacology, 8:46-48 (1953).

Dews, P.B Analysis of the effects of pharmocological agents in behavioral terms. Federation Proceedings, 17:1024-1030 (1958).

Dougherty, J. Personal communication, 1976.

Dougherty, J. and Pickens, R. Fixed-interval schedules of intravenous cocaine presentations in rats. Journal of the Experimental Analysis of Behavior, 20:111-118 (1973).

Dougherty, J. and Pickens, R. Effects of phenobarbital and SKF-525A on cocaine self-administration in rats. In Singh, J.M. and Lal, H. (eds.), Drug Addiction, Vol. 4. Miami, FL: Symposium Specialists, 1974, pp. 135-143.

Downs, A. and Eddy, N.B The effect of repeated doses of cocaine on the dog. Journal of Pharmacology and Experimental Therapeutics, 46:195-198 (1932a).

Downs, A. and Eddy, N.B The effect of repeated doses of cocaine in the rat. Journal of Pharmacology and Experimental Therapeutics, 46:199-200 (1932b).

Downs, D.A. and Woods, J.H. Codeine- and cocaine-reinforced responding in rhesus monkeys: Effects of dose on response rates under a fixed-ratio schedule. Journal of Pharmacology and Experimental Therapeutics, 191:179-188 (1974).

Ferster, C.B. and Skinner, RF. Schedules of Reinforcement. New York, NY: Appleton-Century-Crofts, 1957.

Findley, J., Robinson, W.W. and Peregrino, L. Addiction to secobarbital and chlordiazepoxide in the rhesus monkey by means of a self-infusion preference procedure. Psychopharmacologia, 26:93-114 (1972).

Fog, R. Stereotyped and non-stereotyped behaviour in rats induced by various stimulant drugs. Psychopharmacologia, 14:299-304 (1969).

Galambos,E., Pfeifer, A.K.; Gyorgy, L. and Molnar, J. Study of the excitation induced by amphetamine, cocaine, and alpha-methyltryptamine. Psychopharmacologia, 11:122-129 (1967).

Gill, C.A., Holz, W.C., Zirkle, C. and Hill, H. Pharmacological modification of cocaine and apomorphine self-administration in the squirrel monkey. In Proceedings of the 10th Congress, Collegium Internationale Neuropsychopharmacologicum. Oxford, England: Pergamon Press, in press.

Goldberg, S.R. Comparable behavior maintained under fixed-ratio and second-order schedules of food presentation, cocaine injection, or d-amphetamine injection in the squirrel monkey. Journal of Pharmacology and Experimental Therapeutics, 186:18-30 (1973).

Goldberg, S.R. Second-order schedules of morphine or cocaine injection. Pharmacologist, 18:197 (1976).

Goldberg, S.R. and Gonzalez, F.A. The effects of propranolol on behavior maintained under fixed-ration schedules of cocaine injection or food presentation in squirrel monkeys. Journal of Pharmacology and Experimental Therapeutics, in press.

Goldberg, S.R, Hoffmeister, F., Schlichting, U.U., and Wittke, W. A comparison of pentobarbital and cocaine self-administration in rhesus monkeys: Effects of dose and fixed-ratio parameter. Journal of Pharmacology and Experimental Therapeutics, 179:277-283 (1971).

Goldberg, S.R. and Kelleher, R.T. Behavior controlled by scheduled injections of cocaine in squirrel and rhesus monkeys. Journal of the Experimental Analysis of Behavior, 25:93-104 (1976).

Goldberg, S.R. and Kelleher, R.T. Reinforcement of behavior by cocaine injections. In Ellinwood, E.H. and Kilbey, M.M. (eds.), Cocaine and Other Stimulants. New York, NY: Plenum Press, 1977, pp. 523-543.

Goldberg, S.R., Kelleher, R.T. and Morse, W.H. Second-order schedules of drug injection. Federation Proceedings, 34:1771-1776 (1975).

Goldberg, S.R., Morse, W.H. and Goldberg, D.M. Behavior maintained under a second-order schedule by intramuscular injection of morphine or cocaine in rhesus monkeys. Journal of Pharmacology and Experimental Therapeutics, 199:278-286 (1976).

Gollub, L. and Yanagita, T. Delayed cocaine reinforcement of lever-pressing in rhesus monkeys. Paper presented at Psychonomic Society, Boston, Massachusetts, 1974.

Gonzalez, F.A. and Goldberg, S.R. Effects of cocaine and d-amphetamine on behavior maintained under various schedules of food presentation in squirrel monkeys. Journal of Pharmacology and Experimental Therapeutics, in press.

Griffiths, R.R., Findley, J.D., Brady, J.V., Gutcher, K. and Robinson, W.W. Comparison of progressive ratio performance maintained by cocaine, methylphenidate, and secobarbital. Psychopharmacologia, 43:81-83 (1975).

Grove, R.N. and Schuster, CR Suppression of cocaine self-administration by extinction and punishment. Pharmacology, Biochemistry and Behavior, 2:199-208 (1974).

Hatch, RC. Cocaine-elicited behavior and toxicity with dogs pretreated with methiothepin or p-chlorophenylalanine. Pharmacological Research Communications, 5:321-327 (1973).

Hatch, R.C. and Fischer, R. Cocaine-elicited behavior and toxicity in dogs pretreated with synaptic blocking agents, morphine, or diphenylhydantoin. Pharmacological Research Communications, 4:383-392 (1972).

Hawks, R.L., Kopin, I.J., Colburn, R.W. and Thoa, N.B. Norcocaine: a pharmacologically active metabolite of cocaine found in brain. Life Sciences, 15:2189-2195 (1974).

Herd, J.A., Morse, W.R, Kelleher, R.T. and Jones, L.G. Arterial hypertension in the squirrel monkey during behavioral experiments. American Journal of Physiology, 217:24-29 (1969).

Herling, S., Downs, D.A. and Woods, J.H. Rate-dependent effects of drugs on food- and cocaine-reinforced lever-press responding in rhesus monkeys. Federation Proceedings, 34:765 (1975).

Hill, H.E., Bell, EC. and Wikler, A. Reduction of conditioned suppression: Actions of morphine compared with those of amphetamine, pentobarbital, nalorphine, cocaine, LSD-25 and chlorpromazine. Archives Internationale de Pharmacodynamie, 165:212-226 (1967).

Hodos, W. Progressive ratio as a measure of reward strength. Science, 134:948-944 (1961).

Hodos, W. and Kalman, G. Effects of increment size and reinforcer volume on progressive ratio performance. Journal of the Experimental Analysis of Behavior, 6:387-392 (1963).

Hutchinson, R.R. The environmental causes of aggression. In Cole, J.K. and Jensen, D. D. (eds.), Nebraska Symposium on Motivation, 1972. Lincoln, NE: University of Nebraska Press, 1973, pp. 155-181.

Hutchinson, R. R. , Emley, G. S. and Krasnegor, N. A. The effects of cocaine on the aggressive behavior of mice, pigeons, and squirrel monkeys. In Ellinwood, E.H. and Kilbey, MM. (eds.), Cocaine and Other Stimulants. New York, NY: Plenum Press, 1977, pp. 457-480.

Iglauer, C. and Woods, J.H. Concurrent performances: Reinforcement by different doses of intravenous cocaine in rhesus monkeys. Journal of the Experimental Analysis of Behavior, 22:179-196 (1974).

Johanson, C. E. Pharmacological and environmental variables affecting drug preference in rhesus monkeys. Pharmacological Reviews, 27:343-355 (1975).

Johanson, C. E. The differential effects of intravenous cocaine, diethylproprion, d-amphetamine, and perphenazine on responding maintained by food delivery and shock avoidance under a multiple schedule in rhesus monkey. In press(a).

Johanson, C. E. The effects of electric shock on responding maintained by cocaine injections in a choice procedure in the rhesus monkey. Pharmacology, Biochemistry and Behavior, in press(b).

Johanson, C.E., Balster, R. L. and Bonese, K. Self-administration of psychomotor stimulant drugs: The effects of unlimited access. Pharmacology, Biochemistry and Behavior, 4:45-51 (1976a).

Johanson, C. E. , Kandel, D. A. and Bonese, K. The effects of perphenazine on self-administration behavior. Pharmacology, Biochemistry and Behavior, 4:427-433 (1976b).

Johanson, C. E. and Schuster, C. R. A choice procedure for drug reinforcers: Cocaine and methylphenidate in the rhesus monkey. Journal of Pharmacology and Experimental Therapeutics, 193:676-688 (1975).

Jones, R. E. and Prada, J. Relapse to morphine use in dogs. Psychopharmacologia, 30:1-12 (1973).

Kalsner, S. and Nickerson, M. Mechanism of cocaine potentiation of responses of amines. British Journal of Pharmacology, 35:428-439 (1969).

Kelleher, R.T. Chaining and conditioned reinforcement. In Honig, W.K. (ed.) Operant Behavior: Areas of Research and Application. New York, NY: Appleton-Century-Crofts, 1966, pp. 160-212.

Lal, H. and Chessick, R.D. Lethal effects of aggregation and electric shock in mice treated with cocaine. Nature, 208:295-296 (1965).

Llewellyn, M.E., Iglauer, C. and Woods, J.H. Relative reinforcer magnitude under a non-independent concurrent schedule of intravenous cocaine reinforcement in rhesus monkeys. Journal of the Experimental Analysis of Behavior, 25:81-91 (1976).

MacPhail, R.C. and Seiden, L.S. Time course for the effects of cocaine on fixed-ratio water-reinforced responding in rats. Psychopharmacologia, 44:1-4 (1975).

Matsuzaki, M., Spingler, P.J., Misra, A.L. and Mule, S.J. Cocaine: Tolerance to its convulsant and cardiorespiratory stimulating effects in the monkey. Life Sciences, 19:193-204 (1976).

Misra, A.L., Nayak, P.K., Block, R. and Mule, S.J. Estimation and disposition of (^{3}H)-benzoylecgonine and the pharmacological activity of some cocaine metabolites. Journal of Pharmacy and Pharmacology, 27:784-786 (1975).

Misra, A.L., Nayak, P.K., Patel, M.N., Vadlamani, N.L. and Myle, S.J. Identification of norcocaine as a metabolite of (^{3}H)-cocaine in rat brain. Experientia, 30:1312-1314 (1974a).

Misra, A.L., Vadlamani, N.L., Block, R., Nayak, P.K. and Mule, S.J. Physiological disposition and metabolism of (^{3}H) ecgonine (cocaine metabolite) in the rat. Research Communications in Chemical Pathology and Pharmacology, 8:55-63 (1974b).

Morpurgo, C. Drug-induced modification of discriminated avoidance behavior in rats. Psychopharmacologia, 8:91-99 (1965).

Morse, W.H. and Kelleher, R.T. Schedules as fundamental determinants of behavior. In Schoenfeld, W.N. (ed.), The Theory of Reinforcement Schedules. New York, NY: Appleton-Century-Crofts, 1970, pp. 139-185.

Nayak, P.K., Misra, A.L. and Mule, S.J. Physiological disposition and biotransformation of (H^3)-cocaine in acutely and chronically treated rats. Journal of Pharmacology and Experimental Therapeutics, 196:556-569 (1976).

Overton, D. Discriminative control of behavior by drug states. In Thanpson, T. and Pickens, R. (eds.), Stimulus Properties of Drugs. New York, NY: Appleton-Century-Crofts, 1971, pp. 87-110.

Peterson, D.I. and Hardinge, M.G. The effects of various environmental factors on cocaine and ephedrine toxicity. Journal of Pharmacy and Pharmacology, 19:810-814 (1967).

Pickens, R. and Thompson, T. Cocaine-reinforced behavior in rats: Effects of reinforcement magnitude and fixed-ratio size. Journal of Pharmacology and Experimental Therapeutics, 161:122-129 (1968).

Pickens, R. and Thompson, T. Characteristics of stimulant reinforcement. In Thompson, T. and Pickens, R. (eds.), Stimulus Properties of Drugs. New York, NY: Appleton-Century-Crofts, 1971, pp. 177-192.

Pickens, R. and Thompson, T. Simple schedules of drug self-administration in animals. In Singh, J.M., Miller, L.H. and Lal, H. (eds.), Drug Addiction. Vol. 1. Experimental Pharmacology. Mount Kisco, NY: Futura Publishing Co., 1972, pp. 107-120.

Post, R.M., Kopanda, R.T. and Black, K.E. Progressive effects of cocaine an behavior and central amine metabolism in rhesus monkeys: Relationship to kindling and psychosis. Biological Psychiatry, 11:403-419 (1976).

Post, R.M. and Rose, H. Increasing effects of repetitive cocaine administration in the rat. Nature, 260:731-732 (1976).

Randrup, A. and Munkvad, I. Stereotyped activities produced by amphetamine in several animal species. Psychopharmacologia, 11:300-310 (1967).

Risner, M. Personal communication, 1976.

Risner, M. A comparison of cocaine (c) and d-Amphetamine (A) self-administration by dog. Federation Proceedings, 1977.

Scheel-Kruger, J. Behavioural and biochemical comparison of amphetamine derivatives, cocaine, benztrapine, and tricyclic antidepressant drugs. European Journal of Pharmacology, 18:63-73 (1972).

Schuster, C.R. Personal communication, 1976.

Schuster, C.R., Dockens, W. and Woods, J.H. Behavioral variables affecting the development of amphetamine tolerance. Psychopharmacologia, 9:170-182 (1968).

Siegel, R.K., Johanson, C.A., Brewster, J.M. and Jarvik, M.E. Cocaine self-administration in monkeys by chewing and smoking. Pharmacology, Biochemistry and Behavior, 4:461-467 (1976).

Smith, C.B. Enhancement by reserpine and alpha-methyl dopa of the effects of d-amphetamine upon the locomotor activity of mice. Journal of Pharmacology and Experimental Therapeutics, 142:343-350 (1963).

Smith, C.B. Effects of d-amphetamine upon operant behavior of pigeons: Enhancement by reserpine. Journal of Pharmacology, 146:167-174 (1964).

Smith, C.B. Effects of d-amphetamine upon brain amine content and locomotor activity of mice. Journal of Pharmocology and Experimental Therapeutics, 147:96-102 (1965).

Spealman, R.D., Goldberg, S.R. and Kelleher, R.T. Behavioral effects of cocaine and two cocaine analogs in squirrel monkeys. Pharmacologist, 18:197 (1976).

Spealman, R.D, KELLEHER. R.T., Goldberg, S.R., Goldberg, D.M. and Charlton, J.R. Personal communication, 1976.

Thompson, T. and Pickens, R. Stimulating self-administration by animals: Some comparisons with opiate self-administration. Federation Proceedings, 29:6-12 (1970).

Thompson, T. and Schuster, C.R. Behavioral Pharmacology. Englewood Cliffs, NJ: Prentice-Ball, 1968.

Unna, K. and Thompson, T. (eds.) Testing for dependence liability of stimulants and depressants. Appendix I. New York, NY: Academic Press, in press.

Van Rossum, J.M. and Simons, F. Locomotor activity and anorexigenic action. Psychopharmacologia, 14:248-254 (1969).

Van Rossum, J.M., Van der Schaat, J.B. and Hurkmans, J.A. Mechanisms of action of cocaine and amphetamine in the brain. Experientia, 15:229-231 (1962).

Villarreal, J.E., Guzman, M. and Smith, C.B. A comparison of the effects of d-amphetamine and morphine upon the locomotor activity of mice treated with drugs which alter brain catecholamine context. Journal of Pharmacology and Experimental Therapeutics, 187:1-7 (1973).

Wallach, M.B. and Gershon, S. A neuropsychological comparison of d-amphetamine, L-dopa and cocaine. Neuropharmacology, 10:743-752 (1971).

Wauquier, A. and Niegemeers, G.J.E. Intracranial self-stimulation in rats as a function of stimulus parameters. V. Influence of cocaine on medial forebrain bundle stimulation with monopolar electrodes. Psychopharmacologia, 38:201-210 (1974).

Weeks, J.R. Experimental morphine addiction: method for automatic intravenous injections in unrestrained rats. Science, 138:143-144 (1962).

Wenger, G. Personal communication, 1976.

Wilson, M.C., Bedford, J.A., Buelke, J. and Kibbe, A.H. Acute pharmacological activity of intravenous cocaine in the rhesus monkey. Psychopharmacological communications, 2:251-262 (1976).

Wilson, M.C. and Holbrook, J.M. Cocaine-induced locomotor activity and the effects of catecholamine depletion. Pharmacologist, 16:215 (1974).

Wilson, M.C. and Schuster, C.R. The effects of chlorpromazine on psychomotor-stimulant self-administration in the rhesus monkey. Psychopharmacologia, 26:115-126 (1972).

Wilson, M.C. and Schuster, C.R. The effects of stimulants and depressants on cocaine self-administration behavior in the rhesus monkey. Psychopharmacologia, 31:291-304 (1973a).

Wilson, M.C. and Schuster, C.R. Cholinergic influence on intravenous cocaine self-administration by rhesus monkeys. Pharmacology, Biochemistry and Behavior, 1:643-649 (1973b).

Wilson, M.C. and Schuster, C.R. Aminergic influences on cocaine self-administration by rhesus monkeys. Pharmacology, Biochemistry and Behavior, 2:563-571 (1974).

Wilson, M.C. and Schuster, C.R. Interactions between atropine, chlorprauazine, and cocaine on food-reinforced behavior. Pharmacology, Biochemistry and Behavior, 3:363-375 (1975).

Winger, G.S. and Woods, J.H. The reinforcing property of ethanol in the rhesus monkey. I. Initiation, maintenance and termination of intravenous ethanol-reinforced responding. Annals of the New York Academy of Sciences, 215:162-165, April, 30, 1973.

Winter, J.C. The effect of 2,5-dimethoxy-4-methylamphetamine (DOM), 2,5-dimethoxy-4-ethylamphetamine (DOET), d-amphetamine, and cocaine in rats trained with mescaline as a discriminative stimulus. Psychopharmacologia, 44:29-32 (1975).

Woods, J.H. and Downs, D.A. The psychopharmacology of cocaine. In Drug Use in America: Problem in Perspective. Appendix, Vol. 1: Patterns and Consequences of Drug Use. Washington, DC: U.S. Government Printing Office, 1973, pp. 116-139.

Woods, J.H, Herling, S. and Wihger, G. Chlorpromazine- and haloperidol-induced changes in some behavioral effects of cocaine and amphetamine. In Proceedings of the 10th Congress, Collegium Internationale Neuropsychopharmacologicum. Oxford, England: Pergamon Press, in press.

Woods, J.H. and Schuster, C.R Regulation of drug self-administration In Harris, RT., McIsaac, MM. and Schuster, C.R (eds.) Drug Dependence. Austin, TX: University of Texas Press, 1970 pp. 158-169.

Woods, J.H. and Tessel, R.E Fenfluramine: Amphetamine congener which fails to maintain drug-taking behavior in the rhesus monkey. Science, 185:1067-1069 (1974).

Woolverton, W., Kandel, D. and Schuster, C.R Contingent tolerance to cocaine. Report of Committee oh Problems of Drug Dependence, in press.

Yanagita, T. An experimental framework for evaluation of dependence liability in various types of drugs in monkeys. Bulletin on Narcotics, 1:25-57 (1973).

Chapter V WHAT ARE THE EFFECTS OF COCAINE IN MAN?

Robert Byck, M.D. and Craig Van Dyke, M.D.

The question in the title my not be answered for the reader of this essay. What we know for sure may strike the reader as mundane. What is supported by strong evidence may impress the reader as common knowledge.

This dilemma is not just a reflection of restricted research in cocaine. It is rather a statement. of our inability to describe fully the effects of any agent which alters complex human functions. In order to prepare you for an answer we must first assess the quality of the evidence. This can be phrased in terms of Source and Surety. Myths, street knowledge, animal studies and clinical or laboratory reports in man represent sources of information about cocaine. While surety is in part a function of source (e.g., we are much less certain of the mythological infomation than we are of the clinical information), it is also dependent on other factors. For instance, multiple clinical reports are more certain than single clinical reports. To say we know that an effect occurs means that it has been demonstrated in a controlled experimental situation in a number of independent laboratories. It also means that in clinical or street reports the substance causing the effects can be positively identified. Ideally, the effect should be consistently seen in non-laboratory situations and should be measurable in a reproducible fashion.

Why a laboratory experiment? Why many laboratories? Why a controlled experiment? The history of pharmacology and of psychopharmacology is filled with presumptive errors about the effects of drugs. These errors were clarified only by repeated controlled experiments.

Pharmacologists are concerned with the changing effects of drugs at different dosages. A drug such as alcohol can make people relaxed at one dose, sleepy at another, combative at another and psychotic at another. Nor is every person affected in the same way by these changing dosages. The effects of the surrounding environment (setting) and of the psychological state and history of the subject profoundly modify the action of a drug. Effects seen after chronic use differ from those observed after a single dose -- often they are opposite. Effects seen after injecting a drug often bear little relationship to those seen after swallowing the same substance.

If an effect is measurable by standard instruments or scales, laboratories can compare results. If not, we must, in each instance, make hopeful assumptions about the reliability of the reporting investigators.

SURETY RATING

John Kenneth Galbraith (1975), writing on a subject somewhat unrelated to this article, said:

> These are matters on which there is no proof, and it is unbecoming, however customary, to substitute certainty of statement for hard evidence. But the simple facts are worth a glance.

In order to elude the trap of certainty we have classified the effects of cocaine by assigning a "surety rating" of one to seven to statements made about the drug. The surety rating is numerical and hierarchical. The hierarchy takes into account both the source and surety of the information. For example, although animal experiments may conclusively demonstrate that an effect occurs, one can only presume that this effect does occur in man since we know of many interspecies differences in drug effects. We have summarized in Figure 5-1 all the reported effects of cocaine in man.

Information in column one has been gathered from published research articles where repeated measurements under controlled conditions have shown consistent effects in wan. We can say that we "know[n] that this is an accurate description of the drug's effects at a specific dosage.

Column two encompasses reliable reports from the clinical literature that are consistent in their description and where the dosage of cocaine is known.

Column three includes reports either of controlled experiments in man that have not been replicated or laboratory experiments that are strongly suggestive that the effects observed are probable. (Columns one and three are mutually exclusive.)

Column four indicates that the effects seen are reproducible in animals; but, for a variety of reasons, either have not been evaluated in man or -- for reasons of danger or ethics -- cannot be replicated in man.

In column five effects which are anecdotal in the medical literature are reported. Unpublished reports (referenced as "personal communication") are also included even if the experiments are well controlled.

The sixth column includes popular reports of "Cocaine Effects" -- this is to say we do not know whether cocaine was really the active agent and the "effects" may be distorted in the telling. Much of this information cannot be evaluated by anyone at this time, but some of it may be true.

The seventh column encompasses the real mythology of cocaine. Some of this information is from highly reliable sources and is stated as fact -- but there is no record of the evidence which produced the "fact." The historical myths of the effects of coca chewing are included as well as case reports from the older literature where the reliability of the report, the journal and the subject are all open to question. Some of these effects may occur but their inclusion in the table is only for the purposes of completeness. Many are probably untrue.

There is no way of stating that any effects except those in the first two columns really occur in man as the result of cocaine administration. If we wish to improve our knowledge, the other effects must be evaluated and the quality of the evidence improved.

There is certainly a temptation to include in the "known" effects of a drug in man, those effects which have been seen only in laboratory animals. We cannot rely on such data except in a supportive manner. Certain pertinent effects on psychological phenomena cannot be examined in animals and so the information about the effects of high dosages and chronic usage must remain at the level of street reports and myth. In those instances, in particular, the identity of the drugs causing the effects is unclear. Therefore, in column six, we have been careful not to ascribe to cocaine effects which may be the result of polydrug usage.

Wherever information on human effects is available, we have broken down the data by dosage, route and chronicity. Most drugs produce a spectrum of effects which vary with the amount of drug available at the receptor site. Thus, the some drug can both speed and slow the heart rate, increase and decrease respiratory rate, or cause euphoria and dysphoria.

Dosage alone may not be a clear indicator of the effect to be produced. The concentration of active drug in the blood (now measurable with cocaine) is a closer approximation; but the reader should be aware that even this is not a final answer. Long term exposure to a drug may modify the body and so a drug can be acting in a chemically changed organism.

bearing these caveats in mind, what can we say about the effects of cocaine in man? This question will be answered in narrative form in five parts: local effects, systemic effects, central nervous system effects, social effects and absorption and metabolism; and is also summarized in the first two columns of Figure 5-1. The figure, of course, also presents the less certain "effects" of cocaine which we cannot support with acceptable scientific evidence.

Figure 5-1 lists the reported effects of cocaine in man. In referencing this table we have tended to use single citations. Where many references could be cited, we have used the original reference. The use of early references does not imply that these studies were not replicated in later investigations. We have treated columns one and three as mutually exclusive. Information obtained from "personal communications" has been listed in column five, even if this information resulted from controlled laboratory studies. Ashley (1976) and Mortimer (1901; reprinted, 1974) provide good sources of street knowledge, while most textbooks of pharmacology are good examples of unverifiable information on the effects of cocaine in man. For other reviews of cocaine the reader is referred to: Van Dyke and Ryck (1977), Woods and Downs (1973) and Byck (1975).

References are listed by category and column number. For instance, the reference for the multiple clinical reports of cocaine as au effective local anesthetic is listed under Ia(2) (i.e., I= local effects; a=local anesthesia; (2)=column (2). References for the narrative section are listed separately.

FIGURE 5-1

Reported Effects of Cocaine
Categorized by Type and Reliability of Evidence (Surety)

	CONTROLLED MAN 1	CLINICAL 2	LAB: MAN 3	ANIMAL 4	SINGLE CASE 5	STREET 6	UNVERIFIABLE 7
I. LOCAL EFFECTS							
a. Local Anesthesia	+	+		+		+	+
Pupillary Size:							
b. Topical Application	↑			↑			↑
Blood Vessels: Size							
c. Topical Application		↓		↓			↓
II. SYSTEMIC EFFECTS							
Heart:							
a. Rate	↑	↑		↑↓			↑↓

LEGEND

1. Reproducible in man
2. Many clinical reports in man/reliable sources
3. Laboratory reports in man/not replicated or adequately controlled
4. Animal reports
5. Single case report in man/reliable source
6. Street knowledge
7. Unverifiable report, historical myth, or textbook dogma

\+ report that it occurs
— report that it does not occur
± reports that it both occurs and does not occur
↑ report that it increases
↓ report that it decreases
↑↓ report that it increases and then decreases with higher dosages
↑ ↓ report that it both increases and decreases
0 report that there is no change

Figure 5-1 (cont'd)

	CONTROLLED MAN 1	CLINICAL 2	LAB: MAN 3	ANIMAL 4	SINGLE CASE 5	STREET 6	UNVERIFIABLE 7
II. Systemic Effects - Heart (cont'd)							
b. Strength				↑↓			↑
c. Blood Pressure	↑	↑					↑↓
d. Respiratory Rate			0				↑↓
e. Muscle Strength			0		↑↓		↑
f. Core Temperature			0	↑			↑
III. CENTRAL NERVOUS SYSTEM EFFECTS							
a. Alertness			+			+	+
b. Drowsiness			+			−	

1. Reproductible in man
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Figure 5-1 (cont'd)

	CONTROLLED MAN 1	CLINICAL 2	LAB: MAN 3	ANIMAL 4	SINGLE CASE 5	STREET 6	UNVERIFIABLE 7
III. Central Nervous System Effects (cont'd)							
c. Total Sleep			↓		↓	↓	↓
d. Rapid Eye Movement Sleep			↓				
e. Appetite			↓	↓	↑↓	↓	↓
Mental Performance:							
f. Creativity						↑	↑
Mood:							
g. In Normals	↑				↑	↑	↑
h. In Depressed		↑↓					↑
i. Crash (Post Coke Depression)			+		+	+	+

LEGEND

1. Reproducible in man
2. Many clinical reports in man/reliable sources
3. Laboratory reports in man/not replicated or adequately controlled
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Figure 5-1 (cont'd)

	CONTROLLED MAN 1	CLINICAL 2	LAB: MAN 3	ANIMAL 4	SINGLE CASE 5	STREET 6	UNVERIFIABLE 7
III. Central Nervous System Effects (cont'd)							
Physical Performance:							
j. In Normals					0	↑	↑
k. In Tired					↑	↑	↑
l. High Altitude							↑
IV. SOCIAL EFFECTS							
a. Sexual Performance and Libido						↑↓	↑
b. Crime (Other Than Drug Acquisition or Possession)							↑
c. Aggresssion						±	+

LEGEND

1. Reproducible in man
2. Many clinical reports in man/reliable sources
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Figure 5-1 (cont'd)

	CONTROLLED MAN 1	CLINICAL 2	LAB: MAN 3	ANIMAL 4	SINGLE CASE 5	STREET 6	UNVERIFIABLE 7
V. DRUG DEPENDENCE							
a. Reinforcing Stimulus (Drug-Seeking Behavior)		+		+		+	+
b. Tolerance				±	−	−	±
c. Physical Dependence (Abstinence Syndrome)			+			−	−
VI. TOXIC EFFECTS							
a. Arrhythmias			±		+		+
b. Arrhythmias When Given With Epinephrine				+	+		

LEGEND

1. Reproducible in man
2. Many clinical reports in man/reliable sources
3. Laboratory reports in man/not replicated or adequately controlled
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Figure 5-1 (cont'd)

	CONTROLLED MAN 1	CLINICAL 2	LAB: MAN 3	ANIMAL 4	SINGLE CASE 5	STREET 6	UNVERIFIABLE 7
VI. Toxic Effects (cont'd)							
c. Convulsions				+	+		+
d. Psychosis					+	+	+
e. Vomiting							+
f. Perforation of Nasal Septum					+	+	+

LEGEND

1. Reproducible in man
2. Many clinical reports in man/reliable sources
3. Laboratory reports in man/not replicated or adequately controlled
4. Animal reports
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REFERENCES FOR FIGURE 5-1

What Are the Effects of Cocaine in Man?

Ia(1) Koller, C. Uber die Verwendung des Cocaine zur Anasthesierung am auge. Wiener Medizinische Wochenschrift, 34: Nos. 43 and 44 (1884).

Ia(2) Adriani, J. The clinical pharmacology of local anesthetics. Clinical Phamacology and Therapeutics, 1:645-673 (1960).

Ia(4) Bishop, G.H. Action of nerve depressants on potential. Journal of Cellular and Comparative Physiology, 1:177-194 (1932).

Ib(l) Koller, C. Uber die Verwendung des Cocaine zur Anasthesierung am auge. Wiener Medizinische Wochenschrift, 34: Nos. 43 and 44 (1884).

Ib(4) Kuroda, M. On the action of cocaine. Journal of Pharmacology and Experimental Therapeutics, 7:423-439 (1915).

Ic(2) Barash, P.G. Chapter 9 this volume.

Ic(4) Crosby, W.H. The vasoconstrictor action of cocaine. Journal of Pharmacology and Experimental Therapeutics, 65:150-155 (1939).

IIa(1) Byck, R., Jatlow, P., Barash, P. and Van Dyke, C. Cocaine: Blood concentration and physiological effect after intranasal application in man. In Ellinwood, E.H. and Kilbey, M.M. (eds.), Cocaine and Other Stimulants. New York, NY: Plenum Press, 1977, pp. 629-6 4 .6 .

Resnick, R.B., Kestenbaum, R.S. and Schwartz, L.K. Acute systemic effects of cocaine in man: A controlled study of intranasal and intravenous routes.

Fischman, M.W., Schuster, C.R., Resnekov, L., Shick, J.F.E., Krasnegor, N.A., Fennell, W. and Freedman, D.X. Cardiovascular and subjective effects of intravenous cocaine administration in humans. Archives of General Psychiatry, 33:983-989 (1976).

IIa(2) Post, R.M., Kotin, J. and Goodwin, F.K. The effects of cocaine on depressed patients. American Journal of Psychiatry, 131(5):511-517 (1974).

IIa(4) Trendelenburg, U. The effect of cocaine on the pacemaker of isolated guinea-pig atria. Journal of Pharmacology and Experimental Therapeutics, 161: 222-231 (1968).

IIb(4) Furchgott, R.F., Kirpekar, S.M., Rieker, M. and Schwab, A. Actions and interactions of norepinephrine, tyramine and cocaine on aortic strips of rabbit and left atria of guinea pig and cat. Journal of Pharmacology and Experimental Therapeutics, 142:39-58 (1963).

IIc(1) Byck, R., Jatlow, P., Barash, P. and Van Dyke, C. Cocaine: Blood concentration and physiological effect after intranasal application in man. In Ellinwood, E.H. and Kilbey, M.M. (eds.), Cocaine and Other Stimulants. New York, NY: Plenum Press, 1977, pp. 629-646.

Resnick, R.B., Kestenbaum, R.S. and Schwartz, L.K. Acute systemic effects of cocaine in man: A controlled study by intranasal and intravenous routes. Science, 195:696-698 (1977).

Fischman, M.W., Schuster, C.R., Resnekov, L., Shick, J.F.E., Krasnegor, N.A., Fennell, W. and Freedman, D.X. Cardiovascular and subjective effects of intravenous cocaine administration in humans. Archives of General Psychiatry, 33:983-989 (1976).

IIc(2) Post, R.M., Kotin, J. and Goodwin, F.K. The effects of cocaine on depressed patients. American Journal of Psychiatry, 131(5):511-517 (1974).

IId(3) Resnick, R.B., Kestenbaum, R.S. and Schwartz, L.K. Acute systemic effects of cocaine in man: A controlled study by intranasal and intravenous routes. Psychopharmacological Bulletin, 12(4):44-45 (1976).

Fischman, M.W., Schuster, C.R., Resnekov, L., Shick, J.F.E., Krasnegor, N.A., Fennell, W. and Freedman, D.X. Cardiovascular and subjective effects of intravenous cocaine administration in humans. Archives of General Psychiatry, 33:983-989 (1976).

IIe(3) Resnick, R.B., Kestenbaum, R.S. and Schwartz, L.K. Acute systemic effects of cocaine in man: A controlled study by intranasal and intravenous routes. Science, 195:696:698 (1977).

IIe(5) Freud, S. Contribution to the knowledge of the effect of cocaine. In Byck, R. (ed.) Cocaine Papers: Sigmund Freud. New York, NY: Stonehill Publishing co., 1974.

IIf(3) Resnick, R.B., Kestenbaum, R.S. and Schwartz, L.K. Acute systemic effects of cocaine in man: A controlled study by intranasal aud intravenous routes. Science, 195:696-698 (1977).

Fischman, M.W., Schuster, C.R., Resnekov, L., Shick, J.F.E., Krasnegor, N.A., Fennell, W. and Freedman, D.X. Cardiovascular and subjective effects of intravenous cocaine administration in humans. Archives of Geheral Psychiatry, 33:983-989 (1976).

IIf(4) Barbour, H.G. and Marshall, H.T. Heat regulation and water exchange. XII. The underlying mechanism of fever as illustrated by cocaine poisoned rabbits. Journal of Pharmacology and Experimental Therapeutics, 43:147-162 (1931).

IIIa(3) Fischman, M.W., Schuster, C.R., Resnekov, L., Shick, J.F.E., Krasnegor, N.A., Fennell, W. and Freedman, D.X. Cardiovascular and subjective effects of intravenous cocaine administration in humans. Archives of General Psychiatry, 33:983-989 (1976).

IIIb(3) Byck, R., Jatlow, P., Barash, P. and Van Dyke, C. Cocaine: Blood concentration and physiological effect after intranasal application in man. In Ellinwood, E. H. and Kilbey, M.M. (eds.), Cocaine and Other Stimulants. New York, NY: Plenum Press, 1977, pp. 629-646.

Resnick, R.B., Kestenbaum, R.S. and Schwartz, L.K. Acute systemic effects of cocaine in man: A controlled study of intranasal and intravenous routes. Archives of General Psychiatry, 33:983-989 (1976).

IIIc(3) Post, R.M., Gillin, J.C., Wyatt, R.J. and Goodwin, F.K. The effect of orally administered cocaine on sleep of depressed patients. Psychopharmacologia (Berlin), 37:59-66 (1974).

IIIc(5) Freud, S. Contribution to the knowledge of the effect of cocaine. In Byck, R. (ed.), Cocaine Papers: Sigmund Freud. New York, NY: Stonehill Publishing Co., 1974.

IIId(3) Post, R.M., Gillin, J.C., Wyatt, R.J. and Goodwin, F.K. The effect of orally administered cocaine on sleep of depressed patients. Psychopharmacologia (Berlin), 37:59-66 (1974).

IIIe(3) Resnick, R.B., Kestenbaum, R.S. and Schwartz, L.K. Acute systemic effects of cocaine in man: A controlled study by intranasal and intravenous routes. Science, 195: 696-698 (1977).

IIIe(4) Balster, R.L. and Schuster, C.R. Fixed interval schedule of cocaine reinforcement: Effect of dose and infusion duration. Journal of the Experimental Analysis of Behavior, 20:119-129 (1973).

IIIe(5) Aschenbrandt, T. Die Physiologische Wirkung und Bedeutung des Cocain auf den Menschlichen Organisms. Deutsche Medizinische Wochenschrift, 50:730-732 (1883).

Mortimer, W.G. History of Coca The Divine Plant of the Incas. 1901, reprinted, San Francisco, CA: And/Or Press, 1974.

IIIg(1) Byck, R., Jatlow, P., Barash, P. and Van Dyke, C. Cocaine: Blood concentration and physiological effect after intranasal application in wan. In Ellinwood, E.H. and Kilbey, M.M. (eds.), Cocaine and Other Stimulants. New York, NY: Plenum Press, 1977, pp. 629-646.

Resnick, R.B., Kestenbaum, R.S. and Schwartz, L.K. Acute systemic effects of cocaine in man: A controlled study by intranasal and intravenous routes. Science, 195:696-698 (1977).

Fischman, M.W., Schuster, C.R., Resnekov, L., Shick, J.F.E., Krasnegor, N.A., Fennell, W. and Freedman, D.X. Cardiovascular and subjective effects of intravenous cocaine administration in humans. Archives of General Psychiatry, 33:983-989 (1976).

IIIg(5) Mortimer, W.G. History of Coca The Divine Plant of the Incas. 1901, reprinted, San Francisco, CA: And/Or Press, 1974.

IIIh(2) Post, R.M., Kotin, J. and Goodwin, F.K. The effects of cocaine on depressed patients. American Journal of Psychiatry, 131(5):511-517 (1974).

IIIi(5) Resnick, R.B. and Schuyten-Resnick, E. Clinical aspects of cocaine: Assessment of cocaine abuse behavior in man. In Mule, S.J. (ed.) Cocaine. Cleveland, OH: CRC Press, 1976.

IIIj(5) Byck, R. Personal communication.

IIIk(4) Luco, J.V., Eyzaguirre, C. and Perez, F. Effects of amphetamine and cocaine on neuromuscular function. Journal of Pharmacology and Experimental Therapeutics, 93:961-272 (1948).

Gutierrez-Noriega, C. Action de la cocaina sobre le resistencia a la fatiga en el perro. Revista de Medicina Experimental, 3:329-340 (1944).

IIIk(5) Mortimer, W.G. History of Coca The Divine Plant of the Incas. 1901, reprinted, San Francisco, CA: And/Or Press, 1974.

Va(4) Downs, D.A. and Woods, J.H. Codeine- and cocaine-reinforced responding in rhesus monkeys: Effects of dose on response rates under a fixed ratio schedule. Journal of Pharmacology and Experimental Therapeutics, 191:179-188 (1974).

Woods, J.H. Chapter 4 this volume.

Vb(4) Tatum, A.L. and Seevers, M.H. Experimental cocaine addiction. Journal of Pharmacology and Experimental Therapeutics, 36:401-410 (1929).

Gutierrez-Noriega, C. and Ortiz, V.Z. Cocainismo experimental. I. Toxicologia general, acostumbramiento y sensibilizacion. Revista de Medicina Experimental, 3:279-306 (1944).

Post, R.M., Kopanda, R.T. and Black, K.E. Progressive effects of cocaine on behavior and central amine metabolism in rhesus monkeys: Relationship to kindling and psychosis. Biological Psychiatry, 11:403-419 (1976).

Vb(5) Byck, R. Personal communication.

Vc(3) Post, R.M., Gillin, J.C., Wyatt, R.J. and Goodwin, F.K. The effect of orally administered cocaine on sleep of depressed patients. Psychopharmacologia (Berlin), 37:59-66 (1974).

VIa(3) Byck, R., Jatlow, P., Barash, P. and Van Dyke, C. Cocaine: Blood concentration and physiological effect after intranasal application in man. In Ellinwood, E.H. and Kilbey, M.M. (eds.), Cocaine and Other Stimulants. New York, NY: Plenum Press, 1977, pp. 629-646.

Resnick, R.B., Kestenbaum, R.S. and Schwartz, L.K. Acute systemic effects of cocaine in man: A controlled

study by intranasal and intravenous routes. Science, 195:696-698 (1977).

Orr, D. and Jones, I. Anaesthesia for laryngoscopy. Anaesthesia, 23:194-202 (1968).

VIa(5) Young, D. and Clauber, J.J. Electrocardiographic changes resulting from acute cocaine intoxication. American Heart Journal, 34:272-279 (1947).

VIb(4) Koehntop, D., Liao, J.C. and Van Bergen, F.H. Pharmacological enhancement by cocaine, tropolene, aminophylline, and ketamine of epinephrine-induced arrhythmias during halothane-nitrous oxide anesthesia. American Society of Anesthesiologists Annual Meeting, October, 1975.

VIb(5) Barash, P.G. Personal commication.

VIc(4) Eidelberg, E., Lesse, H. and Gault, F.P. Au experimental model of temporal lobe epilepsy: Studies of the convulsant properties of cocaine. In Glaser, G.H. (ed.), EEG and Behavior. New York, NY: Basic Hooks, 1963, pp. 272-283.

VIc(5) Mayer, E. The toxic effects following the use of local anesthetics. Journal of the American Medical Association, 82:876-885 (1924).

VId(5) Lewin, L. Phantastica, Narcotic and Stimulating Drugs, Their Use and Abuse. New York, NY: E.P. Dutton and co., 1931.

Bergen, A. Personal communication.

Smith, D. Personal communication.

VIf(5) Messinger, E. Narcotic septal perforations due to drug addiction. Journal of the American Medical Association, 179:964-965 (1962).

THE CONFIRMED PHRMACOLOGY OF COCAINE IN MAN

Local Effects

Still widely used today in otolaryngology and anesthesiology, cocaine is an effective local anesthetic when applied topically or injected near nerves. Cocaine constricts blood vessels and thereby limits the amount of bleeding from surgical procedures as well as limiting its own absorption. Cocaine dilates the pupil when applied topically to the eye (Koller, 1884; Kuroda, 1915). The local anesthetic effects of cocaine in man are more fully described in Chapter 9.

Systemic Effects

We know that cocaine produces an increase in heart rate and blood pressure in man. Resnick and co-workers (1977) administered cocaine to 19 human volunteers. They found that 25 mg of cocaine administered intranasally produced only minimal changes in systolic blood pressure, while 100 mg intranasally produced significant changes in heart rate and in both systolic and diastolic blood pressure. When administered intravenously, 10 and 25 mg of cocaine produced a significant increase in heart rate and systolic blood pressure. They reported that the onset of these effects occurred in 2 minutes, peaked in 5-10 minutes after intravenous administration and in 15-20 minutes after intranasal application. Byck et al. (1977) reported similar results after intranasal application of cocaine but noted the powerful modifying effect of psychological factors on cardiovascular variables. Fischman et al. (1976) studied nine human volunteers who received intravenous cocaine in dosages of 4, 8, 16 and 32 mg. Dosages of 4 and 8 mg had no effect on heart rate or blood pressure. However, after 16 mg of cocaine, the mean heart rate increased from a predrug rate of 74 beats per minute (BPM) to 100 BPM; and after 32 mg, from 74 BPM to 112 BPM. These investigators reported that increases in the heart rate occurred 2-5 minutes after intravenous administration, peaked at 10 minutes and returned to the predrug baseline rate at 46 minutes. Similarly, the 16 and 32 mg dosages were the only ones that increased systolic blood pressure. This increase in systolic blood pressure was 10-15 percent above the predrug levels and occurred 10 minutes after drug administration. Post et al. (1974a) studied the effect of intravenous cocaine in 12 depressed patients. They found increases in both heart rate and systolic blood pressure following a range of dosages from 2-16 mg. These four studies by independent investigators indicate that cocaine increases the heart rate and blood pressure in man when administered by either the intranasal or intravenous route. The dosage and time effect relationships remain unclear.

Few cardiac arrhythmias are reported with the clinical use of cocaine (Orr & Jones, 1968; Young & Glauber, 1947). In one

experimental study, Fischman et al. (1976) reported no arrhythmias in nine volunteers who received intravenous cocaine in dosages ranging from 4-32 mg. Neither Resnick et al. (1977) nor Post et al. (1974a) reported arrhythmias and none has been reported by Byck et al. (1977).

CENTRAL NERVOUS SYSTEM EFFECTS

We know that in most people cocaine causes euphoria.[1] This information is consistent with "street knowledge" and "textbook dogma." There is no doubt that many individuals on the street get a pleasant feeling from what is reputed to be cocaine and seek to repeat the experience. Recently, three independent laboratories have begun to describe the subjective effects of cocaine in man. Byck et al. (1977) in a controlled series of experiments found significant euphoria in man following intranasal cocaine in dosages ranging from 13-130 mg. Resnick and his co-workers (1977) found that 25 mg of intranasal cocaine and 10 and 25 mg of intravenous cocaine produced a high and pleasant feeling in their volunteers. Fischman et al. (1976) reported that intravenous cocaine produced subjective effects that were similar to intravenous amphetamine and, in fact, the subjects were often unable to identify whether they had received cocaine or amphetamine. Whether the euphoria of cocaine is due to the local anesthetic or sympathomimetic character of the drug is not yet known.

Absorption and Metabolism

The rate of absorption of cocaine varies with the route of administration. Following intravenous injection, the total dose of cocaine is present in the blood within a few minutes. Van Dyke et al. (1976) found that, after topical application to the nasal mucosa, the concentration of cocaine in the blood rapidly increases for 20 minutes, peaks at 60 minutes and then gradually declines for at least 3 hours after application. There is very little information on the absorption of cocaine after oral administration. Post et al. (1974a; 1974b) did demonstrate changes in mood and sleep patterns following daily oral dosages of 200 mg of cocaine in depressed patients, indicating that cocaine shows activity after oral administration. Woods et al. (1951), using much higher dosages than those used in man, demonstrated in dogs that oral. cocaine was absorbed. The psychopharmacological effects of coca chewing have been extensively reported but never examined in a controlled manner.

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[1]As discussed in Byck et al., 1977; Fischman et al., 1976; Resnick et al., 1977; Post et al., 1974a.

We know that most of the absorbed cocaine is hydrolyzed in the body to benzoylecgonine. The site of this hydrolysis is not known. It has always been presumed to be the liver (Ritchie & Cohen, 1975); however, recent in vitro studies demonstrated that enzymes in the plasma may play a role in the hydrolysis of cocaine (Jatlow et al., 1976). Most cocaine is eliminated in the urine as benzoylecgonine. This occurs within 24-36 hours after administration Nan Dyke et al. in press; Wallace et al., 1976). The drug may also be eliminated as free cocaine in the urine but this usually accounts for less than 20 percent of the total dose. As would be expected, more free cocaine is excreted when the urine is acidic (Fish & Wilson, 1969)

The recent development by Jatlow and Bailey (1975) and Hawks (1974) of sensitive and reliable assays to measure low concentrations of cocaine in the blood has been a major breakthrough in helping us to understand the pharmacology of cocaine in man. Its rate of absorption and sojourn in the blood after different routes of administration are now being studied, as are the metabolic pathways. These assays will permit correlations between the concentration of cocaine in the blood and its psychological and physiological effects.

CONCLUSION

The reader may have an uneasy feeling that most of the actions and effects of cocaine that seemed to be "known" are still open to question. This is, in fact, the case. By the nature of the acceptable evidence, we must concede that some "facts" about cocaine's effects in man will probably never be demonstrated. This, however, does not give us the license to, "substitute certainty of statement for hard evidence" since to do so would be, "unbecoming, however customary."

Robert Byck, M.D. and
Craig Van Dyke, M.D.
Yale University School of Medicine
Department of Pharmacology

REFERENCES

What are the Effects of Cocaine in Man?

Ashley, R. Cocaine: Its History, Uses and Effects. New York, NY: Warner Books, Inc., 1975.

Byck, R. (ed.) Cocaine Papers: Sigmund Freud. New York, NY: Stonehill Publishing Co., 1975.

Byck, R., Jatlow, P., Barash, P. and Van Dyke, C. Cocaine: Blood concentration and physiological effect after intranasal application in man. In Ellinwood, E.H. and Kilbey, M.M. (eds.), Cocaine and Other Stimulants. New York, NY: Plenum Press, 1977, pp. 629-646.

Ellinwood, E.H. and Kilbey, M.M. (eds.) Cocaine and Other Stimulants. New York, NY: Plenum Press, 1977.

Fischman, M.W., Schuster, C.R., Resnekov, L., Shick, J.F.E., Krasnegor, N.A., Fennell, W. and Freedman, D.X. Cardiovascular and subjective effects of intravenous cocaine administration in humans. Archives of General Psychiatry, 33:983-989 (1976).

Fish, F. and Wilson, W.D.C. Excretion of cocaine and its metabolites in man. Journal of Pharmacy and Pharmacology, 21(Suppl.): 135S-138S (1969).

Galbraith, J.K. Money, Whence It Came, Where It Went. Boston, MA: Houghton Mifflin Co., 1975.

Hawks, R.L., Kopin, I.J., Colburn, R.W. and Thoa, N.B. Norcocaine: A pharmacologically active metabolite of cocaine found in brain. Life Sciences, 15:2189-2195 (1974).

Jatlow, P., Barash, P.G., Van Dyke, C. and Byck, R. Impaired hydrolysis of cocaine in plasma from succinylcholine sensitive individuals. Clinical Research, 23(3):255A (1976).

Jatlow, P.I. and Bailey, D.N. Gas-chromatographic analysis for cocaine in human plasma, with use of a nitrogen detector. Clinical Chemistry, 21:1918-1921 (1975).

Koller, C. Uber die Verwendung des Cocaine zur Anasthesierung am auge. Weiner Medizinische Wochenschrift, 34: Nos. 43 and 44 (1884).

Kuroda, M. On the action of cocaine. Journal of Pharmacology and Experimental Therapeutics, 7:423-439 (1915).

Mortimer, W.G. History of Coca The Divine Plant of the Incas. 1901, reprinted, San Francisco, CA: And/Or Press, 1974.

Orr, D. and Jones, I. Anaesthesia for laryngoscopy. Anaesthesia, 23:194-202 (1968).

Post, R.M., Gillin, J.C., Wyatt, R.J. and Goodwin, F.K. The effect of orally administered cocaine on sleep of depressed patients. Psychopharmacologia (Berlin), 37:59-66 (1974b).

Post, R.M., Kotin, J. and Goodwin, F.K. The effects of cocaine on depressed patients. American Journal of Psychiatry, 131(5):511-517 (1974a).

Resnick, R.B., Kestenbaum, R.S. and Schwartz, L.K. Acute systemic effects of cocaine in man: A controlled study by intranasal and intravenous routes. Science, 195:696-698 (1977).

Ritchie, J.M. and Cohen, P.J. Local anesthetics. In Goodman, L.S. and Gilman, A. (eds). The Pharmacological Basis of Therapeutics, 5th Edition. New York, NY: Macmillan, 1975, pp. 379-403.

Van Dyke, C., Barash, P.G., Jatlow, P. and Byck, R. Cocaine: Plasma concentrations after intranasal application in man. Science, 191:859-861 (1976).

Van Dyke, C. and Byck, R. Cocaine: 1884-1974. In Ellinwood, E.H. and Kilbey, M.M. (eds.) Cocaine and Other Stimulants. New York, NY: Plenum Press, 1977, pp. 1-30.

Van Dyke, C., Byck, R., Barash, P.G. and Jatlow, P. Urinary excretion of immunologically reactive metabolite(s) after intranasal administration of cocaine, as followed by enzyme immunoassay. Clinical Chemistry, 1977, in press.

Wallace, J.E., Hamilton, H.E., King, D.E., Bason, D.J., Schwertner, H.A. and Harris, S.C. Gas-liquid chromatographic determination of cocaine and benzoylecgonine in urine. Analytical Chemistry, 48:34-38 (1976).

Woods, J.H. and Downs, D.A. The psychopharmacology of cocaine. In Drug Use In America: Problem in Perspective. Appendix Volume 1: Patterns and Consequences of Drug Use. Washington, DC: U.S. Government Printing Office, 1973, pp. 116-139.

Woods, L.A., McMahon, F.G. and Seevers, M.H. Distribution and metabolism of cocaine in the dog and rabbit. Journal of Pharmacology and Experimental Therapeutics, 101:200-204 (1951).

Young, D. and Glauber, J.J. Electrocardiographic changes resulting from acute cocaine intoxication. American Heart Journal, 34:272-279 (1947).

Chapter VI COCAINE: RECREATIONAL USE AND INTOXICATION

Ronald K. Siegel, Ph.D.

Cocaine is one of several alkaloids obtained from coca leaves Erythroxylon Coca Lam.). The function of alkaloids in plants is generallV unknown as is the reason plants produce them. Alkaloids taste bitter, often produce numbing sensations, and are physiologically active with psychologic, teratogenio and toxic effects. They act as extremely effective feeding deterrents; it has been argued that naturally occurring plant drugs such as cocaine are justified evolutionarily by their potentially maladaptive effects on herbivores (Bever, 1970; Eisner & Halpern, 1971). The major questions concerning the use of cocaine alkaloid by humans are: 1) Why did man bypass these deterrent effects and initiate use of cocaine? 2) Why is use of cocaine maintained? and 3) What are the consequences of such continued use? These questions are addressed in this chapter. It will presently be seen that the psychological intoxication resulting from cocaine use is a primary reason for its continued use. The nature and extent of this intoxication in a group of contemporary users will also be explored. These users reflect social-recreational patterns of intranasal use, and they differ substantially from more compulsive intravenous users discussed elsewhere in this volume (cf., Smith & Wesson, Chapter 6).

DISCOVERY AND INITIAL USE

Folklore and mythology are replete with examples of man's discovery of plant alkaloids through observation and modeling of animal behavior (cf., Siegel, 1973). The legendary discovery of coffee, purportedly around 900 A.D., was made by an Abyssinian tending his herd of goats. The herder noticed that his animals became abnormally "frisky" after eating the bright red fruit of a tree that was later isolated and identified as coffee (Taylor, 1965). In Yemen, another herder discovered that his goats exhibited signs of extraordinary stimulation after eating certain leaves. The shepherd tried the leaves himself and found them quite stimulating even after a day's work. Since that time the use of those leaves (qat leaves which contain the alkaloids cathine, cathedine, and cathenine) has spread through the entire country (Abdo Abbasy, 1957).

Similarly, several stories are told of coca's discovery based on modeling of animal behaviors. One story -- told by an informant from Huanuco, Peru -- claims that coca was first used by pack animals traveling in the mountains and deprived of their normal forage. The coca leaves sustained the animals, and humans quickly

copied the coca-eating behavior. Indeed, Mortimer (1901; reprinted, 1974) notes that coca was used by man, and perhaps by beast, when traveling in the mountains where ingestion was probably induced by irregular eating, improper diet and lack of oxygen at higher altitudes. Such use is similar to that of peyote used in small doses by Huichol Indians traveling in the Sierra Madre mountains of Mexico (Lumholtz, 1902). Recent nutritional analysis has revealed that since 100 grams of coca leaves contains 305 calories, 18.9 grams of protein and 46.2 grams of carbohydrates, and satisfies the Recommended Dietary Allowance for calcium, iron, phosphorus, vitamins A, B_2 and E(Dukeetal., 1975), the coca leaves could, indeed, have sustained Peruvian travelers. However, the full complement of nutrients present in coca leaf may not be fully absorbed in the normal chewing-sucking extraction employed by man.

Another story told by informants from Cuzco and Lima, Peru, claims that a number of birds and insects are fond of coca seeds and leaves and the speed with which they devour the plant suggested the stimulant properties to early man. Mortimer (1901; reprinted, 1974) indicated that ants and other insects avidly devoured the leaves but there was no indication of psychoactive effects from this ingestion. However, he did note that "the birds are great lovers of coca seeds, and when these are lightly sown on the surface of the nursery it is necessary to cover the beds at night with cloths to guard against 'picking and stealing'...." One may speculate that early man modeled his coca use after such observations, much like the Greeks who adopted the habit of eating hempseeds -- and, later, other parts of the cannabis plant -- after watching finches do so (Schultes, 1970).

Man's inevitable ecological encounters with coca would have brought him into contact with the highly reinforcing properties of the cocaine alkaloid. Independent of the nutritional value, the psychoactive effects are considerably more direct and immediate. Animal studies are rich with examples of cocaine's powerful psychoactive and reinforcing effects (cf., Preclinical Behavior, Chapter 4). Lewin (1931) reports a case of an animal modeling human use:

> The case is, however, on record of a monkey which became a cocaine-eater through imitation...The animal searched the pockets and the cupboards of its mistress for cocaine, which it voraciously consumed. The consequences were the same as in men.

MAINTENANCE OF USE

These consequences or effects are undoubtedly responsible for maintaining cocaine use. The effects can be interpreted as a state of intoxication with high reinforcement potential. Indeed, animals such as rats and monkeys, having once experienced unlimited access to cocaine, will self-administer the drug until they die, often ignoring food and water. While many non-pharmacologic factors

(e.g., individual and environmental variables) may affect man's use of a drug such as cocaine, psychological intoxication appears to be the primary reinforcing effect.

Freud described the intoxication in Uber Coca, his famous 1884 monograph on coca:

> The psychic effect (of cocaine) consists of exhilaration and lasting euphoria, which does not differ in any way from the normal euphoria of a healthy person....One senses an increase of self-control and feels more vigorous and more capable of work; on the other hand, if one works, one misses the heightening of the mental powers which alcohol, tea, or coffee induce. One is simply normal, and soon finds it difficult to believe that one is under the influence of any drug at all....Long-lasting. intensive mental or physical work can be performed without fatigue; it is as though the need for food and sleep, which other wise makes itself felt peremptorialy (sic) at certain times of the day, were completely banished. (Byck, 1974)

Aleister Crowley (1917) offers a more romantic description of cocaine intoxication:

> The melancholy vanishes, the eyes shine, the wan mouth smiles. Almost manly vigor returns, or seems to return. At least faith, hope and love throng very eagerly to the dance; all that was lost is found....To one the drug may bring liveliness, to another languor, to another creative force, to another tireless energy, to another glamor, and to yet another lust. But each in his way is happy. Think of it!--so simple and so transcendental! The man is happy!

Throughout the 19th and 20th centuries, the literature on coca and cocaine contained many references to the reinforcing nature of this intoxication. Even current patterns of recreational use appear to be initiated and maintained by the psychoactive effects (Phillips, 1975). A number of recent studies of cocaine users have confirmed the experience of positive drug effects which appear to maintain continued use. Ashley (1975) interviewed and observed 81 cocaine users and found that they experienced euphoria, sexual stimulation, increased energy and a reduction in fatigue and appetite. In another study of 17 cocaine users, Grinspoon and Bakalar (1976) reported additional phenomenological data on the intoxication and these authors emphasized their agreement with reports from literary sources and other studies (cf., Petersen, Chapter 1 this volume).

In yet another interview study with 32 intranasal cocaine users, the subjective effects reported included a subtle exhilaration, increased energy and sociability, and a pleasant feeling of well-being and mastery (Waldorf, pers. comm., 1976).

CONSEQUENCES OF CONTINVED USE

Despite the obvious appeal and romantic attraction of this state of intoxication, the consequences of continued use have been the subject of over a century of research and debate. Most researchers agree that the pleasurable effects diminish with continued use and are replaced by an increasing number of adverse effects which can Only be alleviated through its cessation. Crowley (1917, reprinted 1973) describes this state in a highly stylized account:

> But to one who abuses cocaine for his pleasure nature soon speaks, and is not heard. The nerves weary of the constant stimulation; they need rest and food. There is a point at which the jaded horse no longer answers whip and spur. He stumbles, falls a quivering heap, gasps out his life....So perishes the slave of cocaine. With every nerve clamoring, all he can do is to renew the lash of the poison. The pmarmaceutical effect is over; the toxic effect accumulates . The nerves become insane. The victim begins to have hallucinations.... And alas! The power of the drug diminishes with fearful pace. The doses wax; the pleasures wane. Side-issues, invisible at first, arise; they are like devils with flaming pitchforks in their hands. (Crowley, 1917)

Unfortunately, the language of this passage and others like it, with its connotations of cocaine addiction and psychosis, have influenced many of the medical and scientific opinions to date. With a similar "data base" of self-experimentation, Freud described the state as one of agitation characterized by persecution and hallucinations, but he used less emotional language for his observations (Freud, 1887). Others call the condition one of "delirium"t (e.g., Mantegazza, 1859) or "extreme alarm due to false impressions" (Lewin, 1931). Still others write about mania and psychoses (cf., Grinspoon & Bakalar, 1976). But for most, the critical diagnostic features of this state are the hallucinations, and the presence of tactile hallucinations are the most conspicuous.

One of the more consistent findings is that continued use is associated with tactile hallucinations of animals moving in the skin, or bugs or insects moving under the skin. This phenomenon was described by Magnan and Saury (1889) and has since been known as "Magnan's sign" or "cocaine bugs." Magnan and Saury noted that

these symptoms are the first hallucinatory phenomena to develop with chronic use while hallucinations of sight, hearing and smell come later. Although Magnan's sign and allied symptoms are usually associated with chronic use, a number of hallucinatory experiences have been reported with large acute doses of cocaine (e.g., Mortimer, 1901; reprinted, 1974; Eggleston & Hatcher, 1919). According to Magnan and Saury, the hallucinations subsequently lead to difficulties in thinking and orientation.

Indeed, the diagnosis of psychosis often emerges from the presence of these tactile sensations, independent of other changes. But psychosis involves more than hallucinations and usually implies dysfunction in an individual's mental processes, emotional responses, memory, communication skills, sense of reality and behavior. Furthermore, psychosis is often characterized by regressive behavior, inappropriate mood, diminished impulse control and delusional thinking (cf., American Psychiatric Association, 1969). The presence of such a wide range of phenomena in cocaine intoxication is less clear than the presence of hallucinations. Indeed, descriptions of cocaine hallucinations often include references to clear mental ability (e.g., Mantegazza, 1859).

VARIABLES AFFECTING USE AND INTOXICATION

The precise description of this state of cocaine intoxication requires information about concomitant variations between the characteristics of the behavior and of the drug. Information about the behaviors should be specific with respect to individual variability, type of behavior and behavioral history. Information about the drug should be specific with respect to dose, adulterants, routes of administration, dose-response and time-response relations, among others. Such variables can be further modified by environmental variables such as set and setting. While a full understanding of these interactions is presently restricted by the limited knowledge about cocaine, the presence of such a myriad of interacting variables should temper a desire to simplify use and intoxication with succinct labels such as "euphoria," "mania" or "psychosis." The study described below was undertaken in an attempt to elucidate some of these variables in relation to the psychological intoxication.

THE SAMPLE

A large population of recreational drug users, recruited through advertisements in several Los Angeles area newspapers, was initially screened by a telephone interview and a subsequent drug-history questionnaire. A total of 85 social-recreational cocaine users were eventually selected for the study. All subjects in the sample met the initial requirement of having used a minimum of 1 gram of cocaine per month for 12 months (range = 1-4 grams). All subjects

were male, 21-38-years-old, and were examined and tested in the Neuropsychiatric Institute at UCLA. Examination procedures included a personal history questionnaire, drug history questionnaire, mental status examination, Minnesota Multiphasic Personality Inventory (MMPI), Experiential World Inventory (EWI) (El-Meligi & Osmond, 1970), in-depth interview, physical examination (for most subjects) and visual imagery and perception tests. Two additional groups of subjects were recruited for interview and questionnaire study only. One group consisted of 14 female social-recreational users who all satisfied the 1 gram per month minimum requirement. The second group consisted of both male and female experimental users (n=19) who had only used cocaine 10 times or fewer with a total intake of no more than 1 gram.

Unless otherwise specified, the data discussed below are from the group of 85 male social-recreational users.

PREPARATIONS AND PURITY

All subjects used the hydrochloride salt of cocaine available through illicit markets. The LAC-USC Medical Center street drug analysis laboratory has found that the average purity of street cocaine in the Los Angeles area is 63 percent (Montgomery, personal communication, 1976). Another street drug assay laboratory in Northern California (Pharm Chem, Palo Alto) found that the average street cocaine was 53 percent for samples received in that area. The most common adulterants in these samples are sugars (lactose, mannitol and inositol); local anesthetics (procaine, lidocaine, benzocaine and tetracaine); and, albeit rarely, other drugs (amphetamine, caffeine, phencyclidine, acetaminophen, salicylamide, pemoline and heroin). Several other non-drug adulterants may be present, such as flour and talc, but analysis for these is rarely done (Perry, 1974). Of the 85 subjects, 4 had used the free base of cocaine (primarily for smoking as discussed below) while 6 had occasionally chewed coca leaves, primarily during travels in South America.

MULTIPLE DRUG USE

All subjects had histories of multiple drug use. Concomitant with their use of cocaine, 85 percent were using alcohol; 66 percent, cannabis preparations; 57 percent, caffeine (coffee, tea, chocolate and cola beverages); 8 percent, amphetamines; and 5 percent, hallucinogens other than cannabis. Surprisingly, the figure for caffeine is considerably below national averages, which are estimated to be as high as 90 percent for adults (Gilbert, 1976). It is possible that this represents a substitution of cocaine for caffeine as a stimulant of choice. Furthermore, caffeine interacts with drugs that affect neural transmission and this interaction

with cocaine may have undesirable or non-preferred effects on users.

Prior to their cocaine use, subjects reported experiences with amphetamines and related stimulants (27 percent), barbiturates (20 percent), hallucinogens other than cannabis (10 percent) and opiates (2 percent). All subjects had tried cannabis in the past.

During the 12 month period of the survey, all 85 subjects reported that cocaine was their recreational drug of choice and 73 subjects identified themselves as regular cocaine users and only casual users of other drugs. The average frequency of drug use per week was: caffeine, 5x; cocaine, 3x; alcohol, 2x; and marihuana or other cannabis preparations, 0.25x (1/4x).

ROUTES OF ADMINISTRATION

All subjects employed the intranasal route of self-administration while a few (n=12) had also experimented with smoking cocaine on tobacco or marihuana cigarettes and chewing coca leaves (n=6). One subject had several experiences with intravenous, intramuscular and subcutaneous injections of cocaine. Four subjects had experimented with topical applications of cocaine to the genitalia.

DOSAGES

When cocaine was used intranasally, subjects self-administered one "cokespoonful" per nostril or one "line" per nostril. The amount of pure pharmaceutical cocaine hydrochloride (crushed, flaky crystals) in commercially available "cokespoons" has been determined to range from 5-10 mg for a level cokespoon. Assuming an average street purity of roughly 58 percent, this amounts to an average intranasal dose of 8.7 mg (total for both nostrils) per administration. The average" "line" of cocaine is about 1/8 inch wide by 1 inch long (Gottlieb, 1976) and amounts to approximately 25 mg of cocaine if pure or 14.5 mg of cocaine if street cocaine. When cocaine hydrochloride was used for smoking, small amounts were placed on the burning end of a marihuana or tobacco cigarette or sprinkled throughout the cigarette. When cocaine base was used with tobacco or marihuana for smoking, users distributed approximately 1/3 gram of base throughout a cigarette for each person smoking (cf. Siegel et al., 1976). Cocaine base is an intermediate compound in the manufacture of the hydrochloride salt and is less susceptible to decomposition upon heating. It can be re-obtained from street cocaine via simple chemical procedures.

DOSE REGIMES

While subjects in this sample used 1-4 grams of cocaine per month, doses were not evenly distributed across time. Generally, subjects purchased cocaine in gram quantities, sometimes referred to as "bindles" or "spoons," although a spoon could vary from 0.5 to 2.0 grams (Lee, 1976). This amount was generally consumed in less than one week (49 percent); some subjects used it within two days (34 percent). When cocaine was used intranasally, most subjects repeated the self-administration an average of 3 times per night, usually at 15 or 30 minute intervals (range = 10 minutes to 2 hours). When cocaine base was used for smoking, a cigarette containing approximately 1 gram of cocaine base was smoked by two or three persons over an average period of four hours.

PATTERNS OF USE

The dose regimes together with the set and setting define the pattern of drug use. Five patterns of drug use have been designated by The National Commission on Marihuana and Drug Abuse (1973) and will be used for discussion here.

Experimental Use: The group of 19 subjects classified as experimental users engaged in short-term, non-patterned trials of cocaine with varying intensity and a maximum frequency of 10 times (or a total intake of less than 1 gram). These users were primarily motivated by curiosity about cocaine and a desire to experience the anticipated drug effects of euphoria, stimulation and enhanced sexual motivation. Their use was generally social and among close friends. Only four of these individuals purchased their own cocaine and these, together with two subjects given gifts of cocaine, were the only ones who engaged in individual (non-social) trials. Most (68 percent) expressed a desire to use cocaine more often but were restricted by economic and supply considerations. The remainder (32 percent) experienced little or no drug effect and felt no desire to continue use. Interestingly, most of the experimental users endorsed the street myth that cocaine is a subtle drug (cf., Phillips, 1975) but only those individuals who expressed a desire to continue cocaine use also believed that cocaine gives a "kick" or "rush." This latter finding suggests the importance of psychological set in determining drug reactions.

Social-Recreational Use: All 85 subjects in the formal study were classified as social-recreational users who engaged in more regular use than experimenters. Use generally occurred in social settings among friends or acquaintances who wished to share an experience perceived by them as acceptable and pleasurable. These users were primarily motivated by social factors and their use was always voluntary. It did not tend to escalate to more individually oriented patterns of uncontrollable use. Many of these subjects

started as experimental users and many (71 percent) engaged in episodes of more frequent use (see below), although their primary pattern was social-recreational. Most (75 percent) purchased their own cocaine while the remainder shared use with others in social settings. All 85 subjects experienced drug effects and varying degrees of intoxication (described below).

When asked to rank all drugs in terms of recreational drugs of choice, all users ranked cocaine first. However, when asked to rank all drugs used in terms of potency in producing euphoria and ecstasy, 69 percent of the males and 95 percent of the females ranked cocaine first. Other drugs ranked above cocaine in this category included LSD, marihuana and methamphetamine. Nonetheless, cocaine retained popularity as a recreational drug of choice for these reasons:

1) Cocaine was viewed by users as a social drug which facilitated social behavior. Conversely, LSD and marihuana were generally viewed as individually-oriented and asocial drugs.

2) Cocaine was viewed by users as the "ideal" drug in terms of convenience of use, minimal bulk, rapid onset of effects, minimal duration of action with few side effects, a high degree of safety and no after effects.

3) Cocaine was viewed by users as an exotic drug which had appeal because of its rarity, high price and historical-contemporary associations with popular and often high-status folk heroes.

In connection with this latter attitude, users spent an average of $30 on cocaine paraphernalia during the period surveyed compared to only $4 on marihuana paraphernalia. While cokespoons, vials, mirrors and other cocaine paraphernalia are more expensive than marihuana rolling papers or pipes, users consistently claimed that the cocaine paraphernalia was not essential to their drug use, but represented a desire to share in the illicit status associated with such devices.

Undoubtedly, these attitudes contributed to stable patterns of social-recreational use which did not escalate to individually oriented patterns of uncontrollable use. In addition, most users felt that the high cost and inconsistent quality of street cocaine, together with the short duration of action, were rate-limiting determinants of cocaine use. They also felt that cocaine was not addictive, except perhaps with intravenous use, and thus, social-recreational intranasal use would not result in escalating patterns of use. A number of these subjects were re-interviewed at various times during the months following this study and none of them manifested any signs of increased usage.

Circumstantial-Situational Use: Approximately 53 percent of the males engaged periodically in circumstantial-situational use, defined as a task-specific, self-limited use which was variably patterned, differing in frequency, intensity and duration. This use was motivated by a perceived need or desire to achieve a known and anticipated drug effect deemed desirable to cope with a specific condition or situation. The motivations cited by male users, in order of decreasing frequency, were: to increase performance at work (89 percent); to enhance mood during periods of situational depression (69 percent); and to enhance performance at play (e.g., sports, hiking, sex) (42 percent). Approximately 68 percent of the females engaged in situational use and they cited the following motivations: to enhance mood (90 percent); to increase performance at work (particularly housework) (90 percent); to suppress appetite (60 percent); and to enhance sexual performance (20 percent) .

Intensified Drug Use: Fifteen males (18 percent) and two females (14 percent) engaged in intensified use characterized by long-term patterned use of at least once a day. Such use was motivated chiefly by a perceived need to achieve relief from a persistent problem or stressful situation or a desire to maintain a certain self-prescribed level of performance. Nonetheless, users here still referred to their intensified use as "runs" or "binges" -- -- terms normally used for periods of repeated dosing found in all groups of cocaine users. Only this group of intensified users reported hallucinations (discussed below) and tolerance to behavioral effects. Tolerance was chiefly reported as a lessening in perceived stimulation and anti-fatigue effects with no loss in euphoric effects. While behavioral tolerance to cocaine has been demonstrated in three animal species, reports of tolerance in man are still purely anecdotal at this time (cf., Grinspoon & Bakalar, 1976).

Compulsive Drug Use: None of the subjects studied engaged in compulsive use, which is characterized by high frequency and high intensity levels of relatively long duration, producing some degree of psychological dependence.

PHENOMOLOGY AND INCIDENCE OF INTOXICATION EFFECTS

The acute physiological and psychoactive effects reported by social-recreational users did not differ substantially from those described in the historical literature or elsewhere in this volume (cf., Byck & Van Dyke, Chapter 5). Briefly, subjects repeatedly sought and experienced euphoria (100 percent), stimulation (82 percent), reduced fatigue (70 percent), diminished appetite (67 percent), garrulousness (59 percent), sexual stimulation (13 percent), increased mental ability (12 percent), alertness (7 percent) and increased sociability (6 percent). A number of mtoward effects were also reported by users: restlessness (70 percent), anxiety (34

[1]Matsuzaki et al, 1976; Moerschbaecher, 1976; Whyte, 1976; Thompson, in press.

percent), hyperexcitability (28 percent), irritability (16 percent) and paranoia (5 percent). Taken together, individuals reported experiencing some positive effects in all intoxications and negative or untoward effects in only 3 percent of the intoxications.

The chronic effects reported by these social-recreational users were also similar to those reported elsewhere (Grinspoon & Bakalar, 1976). In addition to acute intoxication phenomena, users experienced both desired and undesired effects. The desired effects included: a generalized feeling of increased energy (65 percent), increased sensitivity to acute effects of cocaine (60 percent) and weight loss (21 percent). The undesired effects included: nervousness and irritability (44 percent), perceptual disturbances (44 percent), nasal problems (28 percent), fatigue or lassitude when effects wore off (26 percent) and situational sexual impotency (4 percent). Overall, chronic positive or desired effects were experienced in all intoxications while negative effects were experienced in approximately 5 percent of the intoxications.

PERCEPTUAL CHANGES

Of the phenomena reported above, the perceptual changes are perhaps the least understood but also among the most important in understanding the precise nature and form of cocaine intoxication. Indeed, Post (1975) has suggested that cocaine users may manifest an orderly progression of clinical syndromes including euphoria, dysphoria and paranoid psychosis. Furthermore, the presence of perceptual changes including hallucinations are key diagnostic criteria in the determination of the psychotic phase. Therefore, these perceptual changes were the subject of concentrated examination and testing in the study.

A total of 37 subjects (44 percent) experienced some perceptual phenomena consisting chiefly of increased sensitivity to light, halos around bright lights and difficulty in focusing the eyes. Some of these subjects were experiencing chronic mydriasis caused by cocaine-induced enhancement of norepinephrine tonically released from sympathetic fibers that innervate the radial muscle of the iris (Woods & Downs, 1973). The mydriasis may have contributed to these perceptual effects. Several users also experienced exophthalmos (protrusion of the eyeball) and cycloplegia (paralysis of the ciliary muscle of the eye) which may have further contributed to these effects.

All 37 subjects of this subsample experienced some lapses of attention, but only 16 of these reported any difficulty in thinking associated with such changes. Such experiences included difficulty in maintaining attention during complicated tasks; difficulty in maintaining thoughts during conversation; and general preoccupation with personal problems. These effects are similar to what Post (1975) has described as "inability to concentrate," a component of cocaine dysphoria.

A total of 15 subjects (18 percent) reported hallucinatory experiences in several modalities including vision, touch, smell, hearing and taste. These phenomena were first noticed after approximately six months of recreational use and subjects usually became aware of them only during episodes of intensified use. Subjects described these events as pseudohallucinations, lacking the concomitant delusion that such events really existed. Pseudohallucinations are characteristic of many drug intoxications (e.g., marihuana) and differ from psychotic or true hallucinations which are accompanied by delusions or beliefs that the perceptions are real (Siegel & Jarvik, 1975).

Visual: Thirteen subjects (15 percent) reported visual hallucinations associated with the use of cocaine. Effects were reported both with the eyes open and closed. In the eyes open condition, subjects reported the sensation of object movement in their peripheral visual fields. For example, subjects stated, "Something just went by the corner of my eye," "Something just flew by," "I feel like something or someone just moved over there," etc. In dim illumination or with eyes closed, these sensations of movement were extremely weak and often appeared only as flashes or spots of light (cf., Wilson, 1973). Indeed, several subjects coined the phrase "snow lights" to indicate the origin and nature of these events. "Snow lights" were described as similar to, but less intense than, the twinkling of sunlight as it is reflected from frozen snow crystals. They were also described as similar to the sparkling of cocaine (i.e., "snow") crystals.

During later stages of use, subjects reported seeing geometric patterns in their peripheral visual field, usually only with open eyes. These patterns were usually black and white and were composed of straight lines, points and curves. Patterns reported by subjects included stars, stripes, zigzags, herring-bones, checkerboards and lattices. Such patterns are virtually identical to those patterns seen as normal entopic phenomena as well as those experienced in states of migraine. Subjects did not report "complex" hallucinations of fully formed or recognizable objects, although such reports are found in the literature (Woods & Downs, 1973).

Four subjects reported occasional polyopia. For example, one subject saw a duplication of a painting hanging on the wall, another subject claimed that a telephone dial appeared to have hundreds of holes, etc. Three subjects experienced the rare phenanenon of dysmegalopsia, including micropsia and macropsia, in which objects and people appeared distorted in size. Only the subjects who smoked cocaine base or injected cocaine had any dysmorphopsia. The single subject who injected cocaine reported seeing an ashtray change into a frying pan and then into a chicken! The phenomena of polyopia, dysmegalopsia and dysmorphopsia are described by Kluver (1942) as appearing in incipient toxic psychoses as well as in cocaine intoxication. Such phenanena are also common in other states of central nervous system excitation where zoopsia -- or hallucination of animals -- are conspicuous (Wolf & Curran, 1935; Feldman & Bender, 1970; Ey, 1973).

Tactile: Eleven subjects reported tactile hallucinations after several days of intensified use. These hallucinations included, in order of occurrence: itching of the skin, primarily of the hands but also including legs and back; the sensation of "moving itchs" or foreign particles moving under the skin; the sensation of small insects moving under or on the skin, primarily confined to the face and hands but including all parts of the body; and the sensation of objects or people brushing against the body. None of the subjects reported any concomitant visual hallucinations; nor did they believe that insects or objects were actually present, although they often scratched or rubbed the skin. Thus, the phenomena seen here appear to be simple pseudohallucinations. Interestingly, one subject who had experience with smoking opium and the consequent itching associated with opium-induced histamine release, found the cocaine experience identical. S.A.K. Wilson (1955) describes this paresthesia of pricking, "working" or "crawling" under the skin as eventually developing into hallucinations of sight and hearing. However, none of the survey subjects experienced this development. Subjects always described the tactile sensations in terms of the similes "like," "as if," or "it is as though" and they insisted that they never suffered from the delusion that insects were, in fact, really present.

Olfactory: Six subjects reported olfactory hallucinations. In most instances, subjects interpreted the perception of smells and odors which were not consensually validated as simply an increased awareness or sensitivity to smells actually present. Smells reported included smoke, gasoline, natural gas, feces, urine and garbage. At the time of examination, three of these subjects had noticeable rhinitis (inflamed nasal mucous membranes) while a fourth had several sores and scars on the interior nares. Such damage to the nasal mucosa may also have caused degenerative changes in olfactory receptors leading to abnormal firings (input) to the olfactory bulb. The presence of "bad" or "foul" odors is strikingly similar to those odors which precede uncinate fits which are also linked to olfactory receptors as well as abnormal brain activity.

Auditory: Three subjects reported auditory hallucinations. One of these experienced recurrent perceptions of a voice calling his name when he was alone in the house. Another subject occasionally heard a noise "like" whispering which appeared to cane from fans and ventilation ducts. The third subject heard whispering while lying in bed alone at night. These whisperings, while unintelligible, often kept the subject awake. Interestingly, he interpreted the noises as "the sound of coke."

Gustatory: Three subjects reported strong gustatory (taste) hallucinations occurring during acute intoxications. In every case, these were negative hallucinations -- the subjects failed to detect strong tastes in foods and drinks, tastes which others could readily perceive. Such negative hallucinations may be associated with olfactory changes as well as with attentional dysfunction.

HALLUCINOSIS OR PSYCHOSIS?

Taken together, the results of this study of perceptual changes in users suggest an orderly progression of hallucinations from simple "snow lights" through geometric forms to tactile sensations. The subjects frequently described the "snow lights" and geometric patterns as being "like" insects, especially in their darting and fleeting movements. Unlike previous accounts of "cocaine bugs," subjects did not see insects but did feel itchs and other sensations which were "like" insects crawling on the skin. Nevertheless, none of the subjects, while manifesting these behaviors, showed any abnormal profiles on either the MMPI or the EWI. Indeed, the EWI scales indicated some elevation of sensory perception scales with no concomitant elevation of time perception, body perception, self perception, perception of others, ideation, dysphoria or impulse regulation (El-Meligi & Osmond, 1970). This latter configuration would seem to indicate that the reported phenomenology may be simply an acute psychopharmacologic effect of cocaine and not a symptom of incipient psychosis. Since the dysphoria generally seen in the development of cocaine clinical syndromes (Post, 1975) was not present here, it is also possible that the recreational doses and patterns of use reflected in this population of subjects were insufficient to produce psychosis. Thus, the perceptual changes suggest only the presence of an hallucinosis, events which users found to be transient and which disappeared when they went from periods of intensified use back to more moderate social-recreational use.

OVERVIEW

The initial use of cocaine by humans appears to have been the result of accidental self-administration of coca, perhaps modeled from animal use of the coca plant. Early coca use was initially maintained by nutritional and psychoactive effects which were instrumental in sustaining work activity. Use of cocaine itself in the 19th and 20th centuries was primarily maintained by the reinforcement value of the intoxication state itself. This state is characterized by euphoria and stimulation. Contemporary experimental use appears to be initiated by a curiosity about the drug and a desire to experience the effects of euphoria and stimulation. Use among social-recreational users is maintained by the social sharing of this highly pleasurable experience. Some negative effects are also reported among this group, and these include irritability, perceptual disturbance, nasal problems and fatigue. When use is intensified, negative effects, particularly perceptual changes, are more noticeable. Such perceptual changes, which include "snow lights" and geometric patterns in the visual modality, are pseudo-hallucinations which users can accurately judge as unreal. Magnan's sign or "cocaine bugs" appear to be little more than tactile sensations of itching. Among social-recreational users,

these pseudohallucinatory events appear to be more acute psychopharmacologic effects than signs of incipient psychosis. Psychometric instruments failed to detect the presence of dysphoria or psychosis in this population. Adverse effects, including perceptual disturbances, seem to disappear when use is shifted from intensified patterns back to more moderate recreational regimes. In this sense, users are capable of titrating their doses so as to circumvent adverse reactions. An important caveat is that these effects are neither uniformly negative nor uniformly predictable. The number of variables affecting their production is presently unknown.

Ronald K. Siegel, Ph.D.
Department of Psychiatry
and Biobehavioral Sciences
University of California,
Los Angeles

REFERENCES

Cocaine: Recreational Use and Intoxication

Abdo Abbasy, M. The habitual use of "qat." Internationales Journal fur Prophylaktische Medizin und Sozialhygiene, 1:20-22 (1957).

American Psychiatric Association. American Psychiatric Glossary. Washington, DC: American Psychiatric Association, 1969.

Ashley, R. Cocaine. Its History, Uses and Effects. New York, NY: St. Martin's Press, 1975.

Bever, O. Why do plants produce drugs? Which is their function in the plants? Quarterly Journal of Crude Drug Research, 10:1541-1549 (1970).

Crowley, A. Cocaine. San Francisco, CA: Level Press, 1973.

Duke, J.A., Aulik, D. and Plowman, T. Nutritional value of coca. Botanical Museum Leaflets, Harvard University, 24(6):113-119 (1975).

Eggleston, C. and Hatcher, R.A. A further contribution to the pharmacology of the local anesthetics. Journal of Pharmacology and Experimental Therapeutics, 13:433-487 (1919).

Eisner, T. and Halpern, B.P. Taste distortion and plant palatability. Science, 172:1362 (1971).

ElMeligi, A.M. and Osmond, H. Manual for the Clinical Use of the Experiential World Inventory. New York, NY: Mens Sana Publishing, 1970.

Ey, H. Traite des hallucinations. Volume 1. Paris, France: Masson et Cie, 1973.

Feldman, M. and Bender,M.B. Visual illusions and hallucinations in parieto-occipital lesions of the brain. In Keup, W. (ed.) Origin and Mechanisms of Hallucinations. New York, NY: Plenum Press, 1970, pp. 23-35.

Freud, S. Uber Coca. In Byck, R. (ed.) Cocaine Papers: Sigmund Freud. New York, NY: Stonehill Publishing Co., 1974, pp. 49-73.

Freud, S. Contributions about the applications of cocaine. Second Series. I. Remarks on craving for and fear of cocaine with reference to a lecture by W.A. Hamond. In Byck, R. (ed.) Cocaine Papers: Sigmund Freud. New York, NY: Stonehill Publishing Co., 1974, pp. 171-176.

Gilbert, R.M. Caffeine as a drug of abuse. In Gibbins, R.J., Israel, Y., Kalant, H., Popham, R.E., Schmidt, W. and Smart, R.G. (eds.) Research Advances in Alcohol and Drug Problems. Volume III. New York, NY: John Wiley & Sons, 1976, pp. 49-176.

Gottlieb, A. The Pleasures of Cocaine. San Francisco, CA: Golden State Publishing Company, 1976.

Grinspoon, L. and Bakalar, J.B. Cocaine: A Drug and its Social Evolution. New York, NY: Basic Books, 1976.

Kluver, H. Mechanisms of hallucinations. In McNemar, Q. and Merrill, M.A. (eds.) Studies in Personality. New York, NY: McGraw Hill, 1942, pp. 175-207.

Lee, D. Cocaine Consumer's Handbook. San Francisco, CA: And/Or Press, 1976.

Lewin, L. Phantastica. Narcotic and Stimulating Drugs. London, England: Kegan Paul, Trench, Trubner & Co., 1931.

Lumholtz, C. Unknown Mexico. Volume 1. New York, NY: Scribner, 1902.

Magnan et Saury. Trois cas de cocainisme chronique. Comptes Rendus des Seances de la Societe de Biologie, 1(4):60-63 (1889).

Mantegazza, P. On the hygienic and medicinal virtues of coca. In Andrews, G. and Solomon, D. (eds.), The Coca Leaf and Cocaine Papers. New York, NY: Harcourt Brace Jovanovich, 1975, pp. 38-42.

Matsuzaki, M., Spingler, P.J., Misra, A.L. and Mule, S.J. Cocaine: Tolerance to its convulsant and cardiorespiratory stimulating effects in the monkey. Life Sciences, 19:193-204 (1976).

Moerschbaecher, J.M. Repeated acquisition and performance of conditional discriminations as a behavioral baseline for studying drug effects. (Doctoral dissertation, American University, 1976). Dissertation Abstracts International, 37:1009B (1976). (University Microfilms No. 76-18, 865).

Mortimer, W.G. History of Coca The Divine Plant of the Incas. 1901, reprinted, San Francisco, CA: And/Or Press, 1974.

National Commission on Marihuana and Drug Abuse. Drug Use in America: Problem in Perspective. Second Report. Washington, DC: U.S. Government Printing Office, 1973.

Perry, D.C. Heroin and cocaine adulteration. Clinical Toxicology, 8(2):239-243 (1975).

Phillips, J.L. Cocaine: The Facts and Myths. Washington, DC: Wynne Associates, 1975.

Post, R.M. Cocaine psychoses: a continuum model. American Journal of Psychiatry, 132:225-231 (1975).

Schultes, R.E. Random thoughts and queries on the botany of Cannabis. In Joyce, C.R.B. and Curry, S.B. (eds.), The Botany and Chemistry of Cannabis. London, England: J & A Churchill, 1970, pp. 11-38.

Siegel, R.K. An ethologic search for self-administration of hallucinogens. International Journal of the Addictions, 8:373-393 (1973).

Siegel, R.K. Cocaine hallucinations. Manuscript in preparation.

Siegel, R.K. and Jarvik, M.E. Drug-induced hallucinations in animals and man. In Siegel, R.K. and West, L. J. (eds.) Hallucinations: Behavior, Experience, and Theory. New York, NY: John Wiley & Sons, 1975, pp. 81-161.

Siegel, R.K., Johnson, C.A., Brewster, J.M. and Jarvik, M.E. Cocaine self-administration in monkeys by chewing and smoking. Pharmacology, Biochemistry and Behavior, 4:461-467 (1976).

Taylor, N. Plant Drugs that Changed the World. New York, NY: Dodd, Mead, 1965.

Thompson, D.M. Stimulus control and drug effects. In Blackman, D. and Sanger, D. (eds.) Contemporary Research in Behavioral Pharmacology. New York, NY: Plenum Press, in press.

Whyte, A.A. Acute and chronic administration of cocaine and d-amphetamine in rats on a multiple schedule. Unpublished doctoral dissertation, American University, 1976.

Wilson, R.A. Sex and Drugs. Chicago, IL: Playboy Press, 1973.

Wilson, S.A.K. Cocainism. In Bruce, A.N. (ed.), Neurology. Baltimore, MD: Williams and Wilkins, 1955, pp. 832-834.

Wolf, H.G. and Curran, D. Nature of delirium and allied states. Archives of Neurology and Psychiatry, 33:1175-1215 (1935).

Woods, J.H. and Downs, D.A. The psychopharmacology of cocaine. In Drug Use in America: Problem in Perspective. Appendix Volume 1: Patterns and Consequences of Drug Use. Washington, DC: U.S. Government Printing Office, 1973, pp. 116-139.

Chapter VII COCAINE: ITS USE FOR CENTRAL NERVOUS SYSTEM STIMULATION INCLUDING RECREATIONAL AND MEDICAL USES

Donald R. Wesson, M.D. and David E. Smith, M.D.

Although the more common medical uses of cocaine (discussed in Chapter 9, Cocaine in Clinical Medicine) involve its local anesthetic properties, the non-medical uses of cocaine are for its central nervous system (CNS) effects. To a lesser extent, the CNS effects of cocaine have been used medically, and periodically receive renewed interest. This chapter considers the social-recreational use patterns, followed by brief considerations of medicinal applications.

SOCIAL-RECREATIONAL USE

The history and changing nature of cocaine use in American society has recently been reviewed by a number of authors (Grinspoon & Bakalar, 1976; Ashley, 1975). The use of cocaine appears to have greatly increased over the past 10 years. Although its use is common among heroin and other seasoned drug users, much cocaine use occurs among young professionals and students not traditionally associated with drug using subcultures. Among these latter groups, cocaine is viewed as analogous to marihuana, and is considered to be free of adverse reactions and dependence liability. The extent to which these beliefs are justified involves consideration of patterns of use and dosage, as well as the pharmacological properties of cocaine. Here we will consider caveats regarding the use patterns and dosage, and leave a detailed discussion of pharmacological issues to other chapters of the monograph specifically devoted to those questions.

Today "coke," "snow," "gold dust," "bernice," "lady," "she," "Dana Blanca," "the rich man's drug," or "the pimp's drug" (all slang terms for cocaine) is widely available and used at a cost of $500-$1500 an ounce, or for about $60-$100 a gram.

Patterns of cocaine use and abuse cannot be completely replicated in a laboratory setting. The subjective effect of any drug experience is a complete interaction of expectations, setting and pharmacological effects of the drug, drug response, idiosyncracies of the drug user, and many additional socio-cultural expectations. Drug use rituals not generally duplicated in laboratory settings may alter the subjective sensations of the drug experience.

Knowledge of patterns of cocaine use is derived primarily from clinical descriptions of adverse drug reactions and descriptions of use patterns through individual interviews by researchers. The

current approach is analogous to studying astronomy by sitting in a cave and asking visitors from the surface to describe the stars. The information thus derived is certainly subject to a marked observer bias, and clinical reports are likely to emphasize the bizarre or, at best, atypical reactions.

Naturalistic observations of cocaine use by trained observers are needed to add perspective to understanding cocaine use patterns. However, because of the variety of individuals who use cocaine, and because of the variety of situations and settings in which cocaine use occurs, extensive observation would be required to comprehensively describe current use. Although the interpretation of field observations is subject to some ambiguity due to the interaction of set and setting and possible contamination due to the presence of an observer, the laboratory situation -- which attempts to control as many variables as possible -- may also lead to erroneous conclusions. There is always the unknown effect of introducing recording apparatus as well as the restrictions of laboratory settings, and it is naive to discount the influence of such factors. Without doubt, careful observation of cocaine use in a natural setting by trained observers could allow greater understanding of patterns of use than is now available. With the knowledge of as many variables as possible, the laboratory researcher would be in a better position to replicate patterns and dosages which are self-administered; and therefore, complement the knowledge acquired in the laboratory with relevance derived from field observations.

Cur observations and opinions regarding cocaine evolved from multiple contacts with cocaine users at the Haight-Ashbury Free Medical Clinic, the San Francisco Polydrug Project, observations at rock concerts, medical-legal consultations to the court, and by treating drug abusers in our private practice. Although our observations are, without question, subject to many of the limitations described above, we believe that some reasonably reliable information about current cocaine use has been developed as a result of these observations. The absolute frequency with which the described patterns actually occur are unknown, and some of the patterns described may well be the exception. Similarly, some of our toxicological findings have not been verified by laboratory studies; therefore, in certain situations, our conclusions may be at variance with laboratory-derived results.

CONSIDERATIONS OF DOSAGE

The absolute single dose of cocaine as used in a natural setting can only be estimated, but based on our analysis of material supplied by patients ranges from 0-200 mg/ingestion. Adverse reactions to non-intraveneously administered cocaine are related primarily to dosage, frequency and route of administration. It is reasonable to assume that the amount of cocaine used per episode in a natural setting occurs along a skewed bellshaped distribution as simulated in Figure 6-1.

As indicated in the top section of Figure 6-1, the hypothetical probability of adverse reaction to snorting cocaine is primarily a function of dosage. If use patterns change, pushing the mean point to the right, the probability of adverse reactions increases. In our opinion, current human administration studies use substantially less cocaine than the doses self-administered by users in a natural setting, thus further confusing the issue of safety since dosage is a major determinant of adverse drug effect. (It should also be added that individual sensitivities to the untoward effect of the drug may vary widely, so that a "safe" dose for one person may be a dangerous one for another.)

Since cocaine's effects are compared to those of other general central nervous system stimulants like amphetamines, rather than the opiates or marihuana, one would expect that the toxicity of cocaine could qualitatively parallel that of amphetamines. Our experience substantiates this premise, as we have seen cocaine-induced depressions, psychological dependence upon cocaine, acute anxiety reactions to cocaine and cocaine psychosis -- all qualitatively similar to other CWS stimulants, such as the amphetamines.

PATTERNS OF USE

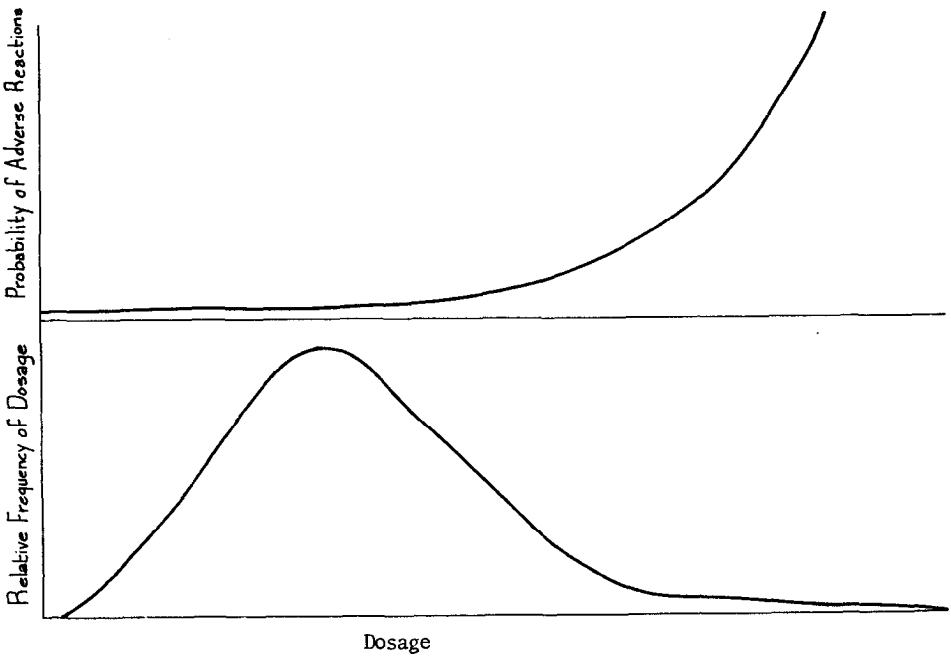
Oral Use

Although atypical of United States usage patterns, oral use of cocaine can be found. In Peru chronic coca use is common. Andean Indians chew coca leaves as a social ritual and mild stimulant and members of upper socio-economic classes brew tea from coca leaves (Weil, 1974). Far from chronic use, we have observed an expanded interest among counter-culture groups in the United States in the chewing of coca leaves for medicinal purposes as a social ritual, and as a mild stimulant. This is interpreted as part of a broader trend from synthetic drugs toward organic drug use.

Snorting

Cocaine is often absorbed through mucous membranes resulting in local anesthesia of the membrane in addition to cocaine systemic effects. The most common method of using cocaine is "snorting," a special case of absorption through mucous membranes as the cocaine is deposited on the mucous membrane lining of the nose. commonly, cocaine is chopped with a razor blade on a piece of glass into a fine powder and arranged into thin lines or columns, 3-5 cm long. A line is then inhaled intranasally, usually through a rolled dollar bill. One gram of cocaine normally produces about 30-40 lines of cocaine so that each line contains approximately 25-30 milligrams.

FIGURE 6-1



An Illustration of the Hypothetical
Relation BetweeIn Dosage and
Frequency of Adverse Reaction

The user experiences 20-40 minutes of stimulation and sometimes euphoria. Typically, the individual becomes talkative, and feels energetic and self-confident. The effects of a single dose diminish after 20-40 minutes, generally with no discernible after effects. Occasional, single dose snorting rarely produces complications sufficiently severe to require medical intervention.

Some individuals may continue to snort lines of cocaine every 10-20 minutes. Under these conditions, cocaine can accumulate in the body and produce a state of extreme agitation with increased suspiciousness and even paranoid psychosis. Realistically, most individuals are unable to afford the quantity of cocaine necessary to produce such adverse reactions. However, we have seen situations in which individuals with large sums of money and access to large quantities of cocaine, such as drug dealers and musicians, have been able to accrue sufficient amounts of cocaine to produce a cocaine psychosis with associated violence, similar to the violence-associated stimulation seen in the high dose amphetamine abuse drug culture (Smith, 1968).

Further, repeated high dose intranasal abuse of cocaine has some potential physical consequences -- such as a perforated nasal septum -- although this condition is quite rare. Our accumulated case experience has revealed only one instance of a perforated nasal septum which was secondary to extreme high dose intranasal abuse of cocaine.

In addition, as with the other stimulants such as the amphetamines (Smith & Wesson, 1973; Smith, 1968), one may see a drug-induced depression after prolonged high dose abuse of cocaine. This depression can occur in individuals who do not have a history of depression and is related primarily to dosage, duration of use and route of administration, as demonstrated by the following case example:

Case I

A 24-year-old white female worked as a secretary and had no history of significant prior depression. She periodically used cocaine by the intranasal route, and, at one point, was given an unusually large quantity of cocaine. (The material was professionally analyzed by a street drug analysis laboratory in the San Francisco Ray Area, which found it to contain 93 percent cocaine.) After "snorting" five to eight lines of the cocaine per night for several days, she began waking up feeling depressed. To overcome this depression, and go to work, she snorted one to two lines of cocaine in the morning. By the end of the second week, she was progressively developing severe anxiety, depression and increasing irritability which was interfering with her interpersonal relationships. Her concern over this drug-induced depression and anxiety faded in approximately two days and she re-established her usual level of positive affect and mood. Since this occurrence, she periodically

uses cocaine in social-recreational settings; however, she is careful to keep her dosage at a low enough level to avoid recurrence of this drug-induced depression.

Absorption Through Other Mucous Membranes

Other methods of absorption include rubbing cocaine on the gums or having cocaine blown from a straw onto the mucosal surface of the back of the throat.

Cocaine can also be absorbed through the mucosa of the vagina and sane individuals have incorporated this phenomena into their cocaine usage. Some users report intercourse is prolonged, and orgasms more intense after cocaine use. Occasionally males have difficulty achieving erections but once acquired, are able to sustain intercourse over an extended period of time. Some females report being unable to have orgasm, but rather are able to achieve a high, prolonged level of sexual excitation.

Intravenous Use

Cocaine may be injected alone or in combination with a longer lasting euphoriant such as heroin. (Mixtures of cocaine and heroin are called "speedballs.")

When cocaine is injected intravenously, the subject experiences an intense "rush" which is not experienced when cocaine is ingested orally or snorted. William Burroughs (1959) described the experience as follows:

> When you shoot coke in the mainline there is a rush of pure pleasure to the head...Ten minutes later you want another shot.. .intravenous C is electricity through the brain, activating cocaine pleasure connections... There is no withdrawal syndrome with C. It is a need of the brain alone.

Although Burroughs paid considerable tribute to cocaine, experienced users may not be able to initially distinguish the cocaine rush from that produced by amphetamines. The distinction can be made after a few minutes, however, because the effects of cocaine dissipate much more rapidly than amphetamines (Kramer et al., 1967).

Fischman et al., (1976) found that the cardiovascular and subjective effects of intravenously administered cocaine in humans was similar to that of dextroamphetamine, and concluded that 10 mg of dextroamphetamine generally had a subjective effect comparable to that of 8-16 mg of cocaine.

Cocaine is a popular drug among methadone maintenance clients since cocaine will exert its stimulant actions even concurrent with methadone. Chambers et al., (1972) in a study of methadone maintenance in Philadelphia, reported that cocaine was detected in 32 out of 173 methadone maintenance clients within one month.

Chronic high dose use in an effort to maintain a constant euphoric state increases the risk of medical sequelae. After a few days the pleasurable effects give way to an intense anxiety state with gross paranoid features, including auditory and visual hallucinations similar to an amphetamine psychosis.

Adverse reactions also may occur when the individual changes route of administration, as demonstrated by the following case:

Case II

A 19-year-old white male had been experimenting with a variety of drugs, including snorting cocaine for approximately two years. He had used cocaine exclusively in a recreational setting and indicated that he found nothing but pleasure in the drug experience and never had any problem, nor had he escalated his dose. One day a group of friends were injecting cocaine and they persuaded him to try this route of administration. As he had had no difficulty with cocaine previously, and as a result of curiosity and peer group pressure, he decided that he would experiment with injection. Following the intense stimulation and rush he became acutely anxious and frightened. Upon arrival at the Medical Section of the Haight-Ashbury Free Medical Clinic, he was found to have a very rapid pulse rate as well as a hyperventilation administered; anxiety. He was treated with 10 mg of i.v. Valium(R) adminestered slowly with reassurance. To cease the carpopedal spasms he had developed as a consequence of his hyperventilation syndrome, he was told to breathe into a paper bag which increased his carbon dioxide levels. The acute anxiety and its subsequent sequelae faded in approximately three hours. Follow-up indicated no recurrences or further experimentation with intravenous injection of cocaine by this individual. This use of intravenous sedative hypnotic medication is controversial and some critics of this approach use oral medication only while others stress reassurance alone without medication. We would recommend intravenous Valium(R) only after non-pharmacological intervention has failed.

Case III

A 31-year-old white male law student in his fourth year of law school had a long history of experimental drug use including alcohol (his first drug), marihuana and LSD; but at no time had he abused a psychoactive drug. Approximately two years ago he was introduced to cocaine in a social setting by a group of friends and fellow law

students. He became a regular recreational user of cocaine and in a social setting during an evening would chop up and snort between 10 and 20 lines of cocaine in the usual fashion. (Often, as with this case, cocaine is used in a recreational setting along with alcohol and marihuana.) With this law student, the pattern of recreational cocaine use continued for sane time, but moved to a more daily pattern when he found that the inhalation of cocaine stimulated his performance and ability to study at night, something he found desirable because he had begun to prepare for the bar examinations.

One evening a female friend with whom he was periodically having sexual relations produced a needle and syringe and indicated that the injection of cocaine produced a pleasurable, orgasmic-like "rush." The law student injected the cocaine simultaneously with his female sexual acquaintance and found the orgasmic "rush" quite desirable. Over a several month period he escalated his intravenous cocaine use on a daily basis, injecting from approximately 10 p.m. until 7 a.m., on a 15 minute to 1 hour repeated schedule, using approximately 2g of cocaine per night.

Despite the fact that the law student was independently wealthy as a result of a family inheritance, he found that he was rapidly consuming his inheritance as his cocaine habit was costing him $50-150 per day. As a consequence he began dealing cocaine to his friends in order to help support his own habit. While the injection of cocaine involved both male and female figures, he would almost invariably inject with a woman in a sexual context, although he reported that as he became more deeply involved with cocaine, his libido dropped dramatically; for both he and his female sexual partners, the orgasmic effects of the cocaine injection became a substitute for actual sexual intercourse.

One evening he injected a female friend in his usual fashion (he would first inject the woman and then himself). She suddenly had a series of seizures, became comatose, required mouth-to-mouth resuscitation and was subsequently transported to an emergency roan. During this particular cocaine run, he also experienced the first evidence of a cocaine psychosis, with auditory and visual hallucinations and extreme paranoia. The negative effects both to himself and to his girlfriend were quite shocking because he had believed cocaine to be as free of adverse consequences as marihuana. Because of these two episodes, he decided to quit cocaine use and seek treatment. During the "withdrawal period" he experienced difficulty sleeping and a severe drug induced depression associated with anxiety that lasted for approximately one week. Most depressive symptoms gradually abated; however, the anxiety continued along with an urge to use cocaine late in the evening at the time for his previous cocaine runs.

To help with the anxiety, depression and sleep disorder, 10 mg of Valium(R) p.o, was administered each night. As there was no evidence of a prolonged underlying depression which preceded the cocaine abuse or that lasted following the "fade out" period of the

drug-induced depression, no tricyclic antidepressants were administered. He made a decision to self-medicate the lethargy and reactive depression with the intranasal use of cocaine which he resumed on a daily basis. He expressed great surprise at the toxic effects of cocaine, but was also quite ambivalent about whether he would completely discontinue cocaine.

DEPENDENCE AND TOXICITY

Although psychological dependence on cocaine does occur, whether cocaine produces true physical dependence remains a question. If deprived of the drug, the cocaine user does not experience withdrawal symptoms such as those experienced by heroin or barbituate addicts. However, the depression following cocaine use may be viewed as a withdrawal state.

The degree of drug-induced depression is dose related and, as described by Blum (1976) and Axelrod (1970), the central stimulant action of both the amphetamines and cocaine is attributed to its effects on brain biogenic amines, especially catecholamines. The mental depression and fatigue which characterizes the depression to large doses of both amphetamine and cocaine in humans may be associated with temporary depletion of catecholamines in the central nervous system. Blum (1976) has also suggested that a mild functional deficiency of any dopamine or 5-hydroxyltryptamine in the central nervous system may serve as a biochemical basis for the drug-induced depression to cocaine.

TREATMENT OF TOXICITY

Treatment of cocaine toxicity is accomplished on a symptomatic basis. A sedative such as diazepam (Valium$^{(R)}$ can be administered orally for acute anxiety and drug-induced depression in dosages of 10-40 mg in repeated doses as indicated. Prolonged depression indicative of an underlying mood disorder can be treated by tricyclic antidepressants and appropriate psychotherapeutic intervention as indicated (Smith, 1976)[1]. With a severe overdose, hospitalization with respiratory assistance and a life support system (described in detail in "Cocaine in Clinical Medicine") may be necessary. Once cardiopulmonary function is assured, prognosis for the recovery from an overdose is greatly increased. Within a few hours, life-threatening signs disappear. After recovery, psychological support is of the utmost importance. For the rare case of cocaine stimulant psychosis, psychiatric hospitalization may be indicated.

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[1]See however Barash, Chapter 9, this volume for a caution on the potentiating effect of tricyclic antidepressants on cocaine.

In general, we find that the cocaine psychosis is of much shorter duration than the amphetamine psychosis. Therefore, if medication is needed, we recommend repeated small doses of Valium(R) to deal with the agitation and anxiety. If the psychosis persists, we recommend increasing the dose of Valium . If it continues for several days then the phenothiazine tranquilizers should be used with additional evaluation in order to determine if the cocaine has precipitated an underlying, endogenous psychotic disorder.

As with any stimulant, cocaine is often used in association with other drugs, very often in an upper-downer cycle (Smith & Wesson, 1973) with the secondary drug usually being a sedative-hypnotic in order to deal with sane of the stimulant side effects of cocaine. Cur experience has been, that the individual is able to titrate his stimulant and sedative use to minimize negative consequences, particularly if the drug is taken in a social-recreational setting. However, our court work has revealed situations in which young, particularly working-class adults, have been arrested for drunk driving and found to have intoxicating levels of alcohol. In interviewing these individuals, either through our field research or medical-legal consultation, we have occasionally found that their intoxication was actually a secondary drinking pattern with the primary social drug being cocaine. None of the laboratory examinations of biological fluids were tested for cocaine and the client was almost always attempting to hide his primary pattern of cocaine use, both from the court and from his defense attorney. Consequently, rarely has the primary pattern of cocaine use been implicated in this upper-downer cycle in which the secondary drug, a sedative-hypnotic, apparently leads to the negative social consequences. Because much of our contact with the cocaine user, as well as the abuser, has occurred outside of any treatment system, we feel that much of the cocaine abuse that is occurring at the street level is hidden from scientific or public analysis to date. This dearth of information actually perpetuates the belief that because the known incidence of cocaine abuse is small, the drug per se has a low abuse potential.

DRUG DECEPTION

Because of its high price and its distribution through black market channels, less expensive, more available materials are likely to be misrepresented as cocaine. This "drug deception" is, in fact, fairly common. Much of what is sold as cocaine is actually amphetamines, or other white (and sometimes brown) substances. Common substitutions for cocaine -- as analyzed by street drug analysis programs -- are amphetamines, tetracaine, or other local anesthetics, such as procaine (Novocain 1 and lidocaine (Xylocaine(R)). While data from street drug analysis programs document the existence of deception, they do not necessarily provide accurate estimates of its prevalence. Drugs are usually submitted for analysis because the owner suspects that the drug has been

misrepresented. Therefore, samples which are analyzed are not generally a random sampling of cocaine within the community.

Nevertheless, review of data on cocaine samples submitted to a street drug analysis laboratory in Palo Alto, California (Perry, 1975), indicates that approximately 73 percent of the cocaine samples submitted for analysis was pure cocaine, while another 21 percent consisted of cocaine infiltrated with synthetic local anesthetics and the remaining 6 percent contained other drugs such as amphetamines, caffeine, phencyclidine or no drug at all. A review of the monthly survey done at the Los Angeles County Hospital Drug Investigation Laboratory (Ritzlin & Lundberg, 1976) showed that of 10 cocaine samples submitted for analysis, 6 contained cocaine. Of the other four, one contained a cocaine/lidocaine combination, one a cocaine/mannitol combination, another contained pure lidocaine, and one was pure heroin. The latter finding of heroin-cocaine mixtures causes both confusion and concern. Presently, cocaine costs more than heroin and an increasing number of analyzed samples are found to have been adulterated with heroin. In addition, the phenanenon of "speed-balling," utilizing both heroin and cocaine, is growing more popular. This may produce difficulty in managing an overdose episode. For example, if an individual snorts or injects a large quantity of material he believes to be cocaine, but, in fact, contains heroin, the overdose experienced may be different than one would expect from ingesting pure cocaine. Treatment of heroin overdose is accomplished with intravenous naloxone, an opiate antagonist, which would have no effect on the cocaine stimulant symptoms. The combination of cocaine and heroin can result in some individuals being exposed to heroin who would probably not otherwise seek a heroin experience, as occurred in the following case example.

Case IV

A 35-year-old white female architect intermittently snorted cocaine in a social-recreational setting, but was introduced to a mixture of cocaine and heroin by a rock musician. She found the heroin prolonged and altered the effects of cocaine which she snorted, and produced an encouraging drug effect which was somewhat like an "acid trip." She snorted this mixture of cocaine and heroin each evening for approximately two weeks, but found that it was disrupting her work, producing a drug-induced depression and raising concerns in her mind about becoming addicted to heroin since she found the caubination so pleasurable. As a result, she discontinued her use and had a moderate drug-induced depression which she thought might be a mild abstinence syndrome. Neither required treatment or medical intervention. Even when examining what appear to be specific drug patterns, it cannot be assumed that the desired effects are the same for all individuals.

Case V

Interviews were done with 15 high dose intravenous cocaine and heroin abusers in a notorious drug dealing house in the Mission District of San Francisco. Of the 15 individuals, 4 indicated that intravenous injection of cocaine was the drug of choice because of the "orgasmic rush" they received when they injected, and the fact that it stimulated them to stay active. They mixed cocaine with heroin in order to calm some of its side-effects and to enhance the pleasurable effects of the cocaine.

The other 11 individuals indicated that the nodding, stoned effect of heroin was much more attractive to them and they did not like the "speedy" effect of the cocaine. They used cocaine combined with heroin only occasionally to have some diversity in their drug experience. Despite the fact that all 15 had experienced adverse drug effects with both cocaine and heroin, none had any interest in stopping their intravenous drug abuse.

MEDICAL USES OF COCAINE

Because of its euphoric effects, cocaine can alleviate a depressed mood. Freud had considered its use for this purpose, and felt it could be a useful psychotherapeutic drug. (Cf., Petersen, Chapter 1 this volume)

Grinspoon and Bakalar (1976) reviewed subsequent uses of cocaine for its CNS effects, and categorize three applications:

1) treatment of mental disorders – mainly depression and catatonic stupor;

2) diagnostic aids for mental disorders; and

3) model psychosis (schizophrenia, paranoid'type).

The use of cocaine (and stimulants in general) in the treatment of depression has been generally disappointing. It is clear that stimulants do not have any role in the treatment of most depressed patients, however, one need not conclude that cocaine is completely without value in every case.

While the authors would not presently advocate cocaine for the treatment of any mental disorder, we believe the potential role of cocaine in selected cases who have not responded to conventional treatment should be re-explored using modern evaluation techniques. The abuse potential, per se, should not necessarily preclude considerations of use. Severe depression unresponsive to treatment can be incapacitating and life-threatening, and can justify treatment techniques with considerable risk of addiction. Responsible use dictates control against diversion and close clinical monitoring and control.

Recently, cocaine has received sane use in the United States as a modified Brompton's Solution (containing methadone, cocaine and alcohol) for the treatment of pain from terminal cancer. The CNS stimulant effects are thought to decrease the clouding of consciousness produced by the methadone, and to potentiate its analgesic effects.

DISCUSSION AND SUMMARY

In summary, cocaine is a central nervous system stimulant of moderately high abuse potential. At the present time the preferred route of administration is intranasal and the dosage patterns are relatively low. The social rituals surrounding the drug endorse primarily recreational use while the high cost and low availability of the drug produce the current low rate of cocaine abuse in the United States.

Unfortunately, the difference between current abuse versus abuse potential is a concept not well understood by many laboratory scientists, drug experts who do not see cocaine abuse in their treatment programs, or by the general public. For example, a recent "San Francisco Chronicle" featured a story on cocaine which included the following quotes from an expert in the drug field:

> ...cocaine is less harmful than many other legal and illegal drugs popular in America.
>
> Most of the evidence is that there aren't any adverse effects to normal cocaine use. It looks to be much safer than barbiturates and amphetamines, and there's no evidence it has the body effects of cigarettes or alcohol.
>
> If I were going to go out and sell a drug to the public, it would probably be cocaine. We might be better off using it as a recreational drug than marihuana. Rut we have a cultural bias against routes of administration. As long as you can drink it or smoke it, it's OK in our society. That's why marihuana is making it. But using it in the nose or with a needle just isn't accepted. That may prove to be the biggest obstacle for cocaine.
>
> San Francisco Chronicle Thursday, October 21, 1976, Page 4)

We believe the closest pharmacological parallel to cocaine is neither marihuana nor alcohol, but rather amphetamines. In projecting the abuse "potential" of cocaine, it would be better to look at the consequences of amphetamine use -- whether swallowed, snorted or injected -- in helping to resolve the major debates now surrounding street use and abuse of cocaine.

Although most cocaine use, even in a social recreational setting, does not produce adverse medical or psychological consequences, one should not necessarily conclude that cocaine use is harmless. In considering the risk to the individual, one must also consider that at least some individuals must contact the illicit drug marketplace to obtain cocaine and may, thus, be exposed to criminal activities. The high cost of cocaine may drain an individual of financial resources. Also, drug-induced depressions and psychosis may occasionally occur.

The combination of cocaine with alcohol or other central nervous system depressants has the effect of combining the poor judgment of sedative intoxication with a high energy level of cocaine, a combination which we have observed to have serious consequences in some individuals.

Thus, we view cocaine to be a drug of moderately high abuse potential, similar to that of amphetamines; but with socio-cultural variables that prevent its widespread abuse, including the set and setting in which the drug is usually taken, and the route of administration which is primarily nasal "snorting" rather than intravenous "shooting." Most users now use cocaine by the intranasal route at moderately low dosages, while a relatively small percentage use cocaine intranasally or intravenously at high dosages. However, if the drug were more readily available at a substantially lower cost, or if certain socio-cultural rituals endorsed and supported the higher dose patterns, more destructive patterns of abuse could develop.

David E. Smith, M.D.
Haight-Ashbury Free Medical Clinic
and SanFrancisco Polydrug
Research Project
and
Donald R. Wesson, M.D.
San Francisco Polydrug Research
Project

REFERENCES

Cocaine: Its Use for Central Nervous System Stimulation Including Recreational and Medical Uses

Ashley, R. Cocaine: Its History, Uses and Effects. New York, NY: St. Martin's Press, 1975.

Axelrod, J. Amphetamine metabolism, physiological disposition and it effects on catecholamine storage. In Costa, E. and Garattini, S. (eds.) International Symposium on Amphetamines and Related Compounds. New York, NY: Raven Press, 1970, pp. 207-216.

Blum, K. Depressive states induced by drugs of abuse: Clinical evidence, theoretical mechanisms and proposed treatment. Part II. Journal of Psychedelic Drugs, 8(3):235-262 (1976).

Burroughs, W.S. Naked Lunch. New York, NY: Grove Press, 1959, pp. 64-65.

Chambers, C.D., Taylor, W.J.R. and Moffett, A.D. The incidence of cocaine abuse among methadone maintenance patients, International Journal of the Addictions, 7(3):427-441 (1972).

Fischman, M.W., Schuster, C.R., Resnekov, L., Shick, J.F.E., Krasnegor, N.A., Fennell, W. and Freedman, D.X. cardiovascular and subjective effects of intravenous cocaine administration in humans. Archives of General Psychiatry, 33:983-989 (1976).

Freud, S. The Cocaine Papers. Vienna, Austria: Dunquin Press, 1963.

Grinspoon, L. and Bakalar, J.B. Cocaine: A Drug and Its Social Evolution. New York, NY: Basic Books, 1976.

Kramer, J.C., Fischman, V.S. and Littlefield, AC. Amphetamine abuse: Pattern and effects of high doses taken intravenously. Journal of the American Medical Association, 201(5):305-309 (1967).

Martin, R.T. The role of coca in the history, religion and medicine of South American Indians. Economic Botany, 24:422-438 (1970).

Perry, D.C. Heroin and cocaine adulteration. Clinical Toxicology, 8(2):239-243 (1975).

Ritzlin, R.S. and Lundberg, G.D. Street Drug Identification Program. County of Los Angeles Department of Health Services, LAC - USC Medical Center Drug Investigation Laboratory, September, 1976.

Smith, D.E. Acute amphetamine toxicity. Journal of Psychedelic Drugs, 11(2): 49-54 (1969).

Smith, D. Polydrug abuse and comprehensive treatment intervention. Presentation at the National Drug Abuse Conference in New York, March, 1976.

Smith, D. and Wesson, D. (eds.). Uppers and Downers. Englewood Cliffs, NJ: Prentice-Hall, 1973.

Weil, A.T. The green and the white. Institute of Current World Affairs Newsletter, March 20, 1974.

Chapter VIII
THE FORENSIC TOXICOLOGY OF COCAINE

Bryan S. Finkle, Ph.D. and Kevin I. McCloskey, Ph.D.

The general purpose of this study-report is to assess the role of cocaine in post-mortem, medico-legal investigations, and a primary objective to determine whether cocaine has caused a significant and 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 the fatalities caused by other abused and misused drugs. A total of only 111 fatalities in which cocaine was involved occurred at 27 study sites between 1971 and 1976. Of these, 26 involved cocaine alone. The population base of these sites totaled 62.9 million.

The report is a retrospective, collaborative survey aimed at answering the above question, and provides incidental data and information which may assist forensic toxicologists and pathologists in their search for a more rational approach to the analysis and interpretation of "cocaine cases." It is not designed or intended as a review of cocaine toxicology-pharmacology, nor as a critique of analytical toxicology methods, much less an evaluation of toxicology laboratories' staffs or individual protocols.

The study was prompted by a growing volume of professional publicity during the past two years that a massive resurgence of cocaine availability and non-medical use was underway. This publicity has aroused controversy concerning the drug's toxicology, between advocates of its recreational use, who claim it is completely safe, and opponents who cite the historical record and apparent dangers indicated by data from the Drug Abuse Warning Network (DAWN) and the experiences of professionals working in drug abuse treatment and rehabilitation programs. Toxicological data to support or refute these claims were not 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 data on fatalities do provide a means of examining some medical hazards of cocaine use. If cocaine is widely available and abused, and also toxic, it will inevitably cane 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, can often provide accurate, objective

information to elucidate problems such as cocaine use. For any drug used and abused for recreational purposes there will be an accompanying body of folk-lore and case-law which serves to support all shades of subjective opinion but seriously clouds and hinders scientific knowledge. Data from cases subject to post-mortem, medico-legal investigation can shed important light through the cloud and help clarify misconceptions. This is an important justification for the rationale of this report.

Although books and papers continue to be published describing apparently new aspects of cocaine,[1] fatalities from the drug are certainly not new. As early as 1891, Mattison discussed cocaine poisoning and reported four well documented fatalities which occurred in 1887 and three in 1888. Mayer (1924) documented 21 deaths attributed to cocaine, and all editions of Webster's (1930) classic text, Legal Medicine and Toxicology discuss fatal cocaine poisonings from the turn of the century through the 1920's. Cocaine is not a benign drug, a fact which is clearly supported by its known pharmacology (Goodman & Gilman, 1975; Byck & Van Dyke, Chapter 5 this volume). Although used clinically as a local anesthetic, its systemic effects as a potent central nervous system, cortical stimulant are most relevant in evaluating its toxicity. After a toxic dose, the subject is likely to be excited, confused and suffer seizures (an early effect of central stimulation) followed rapidly by depression, eventually involving the medullary centers, such that death may result from respiratory failure. Yet, no major toxicological study of cocaine deaths has been attempted in recent years, although isolated cases have been reported in the medical literature since 1970.[2]

DESCRIPTION AND SCOPE OF DATA COLLECTION

The data collection and 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 fatal cases in which cocaine was the specific causative agent. Background information on each victim and the circumstances surrounding death were gathered in order to isolate common factors or trends which might be useful in predicting cocaine fatalities.

Toxicologists and pathologists from the medical examiners' and coroners' offices at 27 sites across the United States and Canada participated in the study. The sites and jurisdictions are shown in

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[1]Ashley, 1975; Gay et al., 1975; Mule, 1976; Van Dyke & Byck, 1976.

[2]De Vito, 1975; Pickett, 1970; Price, 1974; Wright-St. Clair, 1970.

Figure 8-1. Figure 8-2 presents the population of these jurisdictions and the number of cocaine-associated deaths investigated at each site. A total of 62.9 million or 29.8 percent of the United States population was covered by these sites. The large percentage is not only statistically useful, but it includes all sites from which cocaine deaths had been reported to DAWN, and also sites such as New York City and Los Angeles, where drug abuse is recognized as a social problem. This bias was offset by including sites thought less likely to yield cases, but which provided a balanced national geographic and demographic picture. 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.

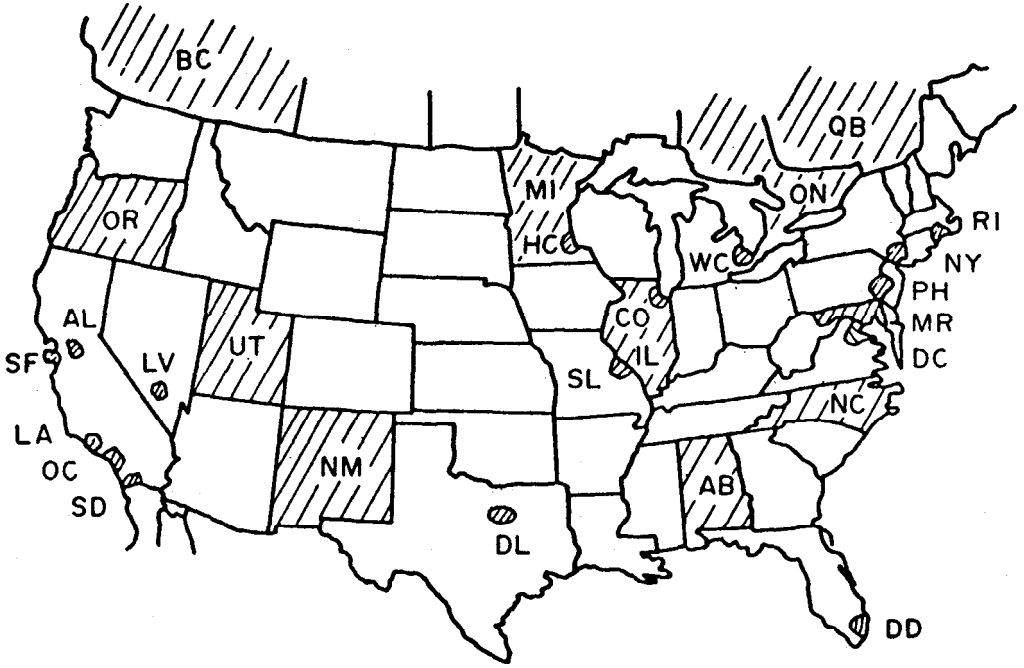
Two instruments were used to gather data at each site. One (Appendix A, page 178) provided information concerning analytical toxicology and laboratory resources and the other (Appendix B, page 179) was used to record individual case data. Appendix B includes definitions for each question and alpha-numeric coded answers. By using the codes, the questionnaire could be completed rapidly and the data entered directly into a mini-computer for analysis. The study included only those cases in which cocaine and/or its metabolites were detected and identified by toxicological analysis. Data were collected by reviewing the case files at each site. Only the information indicated on the forms 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 case.

The total number of fatalities on which data was finally collected which in any way involved cocaine was 111. Figure 8-2 shows the breakdown by site. There were sane surprising results. While the relatively high number of cases from New York City and Los Angeles County was expected, the absence of any cases from Philadelphia, Minneapolis and Las Vegas, and the small number of cases from Wayne County (Detroit) and Cook County (Chicago) -- one and three respectively -- were notable, since these areas all have acknowledged drug abuse problems. Similarly, the finding that the number of cases from Utah and New Mexico virtually matched the number from urban areas of California and Florida was very striking. Information from interviews with forensic scientists and law enforcement officials at several sites confirmed the local case incidence and the overall inference that cocaine use and subsequent fatal episodes is not uniform for urban or rural areas throughout the United States. Its occurrence was not reliably predictable from general demographic considerations or drug abuse histories for particular areas.

The finding of 111 cocaine-related fatalities in a 5-year period represents a relatively low incidence when compared with fatalities attributed to almost any other major drug of abuse -- e.g., heroin or barbiturates -- but, more importantly for this study, it is a

FIGURE 8-1

COCAINE SURVEY SITES



U.S. SURVEY POPULATION = 62.9 MILLION
(29.8% OF U.S. POPULATION)

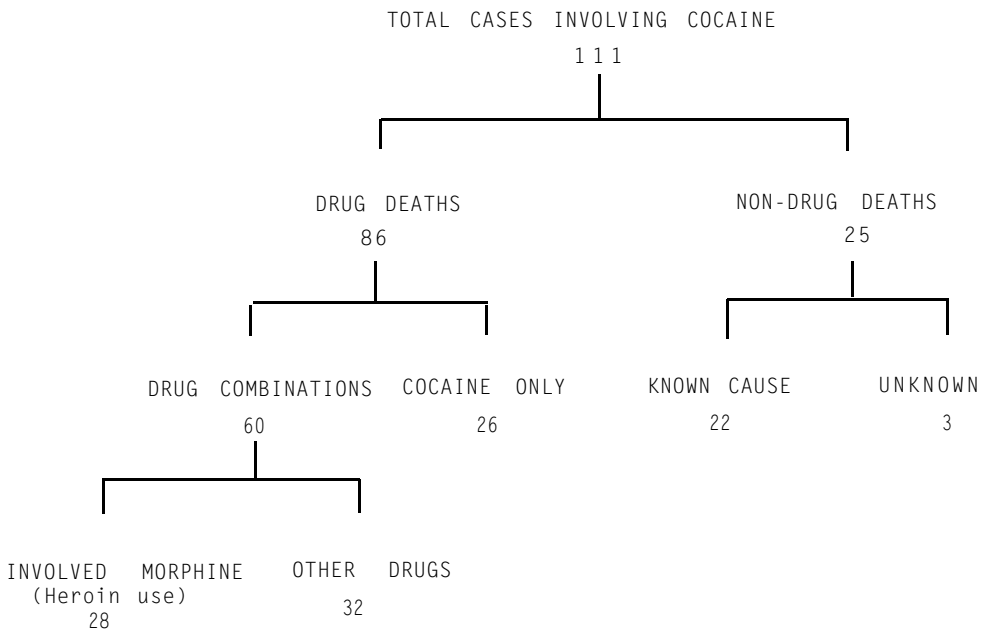
FIGURE 8-2

COCAINE SURVEY: PARTICIPATING SITES, JURISDICTION POPULATION AND INVESTIGATED COCAINE ASSOCIATED DEATHS

SITE	JURISDICTION POPULATION ($x10^6$)	DOCUMENTED COCAINE ASSOCIATED DEATHS (1971-1976)
Alabama State (AB)	3.5	2
Alameda County, CA (LA)	1.1	6
Clark County, NV (LV)	0.3	0
Cook County, IL (CO)	5.4	3
Dade County, FL (DD)	1.5	6
Dallas County, TX (DL)	1.3	2
Hennepin County, MN (HC)	1.0	0
Illinois State, (IL)	6.0	0
Los Angeles County, CA (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 (NY)	7.6	31
North Carolina State (NC)	5.0	1
Orange County, CA (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, CA (SD)	1.4	5
San Francisco County, CA (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, DC (DC)	0.7	7
Wayne County, MI (WC)	3.0	1
TOTAL	79.2	111

FIGURE 8-3

SEGREGATION OF STUDY CASES
ACCORDING TO DRUG OR NON-DRUG DEATHS



small number for useful statistical analysis. This is particularly true since of the 111, death was caused by drugs in 86 cases and by cocaine alone in only 26 cases (see Figure 8-3). Although the data gathered were uniform and therefore appropriate for analysis, the study encompassed a highly specialized population -- fatalities involving cocaine -- and, therefore, great care was taken not to extrapolate from the data in an 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 Figure 8-3, 25 cases (22.5 percent of the total surveyed) were fatalities with a cause other than drugs. Although cocaine and sometimes other drugs were detected in these victims, they did not occur in concentrations considered sufficient to cause death. In any event, 60 percent of these cases were either homicides or suicides and almost all of them (21) were violent deaths via gunshot or stab wounds.

The increasing frequency of cocaine's presence in sudden, unexplained death cases is indicated in the following table:

OCCURRENCE OF COCAINE CASES BY YEAR*

1971	1972	1973	1974	1975	1976
2	3	11	25	37	29(58**)

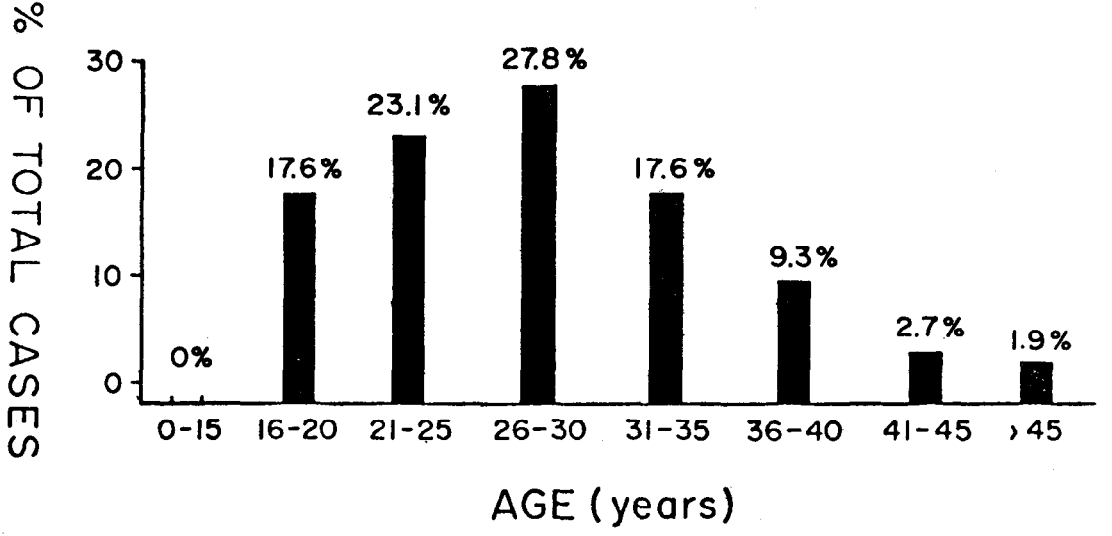
*Total cases for all study sites, 1971-1976
**Extrapolated figure to December 31, 1976

The increase is sharp but care must be taken before inferring at face value that the figures indicate a dramatic increase in cocaine use. Other influences, such as the awareness of medico-legal investigators of cocaine use and improvements in analytical methods available to toxicologists during the past five years, may have contributed to the apparent rise in the incidence of cases involving cocaine.

HISTORY OF THE DECEASED

A general inspection and overview of the survey cases reveals that the deceased were principally young, white males. The great majority were less than 30 years old, and almost 2/3 were Caucasian with an approximate 3:1 bias in favor of males.

Figure 8-4 shows the distribution of age groups as a percentage of total cases. Although more than a quarter were 26-30 years old, 51 percent were in their 20's and 68.5 percent were under 30. There was a negligible number of cases (3) older than 40 years. Further



1 Case = 0.9%

FIGURE 8-4

analysis of the data did not show any other significant trends related to age. For example, the 26 cases involving only cocaine were almost evenly distributed between ages 16 and 35; and for those 28 cases associated with heroin used, as indicated by the detection of morphine in the post-mortem blood and tissues, there was no discernible difference from the overall pattern shown in Figure 8-4.

The racial characteristics of the victims were known in all but four cases. Caucasians accounted for 63.1 percent (70 cases) of the toal, 22.5 percent (25 cases) were black and 10.8 percent (12 cases) were of Spanish-American descent. There were no Native-American Indians or Asian-Americans. Caucasians were represented in greater proportion (80.8 percent, 21 cases) than blacks (11.5 percent, or 3 cases) in the 26 cocaine-only cases, whereas the opposite was true for those victims involved with heroin use -- almost a third (32.1 percent, or 9 cases) were black, while 57.2 percent (16 cases) were caucasian. Spanish-Americans were represented in all categories in about the same proportion as in the total survey.

As mentioned earlier, there was a marked bias toward males among the deceased:

	Number of cases	Percent of total
Males	81	73.0
Females	30	27.0
	111	100.0

Male/female ratio = 2.7

Similar male/female ratios occurred in the cases involving only cocaine (2.9) and in those involving morphine (2.5), while a greater preponderance of males was reported among the non-drug deaths (m/f = 5.25).

The occupational status of the deceased was known for 69 of the 111 cases. Of the 69, 77 percent were employed at the time of their deaths. Approximately 35 percent could be classified as manual blue-collar workers. Relatively few professionals -- medical or clerical personnel -- or students were represented. Occupation was known for half of the cocaine-only deaths but no particular group predominated.

In order to determine the previous health and drug use experience of the deceased, their medical and psychiatric history was evaluated whenever possible. This information was generally available as

part of the investigator's case report to the medical examiner or coroner. For the purposes of this study, medical and psychiatric history was defined by the 12 categories as shown in Appendix B, page 179, items 10 and 12. The categories in these items were assembled from common medical ailments and typical conditions associated with emotional disturbance, and new categories were added in keeping with case findings as the survey proceeded. By the definition of item 10 the total sample population was generally medically healthy prior to demise. There was no defined history of recent acute or chronic illness for 85.6 percent of the cases. For the remaining individuals who did have a medical history, there was no marked single ailment or class of diseases. In all but 2 of the 26 cases involving only cocaine, there was no medical history.

In contrast with the positive medical histories, 61.3 percent (68 cases) of the deceased had, a "psychiatric history" as defined by the criteria in question 12.[1] It is important to note that of those with a psychiatric history, the problems were almost exclusively related to drug abuse or misuse, with a conspicuously low incidence of alcohol abuse (only 2.4 percent of the 86 drug death cases). Morphine, resulting from heroin use, was the drug most commonly detected in combination with cocaine, occurring in 33 percent (28) of the drug-death cases. Lidocaine (encountered as the usual "cutting agent" for cocaine, and not as a medical treatment for the victims), methadone and hypnotic sedatives were the only other drugs frequently associated with the study cases. There were fewer than five occurrences each for diazepam, amitriptyline, phenothiazines and propoxyphene -- drugs often used to treat tension, depression and neuroses. Only 1.2 percent of the victims (one case) had a history of attempted suicide, which is consistent with the low incidence of deaths classified as suicide (16 or 14.4 percent).

Twenty-three of the 111 deceased had a known, documented history of cocaine abuse; of these, 19 (21 percent of the total) were classified by the pathologist as victims of accidental drug-caused deaths (26.7 percent of drug-caused deaths; see Figure 8-5). The causes of death for the remaining cocaine abusers were: natural -- 1; homicide -- 2; suicide -- 1 (gunshot wound). As might be anticipated, the proportion of these cases in which cocaine was ingested nasally was much higher than for the survey population as a whole (see Table 31, but, surprisingly, so was the proportion of cases (56.5 percent; n = 13) in which cocaine was injected intravenously. Throughout this discussion, intravenous use of cocaine, knowingly or otherwise, was revealed as a common Occurrence, even among identified cocaine abusers, as illustrated in Figure 8-6. This is consistent with the reports of Wesson & Smith on street use of cocaine (cf., Chapter 6 this monograph). None of the known cocaine abusers in the study had any reported medical history, in contrast with 14.4 percent of the total cases; nor did they have any notable psychiatric history other than drug abuse.

[1]The reader should note that inclusion in this category might reflect no more than that the deceased had been reported to have used marihuana. . .or even cocaine--Eds.

FIGURE 8-5

CASES INVOLVING PRIOR HISTORY OF DRUG ABUSE

PRIOR HISTORY	N	PERCENT OF DRUG DEATH CASES*
Heroin Abuse	30	34.8
Cocaine Abuse	23	26.7
Unspecified-Drug Abuse	22	25.6
Alcohol Abuse	2	2.3

*Percentage values do not tally because of overlap between categories.

FIGURE 8-6

ROUTE OF ADMINISTRATION OF COCAINE FOR VARIOUS CATEGORIES OF THE SURVEY CASES

ROUTE OF ADMINISTRATION	PERCENT OF TOTAL SURVEY CASES	N	PERCENT OF COCAINE-ONLY DRUG DEATHS	N	PERCENT OF DRUG COMBINATION DEATHS	N	PERCENT OF CASES DECEASED HAS HISTORY OF COCAINE ABUSE	N
Undeterminable	54.1	60	15.4	4	56.8	34	17.4	4
Intravenous	31.5	35	61.5	16	30.0	18	56.5	13
Nasal	7.2	8	7.7	2	8.3	5	17.4	4
Oral	6.3	7	15.4	4	3.3	2	8.7	2
Rectal	0.9	1	-	-	1.6	1	-	-
		111		26		60		23

FIGURE 8-7

CLASSIFIED MANNER OF DEATH FOR TOTAL SURVEY CASES

MANNER	NUMBER OF CASES
Suicide	16 (14.4%)
Accident	48 (43.2%)
Homicide	13 (11.7%)
Natural	5 (4.6%)
Undetermined	29 (26.1%)
TOTAL	111

ATTENDANT CIRCUMSTANCES IN COCAINE ASSOCIATED DEATHS

The manner of death for all the study cases, as classified by the medical examiner or coroner, is shown in Figure 8-7. The high number of accidental deaths and those of undetermined cause is notable because it clearly indicates the unintentional aspect and the appropriately conservative view taken by most pathologists when assessing deaths involving drugs of abuse. In addition, it indicates that the study population as a whole cannot be generally characterized as suicides. Although the proportion of cases classified as accidental or undetermined was the same among those involving only cocaine as for the total cases, the proportion of suicides was higher -- 22.9 percent. There is no obvious explanation for this. In cases involving heroin use, only 1 out of 28 (as compared to 16 cases of the 111 total) was a suicide, and accidental deaths comprised 71.4 percent of the heroin users. This is again indicative of pathologists' cautious approach toward classifying sudden deaths involving opiate narcotics.

The route of administration of the cocaine is shown in Figure 8-6. For slightly over half of the cases (54.1 percent), these data could not be determined. When information was available it generally came from up to three sources: a) witnesses' statements; b) pathology-toxicology findings at autopsy, such as injection sites, needle tracks or cocaine detection on nasal swabs; and c) drug injection paraphernalia found with the body. It is perhaps important to reiterate that, as indicated in Figure 8-6. intravenous self-administration is frequently used. This is particularly true for those cases in which morphine was detected; however, there was no means of determining whether the drugs were acquired and used as a single powder or as separate preparations. In a total of 28 cases -- - a quarter of the total sample or one-third of the drug deaths -- morphine, related to heroin use, was detected analytically. The evidence for a relationship between heroin and cocaine use, at least for this post-mortem population, is, therefore, persuasive.

There was a significant bias towards the oral route for those cases involving only cocaine. Oral ingestion was documented for 15.4 percent of these cases, but most of these were suicidal ingestions of large amounts of the drug or accidental deaths in which the packaged drug was swallowed for smuggling purposes or to elude detection when arrested. Nasal insufflation was the route of cocaine administration for 7.7 percent (2 cases) of this group, a figure which closely matches the incidence for the total sample, and refutes the common assumption by drug users that this route is invariably safe. There is neither sound pharmacology nor case data in the study to support this opinion.

There was nothing remarkable about the location at which the cocaine use or fatal incident took place. Private residences (house or apartment) accounted for 65.9 percent, and 9.4 percent occurred at a motel or hotel. Only 11.8 percent (10) of the drug-death cases

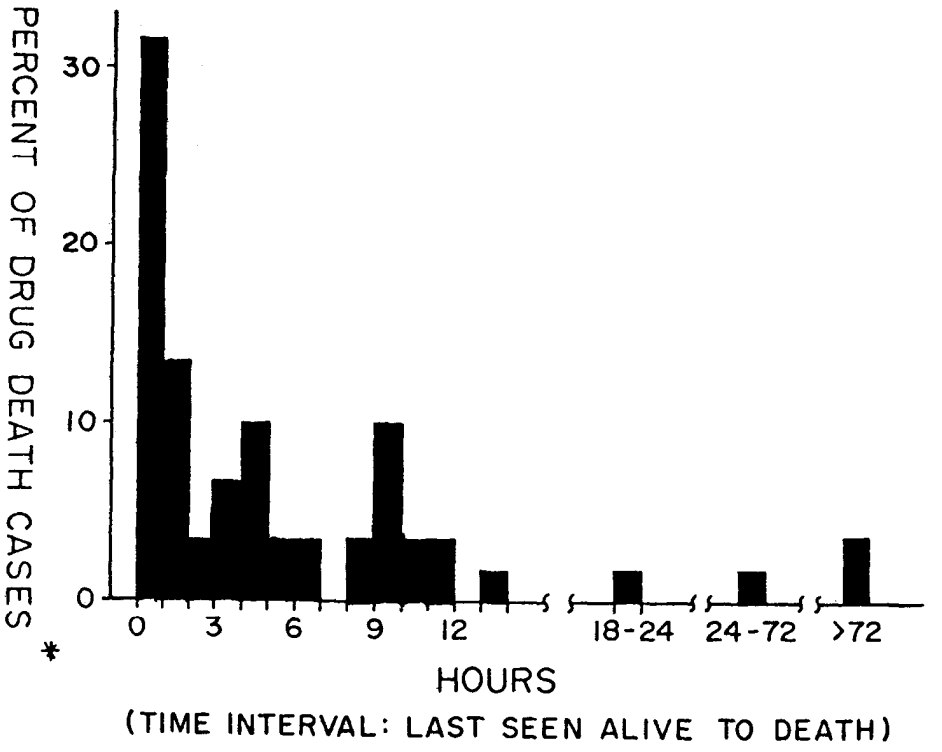
reached a hospital before they died. This small number of hospital cases is undoubtedly a reflection of the short survival time seen in a majority of the total study cases and illustrates the potency of the drug.

The range of survival times following cocaine ingestion or the recorded interval between the last time the deceased was seen alive and was found dead is depicted in Figure 8-8. One case is equivalent to 1.7 percent of the total drug-death cases comprising the graph. The earlier time intervals are undoubtedly the most accurate because for the longer periods, particularly beyond 10 hours or overnight, it becomes increasingly likely that death occurred earlier and the body remained undiscovered. Within these constraints it can be seen from Figure 8-8 that almost two-thirds of the victims (65 percent) died in less than five hours and most of these (31.7 percent of the total drug-deaths) died in the first hour following ingestion. The peak in the 9-10 hour period results from the classification of overnight deaths in this interval; for many of them the time interval may have been shorter. For the 26 cases involving only cocaine the time interval distribution is significantly truncated; 73.9 percent of these victims died in less than 2 hours and more than half within one hour. The pattern for cases involving morphine was not discernibly different from the overall distribution. There was no correlation between survival time and route of drug administration. All routes, including nasal ingestion, were represented among the rapid deaths (less than five hours), highlighting again the potential for insufflation of the drug to produce toxicity.

Although terminal symptom were reliably observed and reported for only half of the deaths involving only cocaine (13 of 26 cases), they were remarkably consistent. The symptoms were entirely central nervous system mediated -- usually seizures followed by respiratory arrest, coma and death. Cardiac arrest was reported in three instances. These observations present a consistent picture of the principal pharmacological actions of cocaine. Almost no other signs or symptoms (e.g., vomiting or dizziness) were reported.

ANALYTICAL TOXICOLOGY METHODS FOR COCAINE, USED AT THE SURVEY SITE

All but two of the toxicology laboratories at the *24* U.S. sites currently use routine analytical screening methods which would detect cocaine if present in the autopsy specimen tested. Not less than 5 mls of blood or urine was generally the sample of choice with stated sensitivity limits for cocaine in the range 1.0-2.0 mcg/ml. Three sites included liver tissue samples in the initial drug screening analysis for cases in which no specific drugs were suspected. Immunological methods applied to urine samples were usually employed followed by thin layer chromatography (TLC) and gas chromatography (GC), with ultraviolet spectrophotometry avail-



1 Case = 1.7%

FIGURE 8-8

able at two sites. The Enzyme Multiplication Immunological Technique (EMIT(R)) was used at nine laboratories and radioimmunoassay at one other)site.(EMIT(R)) 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 and/or metabolite from the biological sample before chranatographic analysis. At 11 laboratories benzoylecgonine was included but the remaining 16 sites relied upon detection of the parent cocaine. XAD-2 resin was used at two sites to separate the drug from the biological matrix. All of the others used organic solvent extraction after adjusting the sample to approximately pH 9 with buffer. Some saturated the aqueous sample 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 chrauatography. It was noted that the stability of cocaine in hydrochloric acid greater than 0.5N was 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. (1976), should be used as a preservative to prevent this problem.

Quantitative analysis for cocaine and/or its metabolite was generally achieved using gas chromatography and an internal standard. At only four sites were other techniques employed: ultraviolet spectrophotometry, 2; EMIT (R), 1; and GC-mass spectrometry, 1. It is interesting that although GC-MS was available at 12 of the 27 survey sites, it was used routinely at only 1 for quantitative work, by multiple ion monitoring. The instrument was used at all sites for specific, qualitative identification purposes. Eight different internal standards were in use: nalorphine, imipramine, mepivacaine, methaqualone, cholestane, trihexyphenidyl, lidocaine and SKF-525A. The common use of lidocaine as a "cutting agent" is a caution against its use as an internal standard for cocaine analysis, and a number of collaborators expressed dissatisfaction with SKF-525A due to unpredictable variations in its extraction characteristics and its susceptibility to thermal degradation during GC analysis.

Excellent critical reviews of available analytical methods, discussing their advantages and limitations, have been written by Jatlow (1976) and Bastos and Hoffman (1976). The extraction procedure followed by GC-MS qualitative and quantitative analysis described and used by Hawks (Hawks et al., 1974; Mule, 1976) might be considered state-of-the-art and is potentially useful for toxicologists at almost half of the study laboratories. For those with GC there are a number of published, proven methods;[1] the method described by Jatlow and Bailey (1975) requires a nitrogen detector, while Jain et al. (1977) described a procedure using a simple derivatization technique which allows the use of flame ionization.

[1]Blake et al., 1974; Jain et al., 1977; Jatlow & Bailey, 1975; Wallace et al., 1976.

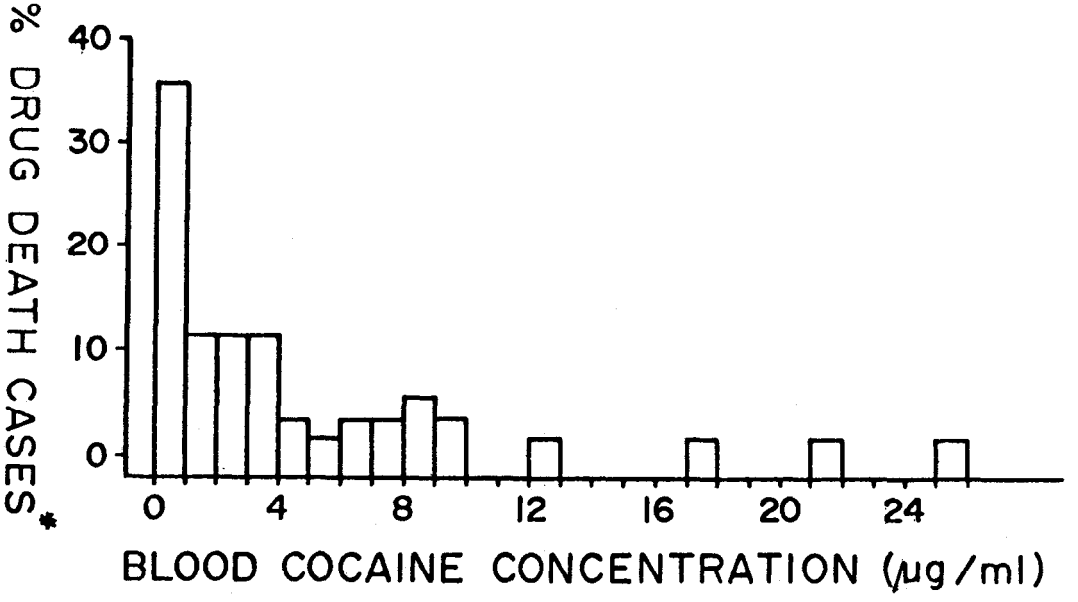
Practical means for the analysis of cocaine and its primary metabolite are available and were in use at almost all of the study sites. It is almost certain that at 22 of the 27 laboratories collaborating in the study, cocaine involvement in a fatal case would have been detected, especially since the advent of immunological testing in 1973-74. The high percentage of study cases in which cocaine was suspected by the investigator or pathologist prior to toxicological analysis adds to this confidence. Similarly, the credibility of sites reporting no cocaine cases during the 5 to 6 year period is also supported by this fact. Initial screening methods should be capable of detecting less than 1.0 mcg/ml cocaine in blood, based on known maximum blood concentrations following effective doses of the drug and the number of study cases in which the blood level was less than 1.0 mcg/ml.

FATAL BLOOD AND TISSUE CONCENNTRATIONS

As seen in Figure 8-3 above, 86 of the 111 study cases were classified as drug-deaths; however, quantitative cocaine blood concentrations were determined for only 53 of these. The distribution of these concentrations as a percentage of the drug-death cases is shown in Figure 8-9 (one case = 1.9 percent of the total). Almost three-quarters of the cases (70 percent) had blood concentrations lower than 4.0 mcg/ml, with one-third between 1.0 and 4.0 mcg/ml and 36 percent 1.0 mcg/ml or lower. Only 4 of the 53 cases had blood levels higher than 10 mcg/ml, one of which had the remarkably high value of 25-26 mcg/ml. The routes of administration for this group were either intravenous or unknown.

Blood cocaine concentrations were reported for 23 of the 26 cases in which only cocaine was involved (see Figure 8-10). Because of the small number of cases, inferences must be cautious, but there is a trend towards higher blood concentrations in these cases than in all of the drug-death cases; 70 percent of all drug-deaths had concentrations lower than 4.0 mcg/ml, while among cases involving only cocaine, 70 percent of the cases were not accounted for until concentrations up to 9.0 mcg/ml are included. Similarly, only 7.5 percent of the total drug-deaths had blood levels higher than 10 mcg/ml, while among the cocaine-only deaths, 17.3 percent were above this level.

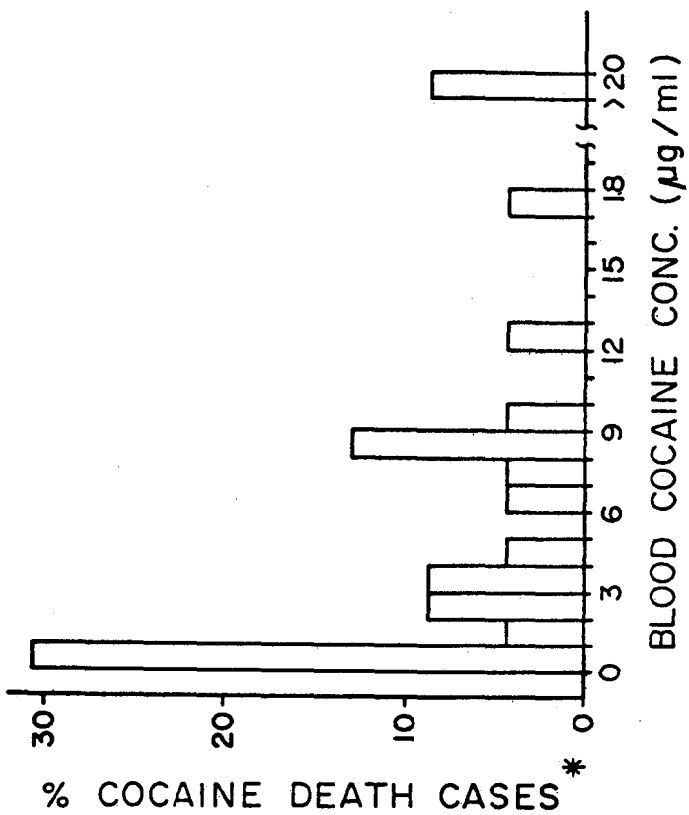
In order to assess the significance of the blood concentrations in fatal cases, reported values from controlled animal and human clinical studies can be used for comparison. A regimen of injections which culminated in convulsions and death within 30 days for monkeys, and the accompanying milligram/kg doses have been reported by Deneau et al. (1969). Approximately 40 mgs of cocaine every 4 hours, with a maximum daily intake of 80-100 mgs/kg, precipitated convulsions. Van Dyke et al. (1976) reported plasma concentrations in the range 120-474 nanograms/ml which persisted for 4-6 hours for humans receiving 1.5 mg/kg cocaine applied to their nasal mucosa, and 'similar data have been reported by Byck et al. (1976) in a



1 Case = 1.9%

FIGURE 8-9

FIGURE 8-10


% COCAINE DEATH CASES*
30
20
10
0
0
3
6
9
12
15
18
>20
BLOOD COCAINE CONC. (µg/ml)
1 Case = 4.3%

variety of human patients. The highest blood concentrations reported for humans following "large" (100-200 mgs?) i.v. street doses were in the range 3-7 mcg/ml, and for monkeys receiving 15 mgs/kg i.p., concentrations were 0.7-1.0 mcg/ml. Obviously, many factors, such as the ability of an individual to hydrolyze cocaine to benzoylecgonine by plasma cholinesterase, can affect these broad estimated ranges. Jatlow et al. (1976) has reported possible impairment of this metabolic pathway in succinylcholine sensitive individuals, which could result in unusually elevated plasma cocaine concentrations.

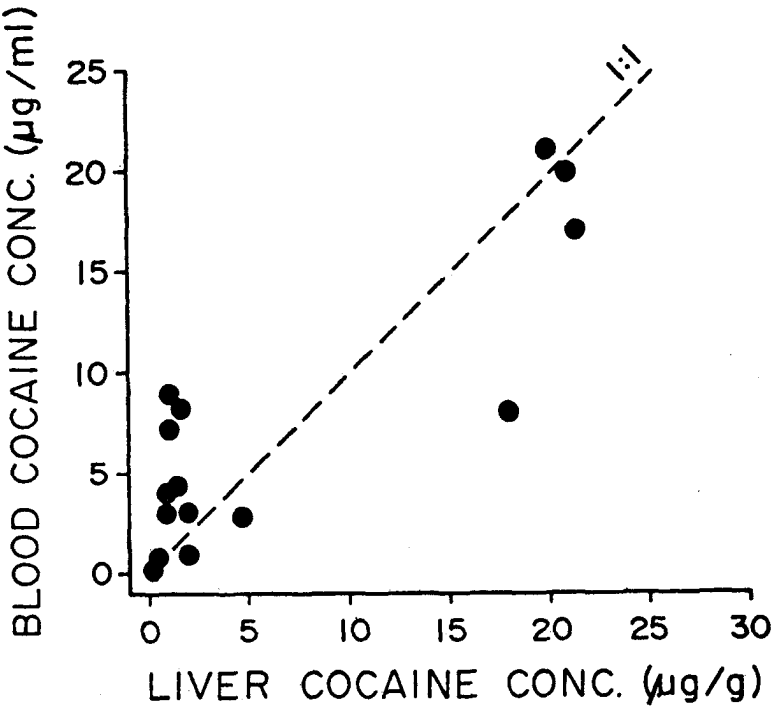
Liver tissue concentrations of cocaine relative to blood levels have been analyzed to determine whether blood:liver ratios are a practical indicator of toxicity, making the liver a useful toxicological specimen, particularly since cocaine is one of the few drugs which undergoes metabolism in blood with a halflife of approximately 1.5 hours. Data for the survey cases are shown in Figure 8-11. Reliable determinations of both blood and liver concentrations were available for only 15 cases. Blood concentrations were generally higher than liver concentrations, with a reversal in only 5 of the 15 cases. Figure 8-11 suggests that blood analysis is more desirable. For cases involving only cocaine, the mean blood/liver ratio was 1.4, and the blood concentration was higher than that of the liver in all of these cases.

Only two other drugs, morphine and alcohol, were considered in evaluating the significance of the toxicological findings in the 111 study cases. Morphine was detected in 28 cases, all of which were classified as drug-deaths. Blood cocaine concentrations were significantly lower in this subset than in either the survey cases as a whole or the cocaine-only cases; all 28 were lower than 4.0 mcg/ml and almost 60 percent were between 1.0 and 4.0 mcg/ml. There is little doubt that the presence of morphine was an important factor in toxicity in these cases.

Although alcoholism and alcohol abuse were not prevalent in the medical and psychiatric histories of the survey population, alcohol was detected in 22 (25.6 percent) of the 86 drug-death cases. In six of these (approximately 7 percent), the only substances detected were alcohol and cocaine. Blood alcohol concentrations for the 22 cases ranged from 0.02 to 0.43 percent. Quitting the 0.43 percent figure, the mean for the sample was 0.10 percent and the median, 0.12 percent, concentrations which would cause significant central nervous system depression and add to the adverse CNS effects of cocaine. The presence of ethanol in pharmacologically effective concentrations is important, but the generalization that alcohol in combination with cocaine is a dominant or predictable factor in cocaine-associated deaths is not justified.

There were only eight cases in which both alcohol and morphine in addition to cocaine were detected in significant amounts.

FIGURE 8-11


BLOOD COCAINE CONC. (µg/ml)
25
20
15
10
5
0
1:1
0
5
10
15
20
25
30
LIVER COCAINE CONC. (µg/g)

FORENSIC PATHOLOGY

All but 2 (1 who died from natural causes and 1 from gunshot wounds) of the 111 study cases were suspected by the pathologist and/or investigator to involve drugs, and in no less than 100 cases cocaine was anticipated. Of the 86 deaths classified as drug fatalities 90 percent were subject to a complete medico-legal autopsy and for 70 percent of the 86 the autopsy was carried out within 24 hours; 20 percent were performed within 6 hours of discovery or report of the death. This prompt response by medical examiners and coroners is particularly important because-of the potential in vitro degradation of cocaine. For those cases in which only cocaine was detected 86 percent were autopsied within 24 hours. The gross observations by the pathologist at autopsy were generally non-specific, consisting almost uniformly of pulmonary edema, and massive pulmonary, visceral and cerebral congestion. For the cocaine deaths a high percentage showed evidence of recent intravenous self-administration correlating with the high incidence of i.v. drug use reported for this group of victims by witnesses and investigators. In the cases with an authenticated prior history of cocaine use 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. It has been reported that Ear, Nose and Throat Surgeons at Yale University School of Medicine and Hospital have never seen a case of nasal necrosis resulting from cocaine use (cf., Barash, Chapter 9 this volume). Apparently the incidence of perforated nasal septum as an effect of intranasal cocaine use has been exaggerated.

The pathologist's microscopic study of autopsy specimen sections were all either reported as unremarkable or confirmed the gross observations.

FATALITIES INVOLVING NASAL ADMINISTRATION OF COCAINE

Of the 111 cases in the study, 8 reported "snorting," "sniffing coke" or insufflation -- all nasal administrations -- as the route of administration. Although cocaine was shown to be present, the immediate cause of death in one of the eight cases was determined to be due to factors other than drugs. Of the remaining seven cases, cocaine was the only drug detected in two of these drug deaths. As shown in Figure 8-6, this is 7.7 percent of the 26 cocaine-only cases. The manners of death for the eight cases were classified as follows: "Accidental (4), "Undetermined" (31, and "Natural" (1); there were no suicides. Of the seven drug-caused deaths, 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, lidocaine had been used to "cut" the cocaine, and the powdered mixture was sniffed. No medical treatment had been given in these cases, eliminating the possibility that lidocaine had been mistakenly administered to the victims as an emergency medical measure. The Drug Enforcement Agency (DEA) reports that lidocaine or procaine is sometimes mixed with heroin and/or cocaine for sale. Consequently, finding these drugs or their metabolites in post-mortem analysis 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 post-mortem blood concentrations of cocaine were high, however, ranging from 2.8 to 5.9 mcg/ml. There was only 1 case in the nanogram range -- at 200 nanograms/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 50-100 nanograms/ml (Byck et al., 1976) and doses as high as 1.5 mg/kg provide peak concentrations of approximately 120 - 500 nanograms/ml after 15-60 minutes (Van Dyke et al., 1976).

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

SUMMARY AND CONCLUSIONS

This retrospective, collaborative study involved 27 medical examiners' and coroners' offices from the United States and Canada. The geographic area surveyed included 62.9 million individuals or 29.8 percent of the U.S. population and provided only 26 cases in which cocaine was the only drug detected. This is not a large number, either absolutely or relative to the number of other drug fatalities from, e.g., sedative-hypnotics, analgesics and opiate narcotics. However, there is evidence that the number of cocaine deaths is increasing.

There were a total of 111 sudden, unexplained deaths in which cocaine was involved. Drugs were causative in 86 cases. (The full spectrum of the 111 study fatalities included some accidental and suicidal deaths from a variety of causes other than drugs. There are 25 such cases.) The national picture of cocaine deaths is not uniform and many cities and counties with major drug abuse problems did not report any fatal cocaine cases. The incidence of cocaine related deaths is not, therefore, predictable from geographic characteristics.

The deceased population consisted predominantly of young, white males, many with a record of opiate narcotic abuse. Most were less than 30-years-old, males out-numbered females almost 3 to 1 and the subjects were employed in a variety of blue-collar jobs at the time of their deaths.

The 111 victims in the study were medically healthy prior to death and without known significant psychiatric problems other than drug abuse. Alcoholism and heavy use of tranquilizers were not evident, although many of the subjects were certainly drinkers.

The manner of death for almost half of the deceased was classified as accidental and for approximately a quarter, as undetermined. Suicides were rare.

There were a significant number of heroin users among the victims, as indicated by case histories, route of administration of the drug and post-mortem toxicological data; 35.3 percent had a history of heroin use, 61.5 percent of the cases involved only cocaine and 30.0 percent of the drug combination deaths involved the intravenous route. Morphine was detected analytically in one-third of the 86 drug-deaths.

Lidocaine was occasionally detected analytically and was apparently used as a "cutting agent" for cocaine. Alcohol was present in significant concentrations in about one-quarter of the drug-deaths with a mean blood value of 0.1 percent.

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

Analytical toxicological methods adequate for detection and quantitative determination of cocaine and/or its primary metabolites in post-mortem biological specimens were available at all laboratories. Immunological techniques (EMIT$^{(R)}$) an 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 1.0-2.0 µg/ml of cocaine. Benzoylecgonine was never analyzed quantitatively.

In 70 percent of the 86 drug-death cases the blood concentrations of cocaine were lower than 4.0 mcg/ml and in more than one-third they were 1.0 mcg/ml or lower. For fatalities involving only cocaine, 70 percent of the cases had blood concentrations lower than 9.0 mcg/ml. Blood concentrations were generally higher than corresponding liver tissue values, confirming blood as the sample of first choice for analysis, although the in vitro instability of cocaine, requires that the blood sample be preserved by sodium fluoride.

Cocaine involvement was suspected in most of the study cases by the investigator or pathologist prior to analysis. Complete and prompt autopsies were performed, often including examination of nasal passages. No instance of perforated nasal septums was found. With the exception of injection sites, gross observations and microscopic findings were unremarkable and without diagnostic character.

For seven of the study cases classified as drug-caused deaths it was established that the cocaine was ingested intranasally. The blood concentrations in six of these cases were very high: 2.8-5.9 mcg/ml, one case had the minimum concentration of 200 nanograms/ml. The overall study findings and these seven cases in particular clearly refute the assumption that nasal insufflation of cocaine is completely safe. There is no pharmacological or toxicological 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 U.S.A. and Canada. Aside from the fact that this was not the purpose of the study, the deceased population does not reflect general use of the drug. Notwithstanding this limitation, the study does indicate that drug abusers are dying from the use of cocaine either alone or, more commonly, in combination with morphine.

Bryan S. Finkle, Ph.D. and
Kevin L. McCloskey, Ph.D.
Center for Human Toxicology
University of Utah
Salt Lake City, Utah

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Wayne County, Detroit, Mich.	Joseph R. Monforte & Werner U. Spitz	Forensic Toxicologist Forensic Pathologist

B.S.F.
K.L. McC.

Appendix A

DATA COLLECTION INSTRUMENT

From Chapter 8, The Forensic Toxicology of Cocaine

The following instrument was used by Drs. Finkle and McCloskey to gather information on analytical toxicology and laboratory procedures during their study of the incidence of cocaine-related deaths in 27 U.S. and Canadian sites over the past five to six years.

CENTER FOR HUMAN TOXICOLOGY - COCAINE DRUG STUDY

DATA COLLECTION INSTRUMENT

ANALYTICAL TOXICOLOGY - METHODOLOGY

DRUG: COCAINE (CURRENT) OBTAIN COPY OF PROCEDURE _____

METHOD OF EXTRACTION (BLOOD & TISSUES) _____

METHOD OF IOENTIFICATION _____

METHOD OF QUANTITATION _____

LIMIT OF SENSITIVITY _____

PRECISION _____ ACCURACY _____ RECOVERY _____

CHANGES IN METHODS: NOTE ALL METHODS USED BETWEEN 1971 - 1976

IS COCAINE INCLUDED IN INITIAL SCREEN ANALYSIS _____

DESCRIBED SCREEN PROCEDURE _____ OBTAIN COPY _____

LAB. FACILITIES:

SPACE _____ STAFF _____

CAPITAL EQUIPMENT (DATES) _____

Appendix B

FORM AND DATA CODES

From Chapter 8, The Forensic Toxicology of Cocaine

The following instruments were used by Drs. Finkle and McCloskey to record individual case data, including definitions for each question and alpha-numeric coded answers, during their study of the incidence of cocaine-related deaths over the past five to six years in 27 U.S. and Canadian study sites.

Appendix B

Survey Form

Official Cause of Death
History of Deceased
Circumstances of Death
Pathology and Toxicology

Data codes

1. Manner
2. Cause of Death, Drug
3. Cause of Death, Cocaine
4. Occupation
5. Age
6. Sex
7. Race
8. Weight
9. Medical History
10. Specific (medical history)
11. Psychiatric History
12. Specific (psychiatric history)
13. Cocaine
14. Source
15. Route
16. Other Drugs
17. Location
18. Time Last Seen Alive or With Drugs
19. Suicide Incidence
20. Specific (suicide evidence)
21. Terminal Symptoms
22. Type (of terminal symptoms)
23. Specific (terminal symptoms)
24. Treatment (immediately prior to death)
25. Type (of treatment)
26. Drugs (used in treatment)
27. Autopsy
28. Time (between death and autopsy)
29. Specimen Conditions
30. Blood Source
31. Approximate Cause of Death
32. Gross
33. Microscopic (findings)
34. Cocaine only
35. Ethyl Alcohol
36. Cocaine and Ethyl Alcohol

CENTER FOR HUMAN TOXICOLOGY
NATIONAL DRUG SURVEY

APPENDIX B
Chapter 8

CHT No. _____
AGENCY No. _____
YEAR OF DEATH. _____

OFFICIAL C. O. D. _____

1. MANNER _____ 2. C.O.D., DRUGS _____ 3. C.O.D., COCAINE _____

HX OF DECEASED

4. OCCUP. _____ 7. RACE _____ 11. PSYCH. HX. _____
5. AGE _____ 8. WT. _____ 12. SPECIFIC _____
6. SEX _____ 9. MED. HX. _____
10. SPECIFIC _____

CIRCUMSTANCES OF DEATH

13. COCAINE _____ 18. TIME(L.S.A-D) _____ 23. SPECIFIC _____
14. SOURCE _____ 19. SUIC. INDIC. _____
15. ROUTE _____ 20. SPECIFIC _____ 24. TREATM. _____
16. OTHER DRUGS _____ 21. TERM. SYMP. _____ 25. TYPE _____
17. LOCATION _____ 22. TERM. SYMP. TYPE _____ 26. DRUGS _____

PATHOLOGY & TOXICOLOGY*

27. AUTOP. _____ 31. APPR. C.O.D. _____ 35. ETOH _____
28. TIME(D.-A.) _____ 32. GROSS _____ 36. COCAINE & ETOH _____
29. SPEC. COND. _____ 33. MICRO _____
30. BLD. SOURCE _____ 34. COCAINE ONLY _____

DRUG	BLOOD	LIVER	URINE	BILE	G. CTN. (mgs)+		
COCAINE							
ALCOHOL							

*CONCENTRATION IN MICROGRAMS/ML OR MICROGRAMS/GM.
+G. CTN = TOTAL WT. OF DRUG IN MGS

DATA CODES

OFFICIAL C.O.D. (CAUSE OF DEATH): Official Cause of Death as stated on final Death Certificate. If unknown, write U.

1. MANNER: Officially determined manner of death as stated on final Death Certificate.

   CODE: S = SUICIDE
   A = ACCIDENT
   N = NATURAL
   H = HOMICIDE
   U = UNDETERMINED

2. C.O.D., DRUGS: Are drugs mentioned in official C.O.D.

   CODE: Y = YES
   N = NO
   U = C.O.D. UNKNOWN

3. C.O.D., COCAINE: Is Cocaine specifically mentioned in official C.O.D.

   CODE: Y = YES
   N = NO
   U = UNKNOWN

4. Occup.: Occupation of the deceased. Select one

   CODE: 01 = BLUE COLLAR WORKER OR MANUAL LABOR
   02 = CLERICAL
   03 = HOUSEWIFE
   04 = STUDENT
   05 = PROFESSIONAL
   06 = PARAMEDICAL (e.g. NURSE, NURSE'S AID. HOSP. ORDERLY, LAB. TECH.)
   07 = MILITARY
   08 = RETIRED
   09 = UNEMPLOYED
   10 = OTHER
   11 = UNKNOWN

5. AGE: Age of Deceased.

   CODE:
   01 = 0-5 YEARS OF AGE
   02 = 6-10 " " "
   03 = 11-15 " " "
   04 = 16-20 " " "
   05 = 21-25 " " "
   06 = 26-30 " " "
   07 = 31-35 " " "
   08 = 36-40 " " "
   09 = 41-45 YEARS OF AGE
   10 = 46-50 " " "
   11 = 51-55 " " "
   12 = 56-60 " " "
   13 = 61-65 " " "
   14 = > 65 " " "
   15 = UNKNOWN

6. Sex: Sex of Deceased.

   CODE: M = MALE
   F = FEMALE
   U = UNKNOWN

7. RACE: Ethnic origin of Deceased.

CODE: C = CAUCASIAN
B = BLACK
A = ASIAN - AMERICAN
S = SPANISH SURNAME
N = NATIVE AMERICAN
U = UNKNOWN

8. WT: Body weight of Deceased.

CODE: 01 = 0.50 lbs
02 = 51-100 lbs
03 = 101-150 lbs
04 = 151-200 lbs
05 = > 200 lbs
06 = UNKNOWN

9. MED. HX.: Pertinent medical history of the deceased relative to the cause of death.

CODE: Y = DECEASED HAD RECENT MEDICAL HISTORY.
N = NO PERTINENT MEDICAL HISTORY KNOWN.

10. SPECIFIC: Specify particulars of medical history. Select one or more categories.

CODE: 01 = RECENT HOSPITALIZATION (INCLUDES REST HOMES)
02 = RECENT SURGERY
03 = RECENT DENTAL PROCEDURES
04 = RECENT PROCEDURE REQUIRING ANESTHETIC
05 = RECENT INJURY OR CHRONIC ILLNESS (e.g. TRAUMA, MUSCULAR
06 = INVALID OR SKELETAL INJURY)
07 = GASTROINTESTINAL HX.
08 = CARDIOVASCULAR HX.
09 = DRUG ABUSE TREATMENT
10 = EPILEPSY
11 = PREGNANCY
12 = OTHER
13 = UNKNOWN
14 = CARCINOMA
15 = DIABETES

11. PSYCH. HX: Indications of recent psychiatric or emotional disturbances of the deceased, as defined by categories listed in Number 12.

CODE: Y = INDICATIONS WERE PRESENT
N = NO INDICATIONS PRESENT

12. SPECIFIC: Specific indications of recent emotional disturbances. Select one or more categories.

CODE: 01 = RECENT OR CHRONIC PSYCHIATRIC TREATMENT
02 = RECENT DESPONDENCY
03 = PRIOR SUICIDE ATTEMPTS
04 = COCAINE USE MEDICAL
05 = HEROIN ABUSE (e.g. PARAPHERNALIA FOUND, METHADONE MAINTENANCE, ETC.)
06 = COCAINE ABUSE (e.g. NON-MEDICAL SELF-MEDICATION, 'RECREATIONAL')
07 = PSYCHOTROPIC ABUSE (LSD, PCP, MARIJUANA, ETC.)
08 = ALCOHOL ABUSE OR MISUSE
09 = GENERAL OR UNSPECIFIED DRUG MISUSE OR ABUSE (SEDATIVES, AMPHETAMINE, ETC.)

12. SPECIFIC (Cont'd)

CODE: 10 = MENTAL RETARDATION OR NEUROLOGICAL IMPAIRMENT
11 = OTHER INDICATIONS
12 = OLD NEEDLE TRACKS

13. COCAINE: Cocaine was known to be available to the deceased.

CODE: Y = WAS AVAILABLE
N = NO INDICATIONS OF AVAILABILITY

14. SOURCE: Origin of the cocaine available to deceased.

CODE: P = PRESCRIPTION OF DECEASED
O = PRESCRIPTION FOR SOMEONE OTHER THAN THE DECEASED
I = ILLICITLY OBTAINED
U = UNKNOWN

15. ROUTE: Apparent route of administration for cocaine used by deceased.

CODE: O = ORAL
V = INTRAVENOUS
M = INTRAMUSCULAR
S = NASAL
T = OTHER
U = UNKNOWN

16. OTHER DRUGS: Other medications known to be available to the deceased. Select one or more.

CODE:

01 = LIBRIUM	15 = UNSPECIFIED BARBITURATES
02 = ELAVIL	16 = DORIDEN
03 = MELLARIL	17 = APC & CODEINE
04 = TRIAVIL	18 = PENICILLIN
05 = MILTOWN	19 = DRUGS OF ABUSE (e.g. LSD, MARIJUANA, PCP. ETC.)
06 = THORAZINE	
07 = DALMANE	20 = OTHERS
08 = SECONAL	21 = UNKNOWN
09 = NEMBUTAL	22 = METHAQUALONE
10 = CHLORAL HYDRATE	23 = METHADONE
11 = TUTNAL	24 = EQUANIL
12 = PHENOBARBITAL	25 = TRANXENE
13 = PLACIDYL	26 = VISTARIL
14 = PROPOXYPHENE	27 = HYDROXYZINE

17. LOCATION: Location where the deceased expired.

CODE:

01 = RESIDENCE (HOUSE OR APARTMENT)	05 = HOSPITAL
02 = MOTEL OR HOTEL	06 = OUT-OF-DOORS
03 = AUTOMOBILE	07 = OTHER
04 = REST HOME	08 = UNKNOWN

18. TIME (LSA-D): Estimate of time interval between 'last seen alive' or when drugs were ingested and death.

CODE:

01 =	0.0 - 0.25 hr	13 =	10.1 - 11.0 hr
02 =	0.25 - 0.50 hr	14 =	11.1 - 12.0 hr
03 =	0.51 - 1.0 hr	15 =	12.1 - 13.0 hr
04 =	1.1 - 2.0 hr	16 =	13.1 - 14.0 hr
05 =	2.1 - 3.0 hr	17 =	14.1 - 15.0 hr
06 =	3.1 - 4.0 hr	18 =	15.1 - 16.0 hr
07 =	4.1 - 5.0 hr	19 =	16.1 - 17.0 hr
08 =	5.1 - 6.0 hr	20 =	17.1 - 18.0 hr
09 =	6.1 - 7.0 hr	21 =	18.1 - 24.0 hr
10 =	7.1 - 8.0 hr	22 =	24.1 - 72 hrs
11 =	8.1 - 9.0 hr	23 =	> 72 hrs
12 =	9.1 - 10.0 hr (also 'overnight')	24 =	UNKNOWN
		25 =	HOSPITALIZATION , >24 hr

19. SUIC. INDIC: Indications that death may have been a suicide.

CODE: Y = INDICATIONS PRESENT
N = NO INDICATIONS

20. SPECIFIC: Specific evidence of suicide. Select one or more.

CODE: N = SUICIDE NOTE
S = VERBAL STATEMENTS
A = ACTIONS (e.g. CUT WRISTS, HIDING. ETC.)
P = PRIOR ATTEMPTS

21. TERM. SYMP: Presence of symptoms relative to drug ingestion observed in the deceased prior to death.

CODE: Y = SYMPTOMS WERE OBSERVED
N = NO SYMPTOMS OBSERVED

22. TYPE: Specify type of terminal symptoms observed. Select one or more.

CODE: C = INVOLVED CNS
V = INVOLVED CARDIOVASCULAR SYSTEM
P = PERIPHERAL MANIFESTATIONS

23. SPECIFIC: Specific terminal symptoms observed. Select one or more.

CODE: 01 = COMA
02 = RESPIRATORY ARREST
03 = CARDIAC ARREST
04 = SEIZURES
05 = INTOXICATION (e.g. DISORIENTATION. ATAXIA. SLURRED SPEECH. ETC.)
06 = CARDIOVASCULAR COLLAPSE
07 = SYNCOPE
08 = VOMITING
09 = HALLUCINATIONS
10 = OTHER

24. TREATM.: Deceased received emergency medical treatment immediately prior to death.

CODE: Y = DECEASED RECEIVED TREATMENT
N = NO RECORD OF DECEASED RECEIVING TREATMENT

25. TYPE: Type of emergency treatment received by deceased. Select one or more.

CODE: 01 = CARDIOPULMONARY RESUSCITATION (CPR)
02 = DEFIBRILLATION
03 = CLOSED CHEST MASSAGE
04 = RESPIRATORY ASSISTANCE
05 = GASTRIC IRRIGATION
06 = DIALYSIS
07 = OTHER
08 = UNKNOWN

26. DRUGS: Drugs used in the course of emergency treatment. Select one or more.

CODE: 01 = VALIUM
02 = LIDOCAINE
03 = NARCAN
04 = ISUPREL
05 = EPINEPHRINE, PHENYLEPHRINE
06 = CARBONATE
07 = OTHER
08 = UNKNOWN

27. AUTOP.: Type of autopsy performed.

CODE: C = COMPLETE
P = PARTIAL
E = EXTERNAL ONLY
U = UNKNOWN

28. TIME (D-A): Time interval between death and autopsy.

CODE: 01 = 0-6 hrs
02 = 7-12 hrs
03 = 13-18 hrs
04 = 19-24 hrs
05 = 25-48 hrs
06 = > 48 hrs
07 = UNKNOWN

29. SPEC. COND.: Condition of tissues and blood specimens.

CODE: F = FRESH
D = DECOMPOSED
E = EMBALMED
U = UNKNOWN

30. BLD. SOURCE: Site from which blood sample was collected.

CODE: J = JUGULAR
H = HEART OR GREAT VEINS
O = OTHER PERIPHERAL SITE
F = FEMORAL
U = UNKNOWN

31. APPR. C.O.D.: Immediate suspected cause of death.

CODE: D = DRUG(S) OVERDOSE
N = NATURAL (DISEASE)
T = TRAUMA (e.g. STRANGULATION, AUTO ACCIDENT, CRUSHING, BLOOD LOSS. BURNS, DROWNING, ETC.)
G = GUNSHOT WOUNDS
S = STABBING
E = ELECTROCUTION
O = OTHER
U = UNKNOWN

32. Gross: Gross autopsy findings. Select one or more.

CODE: 01 = PULMONARY EDEMA & CONGESTION
02 = VISCERAL EDEMA & CONGESTION
03 = CEREBRAL EDEMA & CONGESTION
04 = MEDICATIONS IN GASTRIC CONTENTS
05 = ASPIRATION OF VOMITUS
06 = INTERNAL INJURIES
07 = 'NEEDLE TRACKS'
08 = 'SUICIDE SCARS'
09 = INDICATIONS OF DISEASE PROCESS
10 = UNKNOWN OR NOT PERFORMED
11 = VISCERAL CONGESTION
12 = TRAUMA
13 = UNREMARKABLE
14 = CHEMICAL GASTRITIS

33. MICRO: Microscopic and bacteriological findings.

CODE: 01 = UNREMARKABLE
02 = CONFIRMS GROSS FINDINGS
03 = INDICATIONS OF DISEASE PROCESS NOT SUSPECTED FROM GROSS AUTOPSY
04 = UNKNOWN OR NOT PERFORMED

34. COCAINE ONLY: Laboratory analysis for cocaine and other drugs.

CODE: Y = ONLY COCAINE FOUND
N = OTHER DRUGS (INCLUDING ALCOHOL) WERE FOUND

35. ETOH: Laboratory analysis for ethyl alcohol

CODE: Y = ALCOHOL WAS PRESENT
N = ALCOHOL WAS NOT PRESENT

36. COCAINE & ETOH: Laboratory analysis for cocaine and ethyl alcohol.

CODE: Y = ONLY COCAINE AND ALCOHOL FOUND
N = EITHER COCAINE ALONE OR COCAINE IN COMBINATION WITH DRUGS OTHER THAN ALCOHOL.

REFERENCES
Forensic Toxicology

Ashley, R. Cocaine: Its History, Uses and Effects. New York, NY: St. Martin's Press, 1975.

Bastos, M.L. and Hoffman, D.B. Detection and identification of cocaine, its metabolites and its derivatives. In Mule, S.J. (ed.), Cocaine: Chemical, Biological, Social, and Treatment Aspects. Cleveland, OH: CRC Press, 1977, pp. 33-58.

Blake, J.W., Ray, R.S., Noonan, J.S. and Murdick, P.W. Rapid, sensitive gas-liquid chranatographic screening procedure for cocaine. Analytical Chemistry, 46(2):288 (1974).

Byck, R., Jatlow, P., Barash, P. and Van Dyke, C. Cocaine: Blood concentration and physiological effect after intranasal application in man. In Ellinwood, E.H. and Kilbey, M.M. (eds.), Cocaine and Other Stimulants. New York, NY: Plenum Press, 1977, pp. 629-646.

Deneau, C.W., Yanagita, T. and Seevers, M.H. Self-administration of psychoactive substances by the monkey: A measure of psychological dependence. Psychopharmacologia, 16:30-48 (1969).

De Vito, J.J. Cocaine Intoxication. Medical Times, 103(10):189 (1975).

Gay, G.R., Inaba, D.S., Sheppard, C.W. and Newmyer, J.A. Cocaine: History, epidemiology, human pharmacology and treatment. A perspective on a new debut for an old girl. Clinical Toxicology, 8(2):149-178 (1975).

Goodman, L.S. and Gilman, A. The Pharmacological Basis of Therapeutics. 5th Ed. New York, NY: Macmillan, 1975.

Hawks, R.L., Kopin, I.J., Colburn, R.W. and Thoa, N.B. Norcocaine: A pharmacologically active metabolite of cocaine found in brain. Life Sciences, 15:2189-2195 (1974).

Jain, N.C., Chinn, D.M., Budd, R.D., Sneath, T.S. and Leung, W.J. Simultaneous determination of cocaine and benzoylecgonine in urine by gas chromatography using "on-colunm" alkylation. Journal of Forensic Sciences, 22(1):7-16 (1977).

Jatlow, P. Analysis of cocaine and its metabolites in biological fluids. In Mule, S.J. (ed.) Cocaine: Chemical, Biological, Social, and Treatment Aspects. Cleveland, OH: CRC Press, 1977, pp. 59-70.

Jatlow, P., Barash, P.G., Van Dyke, C. and Byck, R. Impaired hydrolysis of cocaine in plasma from succinylcholine sensitive individuals. Clinical Research, 23(3):255A (1976).

Jatlow, P.I. and Bailey, D.N. Gas chromatographic analysis analysis for cocaine in human plasma, with use of a nitrogen detector. Clinical Chemistry, 21(13):1918 (1975).

Mattison, J.B. Cocaine poisoning. Medical and Surgical Reporter, 65:645 (1891).

Mayer, E. The toxic effects following the use of local anesthetics. Journal of the American Medical Association, 82:8 76-885 (1924).

Mule, S.J. (ed.) Cocaine: Chemical, Biological, Social, and Treatment Aspects. Cleveland, OH: CRC Press, 1977.

Pickett, R.D. Acute toxicity of heroin alone and in combination with cocaine or quinine. British Journal of Pharmacology, 40:145 (1970).

Price, K.R. Fatal cocaine poisoning. Journal of the Forensic Science Society, 14(4):329 (1974).

Van Dyke, C. and Byck, R. Cocaine: 1884-1974. In Ellinwood, E.H. and Kilbey, M.M. (eds.), Cocaine and Other Stimulants. New York, NY: Plenum Press, 1977, pp. 1-30.

Van Dyke, C., Barash, P.G., Jatlow, P. and Byck, R. Cocaine: Plasma concentrations after intranasal application in man. Science, 191:859-861 (1976).

Wallace, J.E., Hamilton, H.E., King, D.E., Bason, D.J., Schwertner, H.A. and Harris, S.C. Gas-liquid chromatographic determination of cocaine and benzoylecgonine in urine. Analytical Chemistry, 48(1):34-38 (1976).

Webster, R.W. Legal Medicine and Toxicology, Philadelphia, PA: Saunders, 1930.

Wright-St. Clair, R.E. Poison or medicine. New Zealand Medical Journal, 71:224 (1970).

Chapter IX
COCAINE IN CLINICAL MEDICINE

Paul G. Barash, M.D.

Cocaine has been used in medical practice for centuries. Although the South American Incas, 800-1200 years ago, probably used cocaine-filled saliva for such complex neurosurgical procedures as trephinization (Gay, 1975), the local anesthetic effects were largely ignored until the 19th century. In the period of 24 years, from 1860-1884, a series of events ushered in one of the greatest medical discoveries of the century (Becker, 1963): Alfred Niemann (1860) extracted the active principle, an alkaloid, and named it cocaine. Von Anrep (1879), commenting on cocaine's possible medical application, noted its anesthetic effect following topical application (tongue) and infiltration (skin). However, it took Carl Koller (1884), a young ophthalmologist who had spent years searching for a local anesthetic for eye surgery, to realize the enormous contribution cocaine could make to anesthesia and surgery. Following Keller's discovery, Jellinek (1884) demonstrated cocaine's unique qualities, as a topical anesthetic and vasoconstrictor of the upper and lower respiratory tract. In short order, Halsted (1885) demonstrated the use of cocaine for nerve block anesthesia, Corning (1885) used cocaine for peridural anesthesia, and Quincke (1898) induced spinal anesthesia with cocaine. With the synthesis of procaine in 1905, newer, less toxic agents supplemented cocaine. However, nearly a century after its introduction to modern clinical medicine, cocaine continues to be the only drug capable of causing both intense vasoconstriction and local anesthesia. The resurgence of research in the physiology and pharmacology of cocaine offers the 20th century clinician a unique opportunity to have an important drug impartially m-evaluated.

INDICATIONS

The only currently accepted indication for the use of cocaine is as a topical local anesthetic and vasooonstrictor of mucous membranes (Local Anesthetics, 1973; Ritchie, et al., 1970). (Local anesthesia is defined as the reversible loss of sensation in a circumscribed area. Topical anesthesia is produced by surface application of the local anesthetic agent.) Cocaine is applied when anesthesia and vasoconstriction of the nose, throat, larynx and lower respiratory passages are required. Without vasoconstriction,

blood loss may be considerable from the highly vascular areas of the respiratory tract. Further, bleeding obscures the operative field, and may thus render surgery difficult.

Cocaine is no longer recommended for use as an ophthalmologic anesthetic because repeated use may be followed by the toxic effects of clouding, pitting and ulceration of the cornea; these are further aggravated by the concomitant loss of the normal protective ocular reflexes.

DOSAGE

Upper limits for the dose of cocaine vary and are somewhat arbitrary. Despite the fact that the AMA Drug Evaluation Handbook (Local Anesthetics, 1973) suggests a maximum dose of 1 mg/kg, standard reference textbooks in pharmacology and anesthesia indicate that the maximal safe dose is 200 mg (= 3mg/kg). Reports of lethal dosages in medical practice range from 22 mg (submucosal injection) to 2,500 mg (subcutaneous injection) (Van Dyke & Byck, 1977).

A consensus emerges from the literature: solutions of cocaine more concentrated than 20 percent should not be used (Ritchie et al., 1970; Reynolds, 1972). Further, 5-10 percent solutions appear more appropriate and minimize the potential of toxic reactions (Campbell & Adriani, 1958). Corssen (1973) using cultured human respiratory epithelim, demonstrated that 10 percent cocaine solution causes reversible cessation of ciliary activity (A similar effect was noted with five percent lidocaine.) If a four percent cocaine solution is used, the latent period (time from application to onset of anesthesia and vasoconstriction) is 4.0 minutes and the duration is 10.2 minutes; with a 10 percent solution latency decreases to 2.0 minutes but duration of action increases to 31.5 minutes (Adriani et al., 1964). Von Dyke and others have demonstrated plasma cocaine concentrations peak within 60 minutes after mucosal application and can persist in the plasma for 180-360 minutes (Van Dyke et al., 1976).

Many factors affect selection of the appropriate dose for a given patient. No absolute dose range can be unequivocally recommended since tolerance varies from patient to patient depending on such factors as physiologic status and the ability to metabolize and excrete the drug. Since cocaine is usually applied to the highly vascular areas of the upper and lower respiratory tract, rapid intravascular absorption oan occur. Thus more dilute solutions (5-10 percent cocaine) should be used if large areas are to be anesthetized. Patients with a decreased cardiovascular and metabolic reserve (elderly and debilitated) should have the dose

[1]As discussed in Ritchie et al., 1970; Pharmacology of drugs used in local analgesia, 1973; Dripps et al., 1972.

reduced appropriately. Recently Jatlow et al. (1976) demonstrated in vitro that serum of patients with pseudocholinesterase deficiency are unable to metabolize cocaine. Until further in vivo information is available, caution should be used in administering cocaine to this group of patients.

When patients are receiving a number of drugs simultaneously, drug interaction with cocaine can be potentially lethal. Since cocaine interferes with the re-uptake of norepinephrine and potentiates the effects of exogenous catecholamines, it should be used with caution in patients receiving tricyclic antidepressants, reserpine, and the monoamine oxidase inhibitors guanethidine, methyldopa and dopamine (Smith, 1973; Davis et al., 1973). The interaction of cocaine with general anesthetics in humans is not well documented. Orr, using thiopental anesthesia with topical cocaine for laryngoscopy, reported that 7/20 patients had significant ectopic ventricular arrhythmias: 3 required intravenous propanolol for reversion to sinus rhythm (Orr & Jones, 1968). However, not only was this study poorly controlled, but the hypercarbia that was present may have caused the arrhythmias.

Recently, two reports demonstrated the relative safety of cocaine in conjunction with halothane, a widely used potent inhalation anesthetic which sensitizes the myocardium to catecholamines. Anderton observed atrial and ventricular extrasystoles in 2/45 patients following topical application of 35 mg cocaine for nasal surgery (Anderton & Nassar, 1975). The arrhythmias resolved in 10 minutes without requiring any specific treatment. For the entire group, no significant changes in pulse rate or systolic blood pressure were observed. Van Dyke and colleagues (1976), using cocaine for topical vasoconstriction in patients with acquired organic heart disease, noted no significant adverse effects. Simultaneous administration of epinephrine, as "cocaine mud" (cocaine flakes and 1:1000 epinephrine) to potentiate the already present intense vasoconstriction is extremely hazardous and has been condemned (Smith, 1973; Myer, 1924; Schenk, 1975). Anderton and Nassar (1975) have shown in a double blind study that doses as low as 20-50 mg produce excellent surgical conditions and were associated with minimal blood loss during surgery. Cocaine should probably be avoided when hypermetabolic disease states such as hyperthyroidism or pheochromocytoma are present Parenthetically, if premeditation is required, diazepam (Valium(R)) might be an excellent choice, since it elevates the threshold for seizure activity and thus may exert some protective effect if an actual or relative overdose is administered (DeJong & Heavner, 1971, 1974).

ADVERSE SYSTEMIC REACTIONS

Contrary to popular opinion, most untoward reactions to local anesthetics are not due to allergy. In a recent review of the world literature Van Dyke and Byck (in press) were unable to find a single documented case of anaphylactic response to cocaine. Although

poorly documented, the report by Dripps et al. (1972) described an anaphylactic reaction in a patient with multiple allergies who developed bronchospasm and cardiac arrest following topical application of cocaine. Moore (1969) has stated that 98 percent of toxic reactions to local anesthetics are caused by intravascular injection or rapid absorption of the drug. Thus, toxic reactions to cocaine are apparently due to: 1) overdose (actual or relative), 2) rapid intravascular absorption or 3) allergy (extremely rare).

Systemic reactions to cocaine are manifested by signs of adrenergic stimulation of the cardiovascular and central nervous systems. These can be divided into progressive stages.[1] In the first stage, (early stimulation) euphoria gives way to cortical stimulation manifested by excitement, emotional lability, restlessness and apprehension. Nausea and vomiting with abdominal pain may ensue, and finally muscular twitching is noted. Stimulation of the cardiovascular system parallels these neurological findings. As a result of medullary stimulation, there 'appear hypertension, tachycardia and skin pallor. Further stimulation of the central nervous system is manifested in tonic and clonic seizures. The sympathetic cardiovascular response is followed by ventricular arrhythmias. As a result of the central nervous system dysfunction, respiratory involvement occurs. An increase in rate and depth of breathing are followed by dyspnea and cyanosis. As respiratory failure occurs in the final stage (pre-morbid depression), unconsciousness occurs, followed by loss of reflexes, blood pressure and pulse. As a result of hypoxia, ventricular arrythmias continue and circulatory failure ensues.

HOSPITAL TREATMENT OF COCAINE TOXICITY

Treatment is directed at prevention. First, the recommended guidelines with modification of dose for the individual patients should be used. Second, cocaine should be used in situations where personnel experienced in resuscitation and basic life support are available.[2]

Preparation is the key to successful resuscitation. Basic equipment required includes:

1) AMBU(R) positive pressure ventilation unit with appropriate size face masks and oropharyngeal airways.
2) Oxygen
3) Suction
4) A stretcher capable of Trendlenberg positioning.
5) EKG monitor and defibrillator

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[1]As discussed in Gay et al., 1975; Ritchie et al., 1970; American Medical Association, 1973.

[2]Moser, R.H. (ed.) Standards for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA, 227 (suppl):835-886

6) Intravenous infusion
7) Medications.[1]

When an adverse reaction occurs, clear any possible airway obstruction and institute positive pressure ventilation with the AMBU(R) bag. If supplemental oxygen is avilable, use it. Place the patient in Trendlenberg position (30° head down) to augment venous return to the heart and facilitate suctioning of the airway to prevent aspiration. As central nervous system manifestations are noted, administer diazepam (Valium(R)) 2.5-5.0 mg, or secobarbital (Seconal(R)) 25-50 mg (an intravenous route is preferred over intramuscular administration). Alternatively, thiopental (50-75 mg) should be administered intravenously. Diazepam is now the treatment of choice for local anesthetic seizures (DeJong & Heavner, 1971, 1974). Although these drugs must be titrated to effect, the suggested upper limits of intravenous dosage are: diazepam 0.5 mg/kg (during an 8 hour period); secobarbital 3 mg/kg; and thiopental 3-5 mg/kg. If seizures continue, long acting non-polarizing muscle relaxants (curare or pancuronium) may be required. At this stage advanced life support will be required.

When ventricular arrhythmias are present without signs of central nervous system involvement, e.g. under general anesthesia, lidocaine (Xylocaine(R)) may be used in a bolus of 50-100 mg intravenously, and repeated with a 50 mg bolus, or by continuous infusion if necessary. If cardiac involvement continues or lidocaine is contraindicated due to seizure activity) the beta-blocker propanolol (Inderal(R)) can be administered (0.5-1.0 mg intravenously, maximum=5mg). Propanolol offers the possible therapeutic advantage of treating the systemic effects of the hypermetabolic state. Temperature should be monitored in anticipation of hyperthermia.

In documentation of the safety of cocaine, a recent survey of 741 plastic surgeons demonstrated the excellent record of cocaine as a local anestheic in clinical practice (Feehan & Mancusi-Ungaro, 1976). some 80 percent (592) of the respondents currently used cocaine for nasal surgery. This group reported that cocaine was used in approximately 93,000 operations. Mild reactions were observed in only 224 patients (0.24 percent) and severe reactions in only 14 cases (0.015 percent). There were no fatal reactions in 93,004 patients.

Debate continues as to whether cocaine should be removed from the U.S. Pharmacopeia. Deletion from this official compendium would eliminate the availability of this unique drug to medical practitioners. At present, no local anesthetic is totally devoid of undesirable properties. Although cocaine cannot be autoclaved or

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[1]Moser, R.H. (ed.) Standards for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA, 227 (suppl):835-886

used for infiltration nerve block anesthesia, it possesses many other properties of an "ideal" local anesthetic agent: Cocaine has a short latency period with a duration of action suited to most otolaryngologic procedures requiring local anesthesia. In concentrations used clinically, there appear to be no signs of permanent mucosal or nerve damage. Since cocaine also produces vasoconstriction, addition of other vasoconstrictor drugs (with their potential for toxic reactions), is not required.

The major area of controversy is the margin of safety of cocaine in clinical medicine. Although sporadic reports of fatalities exist, there is a paucity of data in the medical literature on the incidence of morbidity and mortality associated with the use of cocaine (Feehan & Mancusi-Ungaro, 1976).

As with any anesthetic, successful use of cocaine requires adequate preanesthetic evaluation of the patient, adherence to the appropriate dosage schedule, and the ability and equipment to manage the adverse systemic reaction. With these safeguards, cocaine has an excellent record of safety.

Paul G. Barash, M.D.
Department of Anesthesiology
Yale University School of Medicine
New Haven, Connecticut

REFERENCES

Cocaine in Clinical Medicine

Adriani, J., Zepernick, R., Arens, J. and Authment, E. The comparative potency and effectiveness of topical anesthetics in man. Clinical Pharmacology and Therapeutics, 5:49-62 (1964).

American Medical Association. Department of Drugs. Local Anesthetics. In AMA Drug Evaluations (2nd Ed.). Acton, MA: Publishing Sciences Group, 1973, pp. 212-213

Anderton, J.M. and Nassar, W.Y. Topical cocaine and general anaesthesia: An investigation of the efficacy and side effects of cocaine on the nasal mucosa. Anaesthesia, 30:809-817 (1975).

Becker, H.K. Carl Koller and cocaine. Psychoanalytic Quarterly, 32:304-373 (1963).

Campbell, D. and Adriani, J. Absorption of local anesthetics. Journal of the American Medical Association, 168:873-877 (1958).

Corssen, G. Toxic effects of local anesthetics on human respiratory epithelium. Canadian Anaesthetists Society Journal, 20:17-20 (1973).

Davis, R.S. and McNeil, J.H. Cardiac effects of cocaine and certain antihistamines and antidepressants. Archives Internationales de Pharmacodynamie et de Therapie, 201:262-279 (1973).

DeJong, R.H. and Heavner, J.E. Diazepam prevents local anesthetic seizures. Anesthesiology, 34:523-531 (1971).

DeJong, R.H. and Heavner, J.E. Diazepam prevents and aborts lidocaine convulsions in monkeys. Anesthesiology, 41:226-230 (1974).

Dripps, R.D., Eckenhoff, J.E. and Van Dam, L.D. Introduction to Anesthesia. The Principles of Safe Practice. Local Anesthetics. Philadelphia, PA: Saunders, 1972, pp. 213-217.

Feehan, H.F. and Mancusi-Ungaro, A. The use of cocaine as a topical anesthetic in nasal surgery: A survey report. Plastic and Reconstructive Surgery, 57:62-65 (1976).

Gay, G.R., Inaba, D.S., Sheppard, C.W. and Newmyer, J.A. Cocaine: History, epidemiology, human phamacology and treatment. A perspective on a new debut for an old girl. Clinical Toxicology, 8:149-178 (1975).

Jatlow, P., Barash, P.G., Van Dyke, C. and Byck, R. Impaired hydrolysis of cocaine in plasma from succinylcholine sensitive individuals. Clinical Research, 23(3):255A (1976).

Lee, J.A. and Atkinson, R.S. (eds.), Pharmacology of drugs used in local analgesia. Synopsis of Anaesthesia, 7th Ed. Bristol, England: John Wright & Sons, Ltd., 1973, pp. 336-338.

Mayer, E. The toxic effects following the use of local anesthetics. Journal of the American Medical Association, 82:876-888 (1924).

Moore, D.C. Complications of regional anesthesia. In Bonica, J.J. (ed.), Regional Anesthesia. Philadelphia, PA: Davis, 1969, pp. 217-253

Moser, R.H. (ed.) Standards for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). Journal of the American Medical Association, 227(suppl):835-868 (1974).

Orr, D. and Jones, I. Anaesthesia for laryngoscopy: A comparison of the cardiovascular effects of cocaine and lidocaine. Anaesthesia, 23:194-202 (1968).

Reynolds, F. The pharmacology of local analgesic drugs. In Wylie, W.D. and Churchill-Davidson, H.C. (eds.), A Practice Anesthesia. London, England: Lloyd-Luke Ltd., 1972, pp. 1170-1172.

Ritchie, J.M., Cohen, P.J. and Dripps, R.D. Cocaine, procaine and other local anesthetics. In Goodman, L.S. and Gilman, A. (eds.), The Pharmacological Basis of Therapeutics. New York, NY: Macmillan, 1970, pp. 367-377.

Schenck, N.L. Local anesthesia in otolaryngology: A re-evaluation. Annals of Otology, Rhinology and Laryngolcgy, 84:65-73 (1975).

Smith, R.B. Cocaine and catecholamine interaction: A review. Archives of Otolaryngology, 98:139-141 (1973).

Van Dyke, C., Barash, P., Jatlow, P. and Byck, R. Cocaine: Plasma concentrations after intranasal application in man. Science, 191:859-861 (1976).

Van Dyke, C. and Byck, R. Cocaine: 1884-1974. In Ellinwood, E.H. and Kilbey, M.M. (eds.), Cocaine and Other Stimulants. New York, NY: Plenum Press, 1977, pp. 1-30.

Chapter X
CHARACTERISTICS OF CLIENTS ADMITTED TO TREATMENT FOR COCAINE ABUSE

Eduardo Siguel, Ph.D.

Although the abuse of cocaine is usually obscured by the more prominent difficulties associated with other types of drug abuse, some information about its abuse is available through the Client Oriented Data Acquisition Process (CODAP). CODAP is a data collection system developed and operated by the National Institute on Drug Abuse which obtains information from drug abuse treatment facilities that receive Federal funding. These facilities provide about 50 percent of all drug abuse treatment in the United States, and include about 1,500 clinics across the nation. Thus, CODAP provides a broad data base to assess the characteristics of clients in treatment. The data in this report are derived from 1975-1976 admissions to the 1,500 clinics which participate in CODAP. As a result, the characteristics of clients who report cocaine as a problem can be described using statistics obtained from this data base. Caution should be used in interpreting these statistics since the sample is probably not representative of cocaine users generally. It can, however, be considered representative of cocaine users in Federally supported treatment facilities. For a comprehensive description of CODAP and additional data on cocaine users, the reader is referred to the references at the end of this section.

Of the approximately 55,000 patients admitted to CODAP clinics each quarter, 1.2 percent report cocaine as their primary drug of abuse. The typical cocaine abuser (See Figure 10-l) is: male (82 percent), white (51 percent), without prior treatment experience (67 percent), a voluntary admission to treatment i.e., not referred by the judicial process, (65 percent), unemployed (75 percent), has a formal education higher than the ninth grade (80 percent) and was admitted to treatment between ages 18 and 25 (57 percent).

Among those who report cocaine as a primary problem at admission, about 50 percent report no other drug problem. Of the remaining cocaine clients about 20 percent report marihuana as a secondary drug problem, 10 percent barbiturates or amphetamines, 9 percent opiates, 4 percent alcohol and the rest (7 percent) such other drugs as the inhalants or the hallucinogens.

Although the percentage of clients in treatment who report cocaine as their primary drug problem is low, among those who report other drugs as the primary problem, cocaine plays a slightly more prominent role. As a secondary or tertiary drug problem, it is reported by 5.5 - 6.0 percent of the clients. Among clients who have a primary drug problem other than cocaine, cocaine is mentioned as a secondary drug problem by 4 percent of the approximately 55,000 quarterly admissions. Among clients who report heroin as the primary drug problem, 6.0 percent report cocaine as a secondary drug problem.

When cocaine abuse is examined from a racial or ethnic standpoint, the frequency with which it is reported roughly parallels the ethnic and racial composition of the nation as a whole. The largest group of abusers is white, followed by Black, Puerto Rican, Mexican American and Cuban. However, if cocaine abuse is viewed within different race/ethnic groups the ordering is altered with Cubans having the highest rate of abuse at 6.5 percent. This particular result is normally obscured since Cubans are often grouped with Mexican Americans and Puerto Ricans into one Spanish-speaking ethnic group. It should also be noted that although Cubans have the highest rate of cocaine abuse for those in treatment, cocaine use still ranks fourth behind opiates, marihuana and amphetamines in this ethnic group.

In the attempt to explain patterns of drug abuse, and to target prevention and treatment programs, one must know the age at which clients in treatment use a drug for the first time. The peak age groups for the first use of cocaine is between 16 and 17 years (See Figure 10-2). Looking at age of first use cumulatively, the data shows 20 percent of those in treatment began use before the age of 15, and almost 70 percent began before they were 20 years old. Thus, initial use of cocaine occurs mainly among youth. In addition, cocaine abuse follows a pattern which seems to be closer to the first use of opiates rather than that of alcohol, marihuana and the inhalants. Use of alcohol, marihuana and the inhalants typically begins at an earlier age than does use of cocaine and the opiates.

Cocaine abusers in treatment are similar in some ways but also different from those in treatment who abuse other drugs. If one compares individuals treated in both inpatient and outpatient environments, 95 percent of cocaine abusers versus 60% of abusers of other drugs are treated in drug free modalities.[1] Cocaine users

[1]Drug free modality - a treatment regimen which does not include any chemical agent or medication as the primary part of the drug treatment.

complete treatment at a higher rate than opiate users and at about the same rate as drug users overall. Cocaine users drop out of treatment at a rate which is similar to all other drug users in treatment but transfer at a slightly lower rate than the other drug categories.

The results obtained from CODAP data are valuable for planning strategies for drug abuse prevention and for allocating resources for the treatment of drug abusers.

Eduardo N. Siguel, Ph.D.
Division of Scientific and
Program Information
National Institute on
Drug Abuse

FIGURE 10-1

DISTRIBUTIONS OF SELECTED CLIENT CHARACTERISTICS
FOR CLIENTS ADMITTED WITH PRIMARY DRUG PROBLEM OF COCAINE
(in percent)
(Based on Admissions During April-June, 1976)

Table I: Age at Admission (in years)

<18	18-20	21-25	26-30	31-44	> 44
9.8%	19.8	36.9	22.0	10.5	0.9

Table II: Age at First Use (in years)

<14	14-15	16-17	18-20	21-25	26-30	> 30
6.4	12.7	20.0	30.6	18.6	7.5	4.2

Table III: Race of Clients

White	Black	Am. Indian	Asian-Am.	P. Rican	Mex. Am.	Other
51.0	38.6	0.2	0.5	5.3	2.1	1.4

Figure 10-1, cont'd
Page Two

Table IV: Sex of Clients

Male	Female
82.1	17.9

Table V: Number of Previous Treatments*

None	1 Treatment	2 Treatments	>2 Treatments
66.7	20.5	6.4	6.4

*Individuals may have been in treatment for reasons other than cocaine abuse.

Table VI: Number of Other Drug Problems

1	2	>2
23.0	28.4	48.6

Table VII: Employment Status at Admission (Clients 18 and Older)

Employed Full-time	17.4
Employed Part-time	6.3
Unemployed	76.3

Figure 10-1, cont'd
Page Three

Table VIII: Enrollment in Educational Program

Yes	16.5
No	83.5

Table IX: Enrollment in Skill Development Program

Yes	5.5
No	94.5

Table X: Last Year of Formal Education Completed (Clients 18 and Older)

Years of Education			
0-9	10-11	12	12+
14.6	31.0	31.6	22.8

Figure 10-1, cont'd
Page Four

Table XI: Legal Status at Admission

Voluntary	64.5
Federal Non-Voluntary	11.6
State Non-Voluntary	13.3
Local Non-Voluntary	10.6

N.B. The row percents of Tables I, II, III, IV, V, VI and X add to 100%; the column percents of Tables VII, VIII, IX and XI add to 100% except for rounding errors.

FIGURE 10-2

DISTRIBUTION OF AGE OF FIRST USE FOR CLIENTS WITH COCAINE AS THE PRIMARY DRUG OF ABUSE WHO WERE ADMITTED TO TREATMENT IN 1975

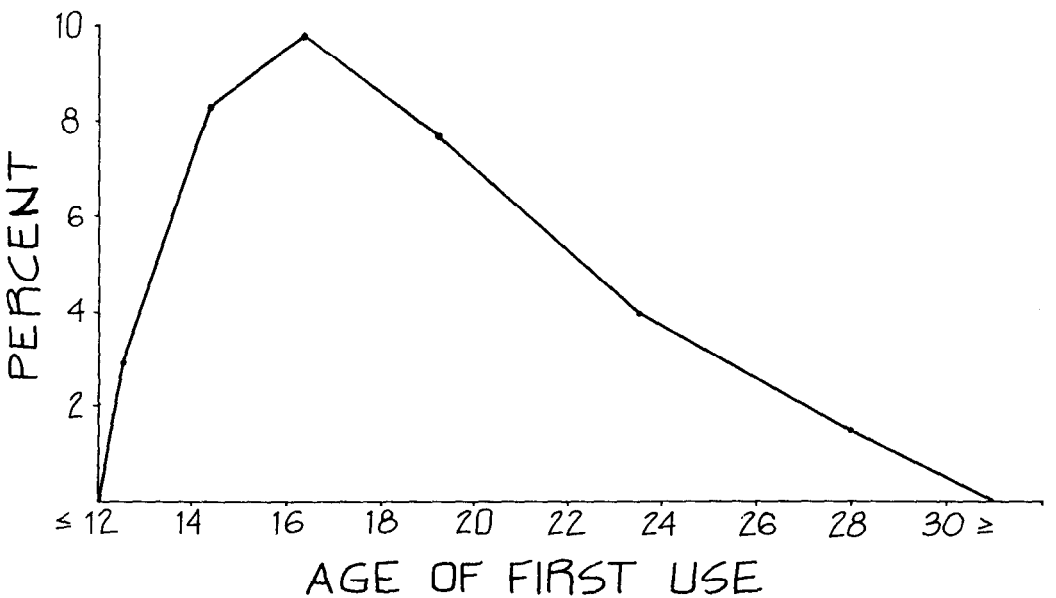

Figure 10-3 DISTRIBUTIONS OF ADMISSIONS BY SELECTED PRIMARY DRUGS OF ABUSE AND MODALITY/ENVIRONMENT AND OF DISCHARGED CLIENTS BY SELECTED PRIMARY DRUG OF ABUSE AND REASON FOR DISCHARGE.

(in percent)

	ADMISSIONS				DISCHARGES				
	DRUG-FREE OUTPATIENT	OTHER DRUG-FREE	ALL OTHER	TOTAL	COMPLETED TREATMENT	TRANSFERRED	DROPPED	OTHER	TOTAL
ALL DRUGS	39.5	19.8	40.4	100	22.7	21.0	52.1	4.2	100
HEROIN	23.3	15.8	60.9	100	18.2	23.4	52.9	5.6	100
COCAINE	60.0	35.9	4.2	100	22.7	18.5	53.9	4.9	100

NOTE: The percents shown in each row for admissions and for discharges add to 100% (except for rounding error).

REFERENCES

Characteristics of Clients Admitted to Treatment for Cocaine Abuse

Siguel, E. N. and Spillane, W. H. The epidemiology of drug abuse: A new data base, new techniques and new findings. The Proceedings of the Social Statistics Section of the American Statistical Association, 1976.

National Institute on Drug Abuse – Statistical Series (Available Quarterly). Washington, DC: Alcohol, Drug Abuse and Mental Health Administration, Public Health Service, U.S. Department of Health, Education, and Welfare.

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