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Cocaine: Pharmacology, Effects, and Treatment of Abuse

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Cocaine: Pharmacology, Effects, and Treatment of Abuse

Editor: John Grabowski, Ph.D.

Division of Clinical Research
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Cocaine: Pharmacology, Effects, and Treatment of Abuse

Dr. John Grabowski, editor of this monograph, was on the staff of the Clinical and Behavioral Pharmacology Branch, Division of Clinical Research, NIDA. He is now affiliated with the Department of Psychiatry, School of Medicine, Tufts University, Boston, MA 02111.

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Foreword

Cocaine is currently the drug of greatest national concern, from a public health point of view, and of particularly high interest from the research and scientific point of view.

The public health concern derives from the following sources: It has shown the highest continuing rate of increase in DAWN mentions (emergency room visits), overdose deaths, and serious clinical problems, despite a leveling of national prevalence since 1980. Animal studies show it to be one of the most potent reinforcers available. It is the one drug most easily and universally accepted in animal self-administration studies without prior induction training, and is widely used to shape animal behavior for the self-administration of other reinforcing drugs. It has one of the highest reinforcing potentials as measured by breaking point studies, and is the drug which animals, with unlimited access, are most likely to select repeatedly in preference to food and water to the point of death. These preclinical observations and related clinical data lead to the conclusion that the prospect of substantial increases in available supply and decreases in price constitutes a major and growing public health danger.

We are still uncertain as to whether the leveling off in overall national prevalence, which as shown by our two major national surveys occurred for cocaine between 1979 and 1982, has continued since then. If so, the increase in medical complications, addiction, and clinical problems described above would represent a higher percentage of a constant total pool of users running into serious problems. This interpretation is consistent with studies showing that an average of 4 to 5 years elapses between first use of cocaine and the need for treatment, and other studies showing that the best predictor of cocaine use is heavy, early marijuana use. The current upsurge in public health related cocaine problems would then be the predictable second stage of the peak of marijuana use which we saw in this country in the late 1970s. An alternative possibility is that greatly increased availability of this most reinforcing illicit drug has broken through powerful cultural and demographic barriers and begun to lead to a substantial increase in the number of users and/or intensified patterns of use. Evidence for this latter alternative may only become evident in future national surveys.

In any event, while we await further clarification of the exact nature of current trends in cocaine use, there is an urgent need for a rapid increase in information on mechanisms of brain action, treatment methods, health consequences, and prevention strategies. This monograph makes an important contribution towards planning future research by reviewing our knowledge base.

Charles R. Schuster, Ph.D.
Director
National Institute on Drug Abuse

Cocaine 1984: Introduction and Overview

John Grabowski

INTRODUCTION

Diverse aspects of cocaine pharmacology, use, and effects have been discussed at length in both the lay press and the scientific literature. Research involving cocaine has a long, interesting history which has been described at intervals, and this volume provides a current review of present knowledge concerning the drug. Dramatic increases in use in the past decade, increasing evidence of untoward consequences of use, and resultant public health concerns also set the stage for a timely and thorough review of scientific and clinical issues concerning cocaine.

Cocaine is an alkaloidal agent and is derived from the plant Erythroxylon coca and other Erythroxylon species in South America. Its multiple behavioral effects constitute those of the prototypic "stimulant" (with all the caveats pertaining to such loose categorizations). The drug is, thus, viewed in the context of amphetamines, caffeine, khat, and a variety of more recently developed synthetic agents. Cocaine, in the leaf form or as the extracted substance, has been used for different purposes, with varying restrictions, in different cultures. Paralleling the accepted medical and cultural uses has been a history of abuse of the drug. There is, as a result, ample evidence that cocaine abuse can have debilitating physical and behavioral-psychological consequences. Since not all users exhibit these symptoms, however, some have assumed that it is inherently safe. As with all drugs, this is an unwarranted assumption, since definable dose-related hazards exist. Thus, there is considerable interest in delineating the drug's characteristics in terms of abuse. Investigation of this and related drugs is also extremely important because of fundamental scientific issues concerning its neurochemical, pharmacological, and behavioral spectra of action.

OVERVIEW OF MONOGRAPH

This monograph was developed with emphasis on major areas of scientific and clinical interest. Thus, the topics range from postulated neurochemical mechanisms of action, through analysis of behavioral effects and patterns of use, to review of therapeutic strategies.

There has been a dramatic resurgence of cocaine use in the last decade. Adams and Durell address this issue and provide a brief overview of the epidemiological sources by which trends have been followed. In particular, they note substantial increases in medical examiner and emergency room "mentions" of cocaine use which strongly indicate a change to patterns of use with more hazardous consequences. In the past, cocaine use among so called "street" heroin users was not common, but was observed. More publicity concerning use has accrued to upper socioeconomic status users. However, as Adams and Durell note, the drug is now used, and untoward consequences of use have been observed in individuals across all socioeconomic groups. It is in this context of a major public health concern and important area of scientific and therapeutic inquiry that the present monograph arises.

A cogent and timely review of one perspective on cocaine s neurochemical mechanisms of action is provided by Wise. In the last decade, inroads have been made in delineating chemical and structural foci at which drugs have their effects. Major breakthroughs were made in identifying the mechanisms by which opiates act at specific "receptors." This, in turn, led to the search for specific sites at which benzodiazepines and other agents including cocaine act. There was, and is, a need to identify integrated neuronal pathways mediating the complex interacting events of behavior, drug action, neural function itself, and environmental conditions. Since drugs constitute but one of many items serving to reinforce and strengthen behavior, there is a further need to relate the mechanisms of their reinforcing properties to those of other events and conditions (food, water, etc.).

Wise and many other scientists have pursued this line of inquiry, and these efforts are reviewed. Differing viewpoints on the specifics of both the relative contribution of various neurochemical systems and/or neural pathways do exist in the scientific literature. Wise notes the interactions in areas of scientific research which have contributed to our enhanced understanding of brain function and reinforcement, including that derived from reports over several decades describing the effects of electrical brain stimulation. This research, integrated with the work of others on neurochemical functions, generated current efforts to define the mechanisms of drug reinforcement. The questions which must be pursued are those related to

examining commonalities and differences in the neural substrates of reinforcement. As Wise notes, these data will contribute to vastly improved understanding of behavior and reinforcement generally, and drug abuse behavior in particular. The great need for further research in this and related areas is evident and advances will be forthcoming. These, in turn, must be related to and integrated with the data which have accumulated concerning complex behavioral-psychological and clinical issues. The need for substantial interdisciplinary research is apparent.

All chapters in this volume refer in one way or another to the pharmacology of cocaine. Thus, the thrust of the chapter entitled "The Pharmacology of Cocaine" simply refers more specifically to issues of absorption, drug onset, distribution of the drug in the body, metabolism, and excretion. Jones has provided an overview of the cocaine literature in the discipline of pharmacology, including discussions of central nervous system (in this case, EEG) effects and physiological function. The need to understand fully how drugs alter physiological functions, are absorbed, distributed, metabolized, and excreted by the body is clear. Other important pharmacological issues are addressed, including those concerning both theoretical and practical questions on tolerance and dependence. Tolerance has been clearly demonstrated and, as Jones notes, dependence with respect to physiological systems may well be related to dosing and duration of action. In any case, presence or absence of physiological dependence is irrelevant in terms of potential hazards of compulsive administration. While the issue is of great scientific interest, many of the discussions which have arisen involve definitional problems rather than scientific questions. From a scientific perspective, it is important to note that many of the related questions are similar or identical to those concerning other drugs. In addition to tolerance and dependence, questions concerning toxicity and route of administration can be discussed reasonably based on Jones' review and presentation of data.

An important bridge between understanding the specific neurochemical and general pharmacologic characteristics of an abused agent and the observation of use in the "real world" emanates from tightly controlled laboratory experiments of behavioral effects. Without such efforts linking the specifics of action within the body and behavioral effects, it would be impossible to describe accurately mechanisms of the therapeutic effects of a drug or the basis for compulsive drug use. Depending on specific scientific questions, the research may proceed with either nonhuman or human subjects. The results of a decade or more of research to determine precisely the behavioral pharmacology of cocaine in the animal laboratory are reviewed by Johanson. Attention is given to those questions

which can only be reasonably and objectively examined using nonhuman subjects. The model described permits precise specification of features of the reinforcing effectiveness and inferred "abuse liability" of cocaine. The mechanisms and character of behaviorally toxic effects are similarly examined. Data on toxicity resulting from this model point to an important distinction: Pharmacologic studies can provide clear indications of physiologic effect as a consequence of increasing doses. It has become apparent through research on effects of drugs of abuse, however, that collateral untoward behavioral consequences (or trends suggesting their impending emergence) may appear long before physiologic damage is evident. Indeed, behavioral disruption may be evident at doses below those which would lead to physiologic toxicity.

Based on the data reviewed by Johanson which describe the nature and generality of cocaine administration across species and disparate environmental conditions, general statements can be made about likely patterns and consequences of chronic human use, but always with appropriate scientific caution and awareness of their limitations. The dose-related toxic behavioral consequences observed in research with nonhuman subjects are well summarized, ranging from stereotypic behavior to anorexia characteristic of stimulant drugs. Also reviewed are the necessary comparisons with other drugs which are always essential in placing in perspective the behavioral effects of an agent.

Some scientific questions concerning behavioral-pharmacological issues are better resolved using human subjects in laboratory settings. The complexities are numerous, but these efforts provide unique information which would not otherwise be obtained, They help to bridge the gaps between studies founded in neurochemistry, pharmacology, behavioral pharmacologic or clinical research, and observations in the natural environment.

Fischman has reviewed the spectrum of available data on cocaine administration in humans under controlled conditions. In the human laboratory, the opportunity exists to study the pharmacologic characteristics, physiologic effects, basic behavioral indicants of reinforcing effectiveness, and other drug response and related these to both results of animal laboratory research and patterns of use and abuse in the natural environment. Thus, as Fischman notes, reports of cardiovascular responses to cocaine and the evolution of tolerance are similar in nonhuman primates and in humans. Such cross-validation and determinations of generalizability of effects are important.

Measuring these responses in relation to subjective effects is likewise important, In particular, specifically relating

these subjective effects to the route of administration in a laboratory setting provides clearer understanding of the effects which are likely to be observed in the natural environment. Thus, this review of the work of numerous Investigators permits reasonable statements about the probability and character of abuse and the subjective effects of cocaine as a consequence of different administration routes. Precision can also be observed in defining the character of tolerance and dependence. Similarly, analysis of the effects of drugs on human performance is clearly important. These effects depend on complex interactions between dosage, environmental conditions and the task at hand.

The relationship between effects of cocaine and other drugs commonly self-administered by humans is likewise of considerable interest. The similarities as well as differences between a range of "stimulants" and other local anesthetics are, thus, discussed. The significance of these issues resides not only in the determination of behavioral and pharmacologic mechanisms of action, but in the practical public health issue that "substances" obtained illegally are often composites of various drugs with differing actions.

An extensive laboratory literature on effects of cocaine is evolving, as are epidemiological data bases and clinical efforts. Siegel reviews an area in which limited data are available and relates this to other issues surrounding cocaine use. Reports of use obtained through careful repeated interviews can be related to both specific laboratory research as described by Jones, Johanson, and Fischman, and clinical research reviewed by Kleber and Gawin. Thus, Siegel cites the limited number of reports concerning perceptions about cocaine and reported effects in chronic, but moderate users. More important, Siegel describes patterns of use, abuse, and abstinence by a group of individuals over time. These unique data provide important insights into the evolution of both problematic use and cessation along with symptomatology that emerges at different points among users in the natural environment. In particular, the information supports laboratory-based predictions concerning dosage and routes of administration. These data also provide a basis from which the clinician can retrospectively interpret or evaluate the patterns of use resulting in a patient's entering treatment.

Of considerable importance are the data indicating that differing dosages are likely to be self-administered via different routes. Reports indicating that, over extended periods, users might not only increase dosage but might have periods of abstinence, point to the importance of long-term followups when evaluating treatment. That is, cessation during treatment may be temporary, just as it would be if initiated independently of formal treatment. This

observation coincides with much that is known about other drug use ranging from tobacco to opiates. That different users explicitly use the drug for different purposes (e.g., social vs. work), suggests that when a cocaine user appears for treatment, rather different stategies may be required in reestablishing nondrug-oriented behavioral repertoires. Data presented on both chronic effects and toxic responses clearly enhance our understanding of these phenomena and, in this case, do so in the context of regular users of the drug. Equally important has been the fact that the review suggests the possibility of predictively separating the probability of dysfunction in relation to conditions correlated with use.

One response of treatment of drug abuse, including cocaine (Crowley 1983) and its correlated problems, has been extensively discussed in another recent NIDA monograph (Grabowski et al. 1983). In the present monograph, Kleber and Gawin provide a thorough review of both the literature and concepts underlying potential therapeutic approaches. The authors provide important clinical background information on both diagnostics and symptomatology. In addition, they discuss, from a somewhat different perspective, the severity of consequences of different forms and patterns of use. Severity of problems is also viewed in the extended framework ranging from neurochemical to socioeconomic issues. The importance of this wide-ranging perspective in drug abuse treatment is clear, and the authors provide cogent indications of the need. Kleber and Gawin note the long history of efforts to treat cocaine abuse and, in so doing, provide a background for the diverse strategies currently available. Again, the need for integrated behavioral-psychiatric and pharmacological strategies is emphasized. They note the importance of emphasizing basic treatment components and, thereby, point to the fact that cocaine abuse has elements in common with other drug abuse. In particular, it is explicitly noted that, as with other drugs, the user must, because of behavioral environmental interactions, spend "drug-free" time in the environment in which drug abuse occurs or relapse is probable. They also point to the advantages and disadvantages of various currently available treatment approaches.

Perhaps most important in the review is attention to the possibility of different generative conditions leading to patterns of abuse. While attending to a range of social and environmental features, reports are cited suggesting a quasi-therapeutic, albeit ineffective, element which may be inherent in some cases of escalating cocaine use. That is, some users may be pursuing self-medication of depression predating cocaine use which is, in turn, exacerbated by the cycles of use. Plausible neurochemical bases for this view are proffered. In addition, the authors provide salient

reviews of pertinent literature on pharmacological adjuncts in the treatment of cocaine abuse. Again, the important focus of this review is its emphasis on the need for integrated therapeutic approaches and, of perhaps greater importance, the need for integrated interdisciplinary perspectives on clinical research in the area.

ISSUES AND QUESTIONS OF SPECIAL INTEREST

Two superordinate categories of questions arise concerning cocaine. One is defined in terms of use, abuse, and correlated social and clinical issues. The other involves numerous scientific, theoretical and technical issues not directly linked to the issue of abuse. Overlap necessarily exists and, in some cases, it is simply the framing of the question which contributes to an apparent difference. In fact, the scientific issues concerning mechanisms of action ultimately have relevance to the clinical concerns. Similarly, the questions raised in the clinical environment often contribute to the formulation of questions addressed in laboratory research. Issues of both categories are discussed in this volume, and it is apparent that there is a wealth of knowledge concerning cocaine. There are, nevertheless, numerous questions which remain to be answered.

Dominant issues of public interest are addressed throughout this volume and in the abundant scientific literature. Specific discussion of these issues can be found elsewhere (e.g., Van Dyke and Byck 1982; Grabowski and Dworkin 1984). It is, thus, sufficient to note here that the most commonly raised questions of public interest are those concerning routes of administration (e.g., nasal vs. inhalation), dosage forms or related issues (e.g., cocaine base vs. hydrochloride), dosage administered acutely and chronically, risks, drug interactions (e.g., cocaine and heroin), predisposition to use the drug, and treatment. One issue not raised in the lay press, but of potential public health interest, is that concerning coca paste. This product, while not used in the United States, is widely used in South American countries where coca is prevalent. Coca paste is a contaminated intermediate product of the cocaine extraction process which has specific health hazards associated with its inhalation through smoking (Jeri 1980: Hawks, personal communication).

A reasonable comparative perspective indicates that our knowledge of cocaine and its effects is considerable. Some questions raised in the past globally, the research issues of significance with respect to cocaine specifically and stimulants generally include: (1) analysis of relationships between neurochemical mechanisms, behavioral mechanisms, and interactions with environmental determinants of effects;

(2) delineation of subjective effects and human performance with emphasis on interactions with other drugs; development of optimal combined pharmacological-behavioral treatment strategies; and, (4) developing epidemiological techniques for examining drug use trends and patterns which reside outside the current drug treatment and medical networks. Finally, given that much is known about this agent and much data will result from ongoing research, cocaine is an important pharmacological tool and metric for analysis of other complex psychopharmacologic and sociopharmacologic phenomena.

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AUTHOR

John Grabowski, Ph.D.
Department of Psychiatry
Louisiana State University Medical Center
Shreveport, Louisiana 71130

Cocaine: A Growing Public Health Problem

Edgar H. Adams and Jack Durell

This monograph, reviewing the pharmacology, behavioral effects, and the treatment of cocaine abuse, appears at a time of intensifying concern regarding what appears to be an epidemic of serious adverse consequences. This chapter outlines some of the epidemiologic data which describe the rise in cocaine use over the past several years. These issues will be further elaborated in a future monograph which will be based on a NIDA-sponsored scientific review held in July 1984.

Cocaine abuse has grown from a relatively minor problem 15 years ago to a major public health threat today. Oral ingestion of cocaine was widespread in the late 19th and early 20th centuries when it was an ingredient in many patent medicines, tonics, and soft drinks. Following the passage of the Harrison Narcotic Act in 1914 and the Narcotic Drugs Import and Export Act in 1922, its use began to decline; between the 1930s and the late 1960s, cocaine had all but disappeared from the American scene. The second report from the National Commission on Marihuana and Drug Abuse in 1973 stated that little social cost related to cocaine had been verified in this country (National Commission 1973). At the same time, the Strategy Council on Drug Abuse stated that the morbidity associated with cocaine use did not appear to be great. They further stated that there virtually were no confirmed cocaine overdose deaths and that a negligible number of users seek medical help or seek the kinds of treatment offered by specialized drug treatment programs (Strategy Council 1973).

Unfortunately, these low rates of actual abuse led the general public, as well as many drug experts, to conclude that cocaine was a safe drug. It was not generally recognized that cocaine has a high abuse potential and that under conditions of greater accessibility of cocaine, much more serious patterns of abuse would become evident. This possibility was recognized by a few clinicians and was clearly enunciated by Drs. Donald R. Wesson and David E. Smith who in the 1977 NIDA monograph on cocaine concluded:

> 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. (p. 150)

Their conclusion was prophetic.

The situation now is vastly different. The adverse consequences of cocaine abuse are abundantly evident, both as reflected in the popular media and in those statistical data sets that are available. Both the print media and television are replete with reported cases of compulsive use which have resulted in wrecked lives and fortunes. Many cocaine victims have been rich and famous--many have not! The statistical data sets, on the other hand, provide us with some aspect of the overall dimensions of the problem. Unfortunately, there are gaps in our data which make it impossible to make precise statements about the full extent of cocaine abuse and dependence.

The data from the National Household Survey indicate that the prevalence of cocaine use rose dramatically during the middle and late seventies. This change is exemplified by the following:

1. The number of people who had tried cocaine at least once had increased from 5.4 million in 1974 to 21.6 million in 1982 (NIDA 1983).

2. The number of current users of cocaine rose from 1.6 million in 1977 to 4.2 million in 1982 (Blanken et al. in press).

While the most recent surveys of prevalence of use indicate that trends have leveled off, at least among those under 26, the impact of the dramatic increases of the late 1970s is becoming more and more visible as both demand for treatment of dependence and medical crises associated with cocaine use increase. For example, "There was more than a threefold increase in the rate of cocaine-related (medical) emergencies (from 0.7 to 2.3/10,000 emergencies) and the rate of cocaine-related deaths per 10,000 medical examiner reports (from 4.5 to 19.1/10,000 deaths) between 1976 and 1980-1981" (Kozel et al. 1982). Over the same time period, the proportion of drug treatment program admissions with cocaine as their primary drug problem increased from 1.2 percent to 5.8 percent. More recent data indicate that these increasing trends have continued unabated. For example, cocaine accounted for almost 9 percent of the treatment admissions reported to NIDA in 1983.

Data on adverse health consequences are reflected by hospital emergency room visits and medical examiner cases as collected by NIDA through the Drug Abuse Warning Network (DAWN). Data on admissions to treatment were collected through the Client Oriented Data Acquisition Process (CODAP) which was the national reporting system through 1981 and during most of 1982.

Previous reports have indicated that emergency room admissions associated with cocaine use increased approximately three and one-half times between 1976 and 1981. More recent data, based on a subset of DAWN emergency rooms that have reported consistently since 1981, indicate that this upward trend continues. Since 1981 through the fourth quarter of 1983, emergency room mentions for cocaine have increased by 75 percent. Early data for 1984 indicate that approximately 2,000 cocaine mentions were recorded for the first

quarter of 1984. This is remarkable in that it equals the cocaine mentions for the entire year of 1978.

Other changes that have occurred between 1978 and 1982 are consistent with the aging of the abusing population. In 1978, 21 percent of the emergency room admissions were over 30, while in 1982, 41 percent were age 30 or over (Blanken et al. in press). Perhaps indicating more chronic use, 52 percent of emergency room admissions for cocaine in 1982 indicated dependence vs. 44 percent in 1978. There has also been an increase in the intravenous use of cocaine and the use of cocaine in combination with other drugs. For example, in 1978, 57 percent of the cocaine mentions were in combination with other drugs, while in 1982, 71 percent were in combination (Blanken et al. in press). As cocaine has become more available, the practice of speedballing, the combination of heroin and cocaine, has increased. In 1979, speedballing mentions accounted for approximately 17 percent of the cocaine mentions in DAWN, whereas in 1983, speedballing accounted for more than 25 percent of the mentions.

Similar to the DAWN trends, CODAP admissions have also shown marked increases over the past several years. In 1977, primary cocaine admissions accounted for 1.8 percent of all admissions to CODAP. while in 1981 they accounted for 5.8 percent (NIDA 1978,1982). This further increased to 7 percent of admissions in 1982 and, as previously mentioned, to 9 percent in 1983. The increase in cocaine admissions is even more striking if admissions for other than for primary use are included. For example, admissions for speedballing generally record heroin as primary and cocaine as secondary. When both primary and secondary admissions are included, cocaine was abused by over 17 percent of all admissions in 1981. This represents in excess of 42,000 people admitted for some problem with cocaine. We know that this is an underestimate, since there are many admissions of cocaine abusers to private drug treatment units and to alcoholism treatment units that are not reflected in CODAP data. Since cocaine is used extensively by the higher socio-economic group, seriously undersampled in the CODAP data, the extent of the underestimate may be quite large. The more recent situation is even worse in estimating the demand for treatment in that CODAP data are no longer collected on a national basis.

As with the DAWN statistics, CODAP admissions presented multiple drug problems; 82 percent of all primary cocaine admissions in 1982 reported having at least a secondary drug problem. The order of frequency in the secondary drug problems was marijuana, alcohol, and heroin. This is the reverse of the order of the frequency of combinations reported in DAWN, where heroin, alcohol, and marijuana were the most cited combinations with cocaine. Of course, DAWN data would be expected to reflect combinations that are more likely to eventuate in acute medical crisis.

Of particular concern has been the tendency of users to shift from snorting cocaine to other routes of administration. In several reports, an increase in the intravenous administration of cocaine, as well as free basing (smoking) has been noted (Kozel et al. 1982;

Adams 1982a; Blanken et al. in press). The 1982 CODAP data indicate a dramatic increase in free basing of cocaine from 1 percent of admissions in 1979 to almost 7 percent in 1982. These changes are important because of the reports that either free basing or intravenous injection of cocaine may lead more readily to intensive use and compulsive drug-seeking behavior (Van Dyke and Byck 1982).

An analysis of CODAP data by frequency of use and route of administration does, in fact, indicate that both intravenous administration and free basing or smoking of cocaine more frequently lead to daily use than does inhalation (Adams 1982b). In recognizing this pattern, however, it should not be forgotten that inhalation (snorting) still accounts for almost 60 percent of all admissions for cocaine problems and that compulsive use has been reported among those who limit their use to the intranasal route. Furthermore, recent evidence suggests that intranasal administration is not without its medical consequences. Recently, a case of myocardial infarction in an otherwise healthy 21-year-old male was reported after intranasal administration of 0.25 gram of cocaine (Schachne et al. 1984). This raises the possibility that cocaine, which has a direct effect on catecholamines, may in fact be a cardiovascular risk factor in some individuals.

In May 1983, a private treatment unit opened a toll-free telephone hotline offering advice to cocaine abusers. The number of callers was a surprise. In the 18 months since the service began, over 450,000 calls, sometimes as many as 1,000 per day, have been received. Hotline staff have conducted 20-40 minute telephone interviews on several samples of the callers. Though there is much uncertainty regarding the representativeness of the sample and the validity of the telephone interview, the technique has provided a rich data source regarding self-reported cocaine abusers. Several findings (Gold and Washington 1984) are of particular interest:

(1) Sixty-one percent of callers used primarily the intranasal route and they reported patterns and consequences of cocaine use comparable to those free-basing (21%) and using IV (18%).

(2) From 66% to 83% reported addictive patterns of use including loss of control over use (75%) and inability to stop using in spite of repeated attempts (67%).

(3) Over 90% reported adverse physical, psychological and consequences associated with its use.

In summary, a wealth of data based on mortality statistics, emergency room admissions, treatment admissions, and calls to the national toll-free cocaine hotline indicate that we are in the midst of an epidemic of adverse consequences of cocaine abuse with no indication of any abatement in the rising tide. Moreover, there is evidence that the cost of cocaine is diminishing and the supply is increasing. This was first seen at the wholesale level and is now being seen on the retail level. Since the high cost of cocaine has been a barrier that helped to prevent many users from compulsive, uncontrolled use, the decrease in cost increases the possibility

that compulsive use will increase. Indeed, there is reason to be concerned about the possibility of increased use by adolescents and young adults, age groups that have not as yet developed a widespread problem with cocaine.

One example of the spread of cocaine use in a population in which it is not thought to be predominant is reflected by a study of arrestees in a police initiative aimed at drug-related offenses in East Harlem (Wish et al. 1984). Urine samples, obtained from 84 percent of a sample of arrestees, were 87 percent drug positive. Of the positive urines, 79 percent were positive for cocaine vs. 58 percent for opiates. In this street population, cocaine use was prevalent over opiate use in all age groups. Furthermore, 46 percent of the sample reported that they had been dependent on cocaine for some time vs. 24 percent for heroin. These findings, while they are a small sample, suggest that cocaine is prevalent among street drug users and is not the sole preserve of the affluent.

Though previous upsurges in stimulant use have tended to be passing fads, the current epidemic is unprecedented. Increased production and profits have resulted in a growing illicit industry with a vested interest in sustaining, and even increasing, cocaine use. The one hopeful fact is that prevalence of use appears to have leveled off. If that is so, the current continuing increase in adverse consequences may be the result of the reported lag, averaging about 4 years, between the onset of cocaine use and entrance into treatment and also of an increase in the occurrence of intensified patterns of use. Thus, the residual effects of the epidemic and continuing effects of endemic levels of use may be seen for some time. Perhaps increased public knowledge of cocaine's dangers will contribute to a decrease in its use. For the moment, however, if prices continue to decline, there is ample reason to fear even more widespread use of cocaine.

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AUTHORS

Edgar H. Adams, M.S.
Division of Epidemiology and Statistical Analysis
National Institute on Drug Abuse
Rockville, Maryland 20857

Jack Durell, M.D.
Office of Science
National Institute on Drug Abuse
Rockville, Maryland 10857

Neural Mechanisms of the Reinforcing Action of Cocaine

Roy A. Wise

Cocaine shares with a number of drugs the property of strong abuse potential. In attempting to understand abuse potential it is useful to consider the factors in common and the factors not in common between cocaine and other abused drugs; every drug has multiple effects, and only those effects shared by the variety of abused drugs are likely to account for abuse liability. Cocaine is, over most of its effective dose range, a psychomotor stimulant; it shares this property with amphetamine but not, over most of their effective dose ranges, with opiates, barbiturates, benzodiazepines, or ethanol. Cocaine does not share the physical dependence-producing property of the sedative hypnotics. Cocaine has local anesthetic properties which are not shared with the other major classes of drugs of abuse; other local anesthetics, while sometimes self-administered, are not significantly or knowingly abused by man. These drug actions, then, would not seem to provide likely explanations for the development of compulsive drug intake which can develop across the variety of abused agents.

What cocaine does share with opiates, barbiturates, benzodiazepines, and ethanol is a rewarding or "reinforcing" property. When behavioral acts are regularly followed by intravenous, or, in some cases, oral, administration of drugs in these classes, such behavioral acts become more and more frequently repeated. Of the habit-forming drugs, cocaine and heroin stand out as perhaps the most powerful reinforcers as defined by the rapidity of acquisition of self-administration. Thus the property shared by cocaine, a stimulant, and other drugs of abuse, primarily depressants, is the quality of reinforcement. In the attempt to understand the neural mechanisms underlying the abuse liability of cocaine and other drugs one important place to start is with brain structures implicated in the process of reinforcement.

For a number of reasons it is believed, first, that the brain has specialized neural circuits that are activated by the various reinforcers capable of influencing behavior (Olds 1962), and, second, that the activation of these circuits is necessary for natural re-

inforcers to be effective (Wise 1982). Just as it proved reasonable to assume that opiate receptors did not evolve only to serve the need of modern man for synthetic analgesics, so is it reasonable to assume that the neural substrates of drugs of abuse did not evolve only to serve our nonmedical impulses. Analgesics suppress pain by centrally activating endogenous pain control circuits (Mayer and Price 1976; Basbaum and Fields 1978); similarly, we might expect drugs of abuse to be reinforcing by centrally activating endogenous reward circuits (Olds and Travis 1960; C.D. Wise and Stein 1970; Belluzzi and Stein 1977). It is from this perspective that students of drug abuse might hope to benefit from the study of reward circuits in the brain.

The notion that cocaine and amphetamine can centrally activate natural reward mechanisms and that they owe their reinforcing action to such activation (C.D. Wise and Stein 1970) is consistent with the fact that these agents have the traditional properties of conventional reinforcers (Johanson 1978). If animals are reinforced with amphetamine or cocaine on fixed or variable ratio schedules or fixed or variable interval schedules, the patterns of responding seen are similar to those characteristic patterns which would be established with the same reinforcement schedules in an operant chamber delivering food or at a slot machine delivering silver dollars. Amphetamine reinforcement also shares several of the characteristics of reinforcement by electrical stimulation of the brain (Pickens and Harris 1968). In both cases responding is sustained for long periods of time, with occasional periods of abstinence that are unpredictable as to onset and duration. In both cases the rate of responding is regular, depending on the parameters of reinforcement and on the response demands of the task, but not depending on the length of preceding abstinence periods. In both cases voluntary abstinence periods can be terminated by the experimenter if unearned reinforcement or "priming" is given. In both cases the central reinforcer can be more powerful than more "natural" reinforcers, even in cases of acute need; access to psychomotor stimulant reinforcement (Pickens and Harris 1968) or to electrical brain stimulation reinforcement (Routtenberg 1964) can cause self-starvation to the point of severe weight loss.

Our present understanding of neural mechanisms of reinforcement began with the discovery that rats would work for electrical stimulation of some but not all portions of their own brains (Olds and Milner 1954). Early studies followed two major directions: anatomical mapping (Olds and Olds 1963) and pharmacological challenge (Olds and Travis 1960). The mapping studies exploited the relative anatomical selectivity of brain stimulation and generated hypotheses as to what anatomical circuitry might participate in reward function (Olds 1962). The pharmacological studies soon implicated catecholamine systems as likely links in reward circuitry, and the study of psychomotor stimulant reward became a useful adjunct to brain stimulation (Baxter et al. 1974; Yokel and Wise 1975; Davis and Smith 1977), since stimulants activate catecholamine systems with a degree of neurochemical selectivity that the anatomically selective brain stimulation lacks. Recently it has proven pos-

sible to train animals to work for reasonably localized central injections of drugs; with this approach it is possible to activate reward circuits with useful degrees of both anatomical and neurochemical selectivity (Bozarth 1983). Current evidence from studies involving these techniques suggests the view that different drugs and even drugs of different classes may activate common reward circuitry of the brain--reward circuitry essential for the rewarding impact not only of drugs of abuse but also of food, water, and rewarding hypothalamic brain stimulation. This evidence on the mechanisms of cocaine and opiate reinforcement, evidence on their relation to the anatomical substrate of opiate physical dependence, and the implications of this evidence for theories of drug abuse are the subjects of the present chapter.

SUBSTRATE OF BRAIN STIMULATION REWARD

In the three decades of research on brain stimulation reward three dozen or so distinct reward sites have been studied (German and Bowden 1974) . Brain stimulation has been found to be rewarding at all supra-spinal levels of the central nervous system, though not in all portions of each level. A major goal of workers in the field has been to find anatomical common denominators for the diverse reward sites that have been identified. Olds' early (1962) theory of limbic and hypothalamic subsystems has been superseded by the catecholamine theories of Stein and others (German and Bowden 1974; Fibiger 1978; Wise 1978), and Stein's early (1962) noradrenergic hypothesis has been superseded by the various dopamine hypotheses (see Fibiger 1978; Wise 1980, 1981a). Current evidence now rules out the view that either noradrenergic or dopaminergic circuits are the primary (directly activated) fibers of brain stimulation reward (Shizgal et al. 1980a; Gallistel et al. 1981), and there is currently no viable theory of brain reward mechanisms which ties together more than a few of the dozens of known reward sites.

The most frequently studied brain stimulation reward site is the lateral hypothalamic portion of the medial forebrain bundle. It now seems clear that rewarding stimulation in this region depends primarily on the direct activation of descending fibers of passage. The refractory periods of the directly activated neurons of the lateral hypothalamus can be estimated by stimulating with trains of pulse pairs of different inter-pulse intervals. When the intervals are shorter than the refractory periods of the directly activated fibers, performance drops precipitously; the critical interval at which this change occurs indicates the length of the refractory period for that portion of the directly activated population of neurons which plays a role in the behavior. In the case of lateral hypothalamic self-stimulation, the refractory periods are short (Yeomans 1979), suggesting that the directly activated fibers are probably myelinated, and ruling out the possibility that they are catecholaminergic (Gallistel et al. 1981).

The conduction velocities and direction of conduction of the reward-relevant fibers of the medial forebrain bundle can also be

determined. In this case it is necessary to place two electrodes at different points on the hypothesized path of the reward-relevant fibers. Pulse pairs are again administered, with one member of each pair going to each of the two electrodes. When the inter-pulse interval is long, both pulses are behaviorally effective and performance is strong; this is usually true whether or not the two electrodes activate the same fibers. When the second pulse loses behavioral effectiveness as a result of decreasing the inter-pulse interval, however, it can be concluded that the electrodes must lie at different sites along the same continuous fibers (Shizgal et al. 1980a). With short inter-pulse intervals, stimulation at the more efferent electrode site effectively cancels the effects of stimulation at the more afferent site; stimulation at the efferent site elicits (along with the orthodromic or "normally" conducting impulse) an antidromic or "backwards" conducting impulse. When the inter-pulse interval is short, the antidromic impulse collides with and inactivates the oncoming impulse from the other stimulation site.

When long inter-pulse intervals are used, on the other hand, the first impulse bypasses the site of the second electrode before the second pulse is administered, and, if sufficient extra time is given for membrane recovery, a normal second impulse will be elicited and performance will reflect it. The critical time in this case is equal to the sum of the time necessary for the first impulse to travel from the tip of the first to the tip of the second electrode (conduction time) , plus the time necessary for the membrane to recover from the first impulse (refractory period). In the case of lateral hypothalamic self-stimulation, the critical fibers extend to the ventral tegmental area, and the conduction velocities are fast (Shizgal et al. 198Oa; Bielajew and Shizgal 1982), again suggesting that the fibers are probably myelinated and again ruling out catecholaminergic fibers as the directly activated substrate (Shizgal et al. 1980a; Bielajew and Shizgal 1982).

The two-electrode preparation used for conduction velocity tests can also be used to determine the direction of conduction of the reward-relevant fibers. If stimulation is given through one electrode and tissue is hyperpolarized at the other, stimulation will be effective only when it is administered at a site efferent to the hyperpolarization (Kuffler and Vaughan Williams 1953). In the case of medial forebrain bundle self-stimulation, this test reveals that at least the major portion of the directly activated reward system projects caudally from the lateral hypothalamic area to the ventral tegmental area (Shizgal et al. 1980b).

The descending reward fibers of the medial forebrain bundle terminate in a region sharing the precise dorsal, ventral and lateral, and the approximate caudal boundaries of the dopaminergic cell groups of the ventral tegmental area and substantia nigra (Corbett and Wise 1980; Wise 1981b). Since pharmacological interference with dopaminergic transmission attenuates the rewarding impact of lateral hypothalamic stimulation (Fouriezos and Wise 1976; Fouriezos

et al. 1978; Franklin 1978; Franklin and McCoy 1979; Gallistel et al. 1982; Zarevics and Setler 1979), it seems likely that the descending fibers make synaptic contact with either the dopaminergic cells or the terminals of their afferents (both the reward sites and the terminals of any dopaminergic afferents share the anatomical dispersion of the dopaminergic cells). Opiates and psychomotor stimulants both appear to have their effect in this circuitry, opiates at the level of the dopamine cell bodies and stimulants at the terminals of the dopaminergic nerve fibers. It is not yet known which of the efferents of the dopaminergic fiber projections represent the next link in the reward circuitry, but cells of the nucleus accumbens are most strongly implicated from studies of psychomotor stimulant reinforcement.

MECHANISM OF REWARDING ACTION OF COCAINE AND AMPHETAMINE

Several lines of evidence suggest the dopaminergic synapse to be the site of the rewarding actions of the psychomotor stimulants cocaine and amphetamine. Amphetamine and cocaine share the ability to increase transmitter concentrations in both the noradrenergic and the dopaminergic synapse, cocaine by blocking the reuptake mechanism (which usually terminates catecholamine synaptic action) and amphetamine by blocking reuptake and also by directly causing or augmenting synaptic catecholamine release (Axelrod 1970; Carlsson 1970; Heikkila et al. 1975). The rewarding effects of cocaine and amphetamine are attenuated by nonselective catecholamine synthesis and receptor blockade (Pickens et al. 1968; Wilson and Schuster 1972), and whereas selective blockade of noradrenergic synapses alone does not have similar effects, selective blockade of dopaminergic synapses does (Yokel and Wise 1975, 1976; Risner and Jones 1976, 1980; deWit and Wise 1977). When low doses of dopamine antagonists are given, stimulant self-administration is maintained, but it is maintained at a higher than normal level of hourly intake (Yokel and Wise 1975; Risner and Jones 1976, 1980; deWit and Wise 1977). There is no question of response debilitation from the dopamine antagonism; the animals actually respond more under dopamine receptor blockade than they would under normal conditions. Rather, it seems clear that dopaminergic antagonism attenuates the reinforcing effectiveness of the stimulants; higher than normal concentrations of stimulants are earned before the animal shows signs of drug satiety.

When higher doses of dopamine antagonists are given, the animals cease responding for stimulants (Yokel and Wise 1975, 1976; deWit and Wise 1977). Response cessation is not imnediate, however, and in the case of the rat, at least, responding is accelerated for an hour or two before it ceases (Yokel and Wise 1975, 1976; deWit and Wise 1977). The response acceleration parallels what is seen when nonrewarding saline is substituted for rewarding amphetamine. This has been conceptualized as reflecting the "frustration" of responding in the absence of the expected rewarding payoff (Amsel and Roussel 1952); descriptively and procedurally it is an extinction-induced rate increase. The period of response acceleration makes it clear that the animals are not critically incapacitated by the

dopaminergic antagonists (even at the time of peak antagonist action: Yokel and Wise 1976) and suggests that response cessation results from an absence or attenuation of the usual reinforcing impact of the stimulant. With high doses of dopamine antagonists it appears that the reinforcing efficacy of amphetamine and cocaine is either eliminated or reduced to levels inadequate to sustain responding.

That activation of some dopaminergic receptor population accounts for psychomotor stimulant reinforcement is also consistent with the fact that apomorphine and piribedil, direct dopamine receptor agonists, have amphetamine-like rewarding actions in rats and dogs (Baxter et al. 1974; Risner and Jones 1976; Wise et al. 1976; Davis and Smith 1977; Yokel and Wise 1978). Clonidine, a noradrenergic receptor agonist, has reinforcing properties at very low doses, though the behavioral side-effects are more like opiate effects than like stimulant effects (Davis and Smith 1977). Clonidine and methoxamine, another noradrenergic agonist, do not have amphetamine-like reinforcing properties, as reflected in a number of tests (Risner and Jones 1976; Yokel and Wise 1978). The reinforcing action of apomorphine is not altered by dopamine synthesis inhibition (Baxter et al. 1976), and thus it is post-synaptic dopamine receptors and not dopamine autoreceptors that mediate the rewarding effect of dopamine agonists (normal dopamine function would be needed to express effects of apomorphine that were mediated at the autoreceptor).

The conclusion derived from animal studies, that the reinforcing effect of psychomotor stimulants is attenuated by dopamine antagonists, is confirmed by human studies. The subjectively rated euphoria produced by intravenous amphetamine is reduced by nonselective catecholamine antagonists (Jonsson et al. 1971) or by the selective dopamine antagonist pimozide (Gunne et al. 1972), but it is enhanced, if anything, by the selective noradrenaline antagonists propranolol, phentolamine and phenoxybenzamine (Gunne et al. 1972). It thus seems clear that of the shared pharmacological actions of amphetamine and cocaine it is the action in the dopaminergic synapse that is critical to the phenomenon of reinforcement.

Which of the various dopaminergic pathways are implicated? There are three major anatomical projections of the dopaminergic cells of the ventral tegmentum: the striatum, the limbic system, and the cortex. Of these the nucleus accumbens, most frequently treated as a limbic structure, is most clearly implicated in psychomotor stimulant reinforcement. Neurotoxin-induced lesions of this structure reduce or eliminate amphetamine and cocaine reinforcement (Roberts et al. 1977, 1980; Lyness et al. 1979), as do local injections of dopamine antagonists (Phillips and Broekkamp 1980). Direct injections of amphetamine into nucleus accumbens are rewarding in their own right (Monaco et al. 1980). Injections of amphetamine into the cortex of monkeys are also reported to be reinforcing (Phillips et al. 1981) as are injections of cocaine into the cortex of rats (Goeders and Smith 1983); thus there may be more than one dopaminergic projection that participates in brain reward circuitry.

The nucleus accumbens seems particularly important, however, at least in the rat.

Thus the mechanism of psychomotor stimulant reinforcement and the mechanism of lateral hypothalamic brain stimulation reinforcement seem to share common elements. The brain stimulation reinforcement seems to activate dopaminergic synapses indirectly, by stimulating the fibers that make anatomical contact with the dopamine cells or their afferents; the cocaine and amphetamine reinforcements activate the dopaminergic synapse directly, by increasing dopamine concentrations at the post-synaptic receptor.

DOPAMINE INVOLEVMENT IN FOOD AND WATER REINFORCEMENT

The dopaminergic synapse also seems involved in the mechanisms of food and water reinforcement. If the dopaminergic synapse is pharmacologically blocked, several findings suggest the reinforcing impact of food and water to be compromised (Wise et al. 1978a, b; Wise 1982; Spiraki et al. 1982; Xenakis and Sclafani 1982). Briefly, the effects of dopaminergic blockade are as follows: food loses the ability to establish the lever-pressing habit in untrained hungry rats; food loses the ability to sustain such habits in trained rats; rats with experience lever-pressing for food under dopaminergic blockade initiate responding progressively less on subsequent test days; and food continues to be a potent elicitor of free-feeding responses but loses much of its ability to maintain free feeding after food is tasted (Wise 1982). Responding also fails to be maintained by water reinforcement under dopamine blockade (Gerber et al. 1981) .

Attenuation of the rewarding effects of food by neuroleptics can also be demonstrated on the day after the neuroleptic treatment, when the animal is no longer under the influence of the blocker; hungry animals having received food previously under pimozide treatment do not subsequently return, as do normal animals, to the part of the environment where food was last found (Spiraki et al. 1982). The effects of dopaminergic blockade do not always and do not perfectly parallel the effects of withholding reinforcement; thus it is clear that dopamine blockers do more than simply block reinforcement (they probably produce motoric impairment as well) and that they usually block reinforcement only partially, at least in the dose range most frequently tested (Wise 1982). While they do not block responding in all paradigms at equal doses, dopaminergic blockers decrease responding in the same manner over a wide enough range of paradigms to make it clear that, whatever its side effects, dopamine blockade alters the reinforcing efficacy of both food and water.

This evidence thus relates food and water reward to an anatomical mechanism having a critical dopaminergic link, though it is not yet known by which anatomical pathways the reward message reaches the dopaminergic cells. While the dopaminergic link in the mechanism of food reward may not be identical to the dopaminergic link in the mechanism of brain stimulation and psychomotor stimulant

reward, a common link does become one of the more attractive of the obvious possibilities.

DOPAMINE INVOLVEMENT IN OPIATE REINFORCEMENT

Other drugs of abuse might be suspected to act through the same reward mechanism, though there is no logical necessity that they must do so. In the case of opiates, however, there is strong recent evidence that a dopaminergic mechanism of rewarding action is again involved. Whereas reward-relevant dopaminergic neurons appear to be transsynaptically activated by brain stimulation reward, they seem more likely to be directly activated by reinforcing injections of morphine. This is not so clear from pharmacological challenge of intravenous opiate self-administration; while moderate doses of dopamine blockers cause response cessation in this paradigm (G.J. Gerber, M.A. Bozarth, and R.A. Wise, unpublished observations), they do not cause the low-dose response acceleration (Ettenberg et al. 1982) which helps make their effects on psychomotor stimulant self-administration so clearly interpretable as a reward deficit (Yokel and Wise 1975). It is not clear why animals do not compensate for dopaminergic blockade by increasing their opiate intake, particularly when they do increase intake to compensate for opiate receptor blockade (Ettenberg et al. 1982); however, a similar lack of compensatory response acceleration is also seen when apomorphine self-administration is challenged by dopamine receptor blockade (Yokel and Wise 1978); thus the lack of compensatory response acceleration in response to low dose neuroleptics cannot be taken as reason to disregard the decreases in drug intake caused by higher neuroleptic doses. Nor can the lack of accelerated responding, before response cessation, following moderate doses of neuroleptics (Ettenberg et al. 1982) be taken as reason to disregard the response cessation. Responding for apomorphine also ceases without response acceleration after moderate dose of neuroleptics (Yokel and Wise 1978), and this does not rule out a role for dop amine in apomorphine reinforcement. Additional paradigms are needed, however, to make it clear (a) that reinforcing opiates do activate dopaminergic neurons and (b) that such activation is critical to their reinforcing action. Several are now available.

First, direct injections of morphine (Phillips and LePiane 1980; Bozarth and Wise 1981a, 1982) and other opiates and opioid peptides (van Ree and de Wied 1980; Phillips and LePiane 1982) are reinforcing when administered into the region of the dopaminergic cells of the ventral tegmentum. This is seen in a conditioned place preference paradigm, where animals learn to return to the place where they have experienced opiates in the past (Phillips and LePiane 1980, 1982; Bozarth and Wise 1982), and also in a lever-pressing paradigm where responding is reinforced by direct brain injections of morphine (Bozarth and Wise 1981a) or fentanyl (van Ree and de Wied 1980). Injections dorsal (Phillips and LePiane 1980), anterior or posterior (Bozarth and Wise 1982) to the dopaminergic cell group are not reinforcing. Injections of morphine in other regions, particularly the lateral hypothalamus (Stein and Olds 1977; M.E. Olds 1979), have also been reported to be reinforcing, but

it seems most likely that such injections diffuse and have their reinforcing action in the ventral tegmental area (Broekkamp 1975; Wise and Bozarth 1981; Bozarth 1983). Intravenous heroin reinforcement is not altered by destruction of the cells of the lateral hypothalamus, as it would be if there were important reward-relevant opiate receptors in this region (Britt and Wise 1981), and rats do not learn to lever-press for hypothalamic injections as rapidly or as reliably as they learn to lever-press for ventral tegmental injections (Bozarth and Wise 1982).

On the other hand, ventral tegmental microinjections of opiate antagonists cause compensatory increases at low doses and extinguish responding for intravenous opiates at high doses (Britt and Wise 1983). Ventral tegmental microinjections of the enkephalinase inhibitor thiorphan produce a reinforcing state, presumably mediated by an endogenous opioid peptide transmitter, as shown by the place preference test (Glimcher et al. 1983). Thus the reinforcing action of opiates seems localized to the region of the dopamine-containing cells that are implicated in psychomotor stimulant reward.

That rewarding ventral tegmental morphine injections pharmacologically activate the dopaminergic cells of this region is inferred from the fact that they cause contralateral circling (Bozarth and Wise 1982). Such circling is known to accompany activation of the dopaminergic projection to the striatum (Ungerstedt 1971), and dopaminergic antagonists block the circling elicited by morphine in this region (Holmes et al. 1983). The fact that the circling is directed away from the side of morphine injection indicates that the injections excite rather than inhibit the dopaminergic cells in question (Ungerstedt 1971), and electrophysiological evidence confirms that there is a population of dopaminergic cells in the ventral tegmentum which is excited by morphine (Matthews and German 1982; Ostrowski et al. 1982). That this dopaminergic activation plays a necessary role in opiate reinforcement is confirmed in the conditioned place preference task; if morphine is given during dopaminergic receptor blockade, the animals do not show learned approach to the morphine-associated portion of the environment (Bozarth and Wise 1981b; Spiraki et al. 1983).

The emerging picture is, then, one of a reward circuit involving a descending myelinated fiber system in the medial forebrain bundle (activated directly in the case of brain stimulation reward), communicating with dopaminergic cell bodies of the ventral tegmental area (where morphine initiates its reinforcing action), and ultimately resulting in synaptic release of dopamine at terminals where the reinforcing effects of psychomotor stimulants are pharmacologically initiated. Food and water reward are thought to depend on at least the dopaminergic portion of this circuitry, but it is not known by what input fibers the message arrives at the dopaminergic cells.

DOPAMINERGIC MECHANISMS AND OTHER HABIT-FORMING DRUGS

At least two other drugs with some degree of abuse liability appear likely to have actions at the dopaminergic link of this same re-

inforcement system. Phencyclidine, which has amphetamine-like reinforcing properties (along with several non-amphetamine-like side effects), shares amphetamine's approximate site of reinforcing action in nucleus accumbens; phencyclidine injections in this region cause conditioned place preference (Giovino et al. 1983). It is not known whether phencyclidine has presynaptic or postsynaptic effects in the dopaminergic synapse, like cocaine or apomorphine, respectively, or whether it acts in other synaptic junctions to influence the same output cells. Nicotine, which is self-administered intravenously in man (Henningfield et al. 1983) and in lower animals (Dougherty et al. 1981), is also capable of activating dopaminergic cells (Giorguieff-Chesselet et al. 1979; Lichtensteiger et al. 1982), although, again, the mechanism of interaction is not known in any detail. Thus there is a good chance that future research will link the reinforcing mechanisms of action of at least some other drugs of abuse to the mechanism shared by food, water, lateral hypothalamic brain stimulation, amphetamine, cocaine, and opiates. Other neurotransmitter systems are also likely to be linked to the mechanisms under discussion; for example, neurotensin, an endogenous peptide transmitter, is reinforcing when injected into the ventral tegmental area, as shown in both place preference and self-administration tests. The rewarding effects are dopamine-dependent, as they are blocked by neuroleptics (Glimcher et al. 1983b).

RELATION OF DRUG DEPENDENCE TO DRUG REINFORCEMENT

In considering the mechanism of cocaine's abuse liability it has been useful to consider cocaine actions that are shared with other drugs of abuse. It is unlikely that the peripheral autonomic effects or local anesthetic effects of cocaine are critical, since these are not effects common to other classes of abused drugs. Similarly, it seems clear that actions other than physical dependence-producing actions such as those of opiates, ethanol, barbiturates, and benzodiazepines must explain the habit-forming consequences at least of cocaine; cocaine shares the habit-forming property but not the dependence-producing property of these drugs.

Based on this conclusion, it is tempting to accept the currently popular notion that cocaine is less dangerous (less "addicting" or less compulsively habit-forming) than so-called "hard drugs" that do produce physical dependence syndromes. It is widely held that cocaine is a much safer drug for recreational use than is heroin, for example, because heroin "addicts" the user while cocaine does not. This unfortunate and erroneous belief is based on two fallacies, one empirical and one logical. The empirical fallacy is that humans seem usually not to endanger their health by taking cocaine to excess; the logical fallacy is that it is the ability to produce physiological dependence that makes drugs most dangerous. The first fallacy is refuted by direct evidence; the second is refuted by the fact that even opiate self-administration can be shown to derive from opiate actions unrelated to physical dependence.

Studies in animals suggest that cocaine is a far more inherently health-threatening pharmacological agent than heroin. Rats given free access to intravenous cocaine or amphetamine take drug to the exclusion of food. These animals lose weight and usually die in a few weeks (Pickens and Harris 1968; Bozarth and Wise, unpublished observations); rewarding brain stimulation can have similar effects (Routtenberg 1964). Widespread human experience with cocaine suggests that cocaine does not have such compelling effects in man; but it must be remembered that few humans have unlimited access to cocaine, and among those that do, compulsive and potentially lethal cocaine abuse are increasingly reported. The seeming safety of cocaine as used recreationally by man may be an illusion that depends more on the intake-limiting effects of cocaine price and availability than on any inherent safety in the drug itself. In as much as cocaine and amphetamine have very similar effects in the reward circuitry of the brain, the lessons learned with intravenous amphetamine in both man and animals are very relevant: the psychomotor stimulants do not impose reasonable limits on their own intake; they have a dangerous tendency to be self-administered to the detriment of health when they are freely available in unlimited quantity. Positive reinforcing properties alone, as shared with rewarding brain stimulation, are enough to produce this high degree of health risk (Routtenberg 1964).

Whatever the safety factor we attribute to cocaine, it is clear that its habit-forming property, and thus its abuse liability, is independent of a classic physical dependence syndrome. In considering the degree to which cocaine shares common mechanisms of reinforcing action with other drugs, it is important to determine how critical the physical dependence syndrome is for the reinforcing effects of those drugs that do produce it. Recent evidence on the nature of opiate reinforcement suggests that physical dependence is not a necessary condition for reinforcement even in the case of opiates. Thus the primary mechanisms of opiate and cocaine reinforcement do, indeed, seem shared.

There are two major principles of reinforcement as analyzed in the literature of experimental psychology, and each has been suggested to underlie opiate reinforcement (Beach 1957). The first is the principle of "positive reinforcement," in which a positive state caused by the drug--euphoria--is seen to account for the reinforcing effects of the drug. Although many of the subjective effects are different, euphoria is a property that opiates share with cocaine and amphetamine; stimulant euphoria and opiate euphoria are sufficiently similar to make it appropriate to rate them on the same mood scale (Jasinski 1973). The second principle is the principle of "negative reinforcement," in which a negative state which the drug reduces--withdrawal dysphoria--is seen to account for opiate reinforcement. Stimulants do not share with opiates the ability to block the opiate withdrawal syndrome, and there is no comp arable withdrawal syndrome, in severity or quality, associated with psychomotor stimulants; thus the negative reinforcement principle is not a satisfying explanation of cocaine self-administration and is not a common denominator of drugs of abuse, despite the fact

that it is a principle widely held to explain compulsive intake of opiates and other sedative-hypnotics.

There is now strong and direct evidence that the primary reinforcing effects of even opiates are positive and not negative reinforcement effects. First, no obvious signs of opiate dependence develop in animals allowed to work for low doses of intravenous opiates (Woods and Schuster 1968; Deneau et al. 1969) or for limited access to central (ventral tegmental) morphine injections (Bozarth and Wise 1983). Thus opiates can be reinforcing, producing strong self-administration habits, when given in dose regimens and by routes of administration that do not lead to obvious dependence signs.

It is always possible, however, that some degree of dependence develops, but goes undetected, in any paradigm where drug is given more than once; dependence signs need not be obvious to outside observers in order to play a role in drug reinforcement. However, opiate reinforcement can also be demonstrated in a place-preference paradigm where drug is administered only once (Bozarth and Wise 1983); here there is never any opportunity for drug to relieve withdrawal distress. Thus opiate dependence is not a necessary condition for opiate reinforcement.

There is even clearer recent evidence, however, that morphine dependence and primary morphine reinforcement are not causally linked; opiate reinforcement and opiate dependence are now known to be mediated by anatomically distinct neural mechanisms, each with its own population of central opiate receptors. Even 72 hours of continuous infusion of morphine into the opiate reward site of the ventral tegmental area fails to produce the opiate dependence syndrome as reflected in naloxone-precipitated withdrawal symptoms (Bozarth and Wise 1983). When the same dose is infused into the periaqueductal gray matter, on the other hand, strong dependence signs develop (Wei and Loh 1976; Wei 1981; Bozarth and Wise 1983). Drug-naive rats do not work for injections into this region, however (Bozarth and Wise 1981a) , nor do injections in this region produce conditioned place preference (see the control group of Phillips and LePiane 1980). Thus the primary reinforcing effect of opiates involves a population of opiate receptors that interacts with reward circuitry of the ventral tegmental area and that is not involved in dependence phenomena, whereas the dependence-producing effect of opiates involves an anatomically distinct pop ulation of opiate receptors that interacts with circuitry of the periaqueductal gray matter and is not involved in positive reinforcement phenomena. Thus opiates, along with cocaine, have habit-forming actions involving positive reinforcement mechanisms. It remains possible that opiates can produce, in addition, negative reinforcement; it is not yet known whether morphine-dependent animals will work for morphine injections into the periaqueductal gray; it seems likely that in dependent subjects both factors may come into play (Beach 1957).

The potent reinforcing actions of opiates and cocaine which are

common actions, however, would appear to be positive reinforcing actions. Whatever the influence of withdrawal distress in dependent subjects, it would appear that the mood elevation associated with cocaine and opiates in nondependent subjects is sufficiently powerful to account for the initial acquisition of drug self-administration habits and is likely to account as well for the rapid reacquisition of such habits in detoxified subjects. This positive reinforcement property and the mood elevation that tends to accompany it appear to result from the activation of neural systems which evolved to serve the control of behavior by conventional reinforcers such as food and water. The fact that drugs and rewarding brain stimulation can activate these endogenous reward systems powerfully and centrally may account for the fact that these reinforcers which do not offer obvious survival value to either the individual or the species can sometimes exert more effective behavioral control than substances or events that do.

SUMMARY AND CONCLUSIONS

Cocaine has multiple central and peripheral pharmacological actions. The action responsible for the rewarding property, and hence the abuse liability, of cocaine is an action in the dopaminergic synapse; in the rat the major set of critical dopaminergic synapses appears to be in the nucleus accumbens. Cocaine prolongs the activity of dopamine in the synapse by blocking the dopamine reuptake mechanism (which usually inactivates the transmitter by removing it from the proximity of its synaptic targets). This is an action shared with amphetamine; in addition to blocking the dopamine reuptake mechanism, amphetamine also augments dopaminergic function by augmenting dopamine release directly into the synapse. While amphetamine and cocaine have discriminable subjective effects, perhaps due to differences in rate of onset and metabolism or perhaps due to different side effects, cocaine shares its rewarding impact and abuse liability very closely with amphetamine. When drug access is unlimited, cocaine and amphetamine have the same ability to dominate behavior, reducing other behaviors such as feeding and sleeping and, in the process, reducing stress resistance to life-threatening levels.

Opiates also owe their reinforcing properties to their ability to activate dopaminergic synapses in brain reward circuitry, though they activate the system at a different site and by a different local mechanism than those of amphetamine and cocaine. Where amphetamine and cocaine activate dopaminergic activity in the dop aminergic synapse, opiates activate dopaminergic activity by activating (or disinhibiting) the dopaminergic cell bodies. The site of rewarding action of opiates is the ventral tegmental area, where the dopaminergic cells projecting to the nucleus accumbens (as well as other targets) are located. Opiate actions that are restricted to this mechanism do not include opiate physical dependence; the dependence syndrome involves anatomically distinct systems in the brain, systems not activated by amphetamine or cocaine. While opiate physical dependence may contribute to the motivation for opiate intake in dependent subjects, it is not necessary for

opiates to be habit-forming.

The neural circuitry involved in the rewarding actions of cocaine, amphetamine, and the opiates is circuitry thought to be specialized for natural reward function. The circuit activated by these drugs is also activated by some cases of rewarding brain stimulation. While there may be more than one reward circuit in the brain, the rewarding effects of food and water appear to depend, along with those of cocaine, amphetamine, opiates and lateral hypothalamic brain stimulation, on the integrity of a dopaminergic link in such circuitry. The rewarding effects of cocaine, however, need not be conveyed to the central nervous system over networks of sensory nerves, as are those of food and water; cocaine can activate, powerfully and directly, the central circuits of goal-directed behavior. Given this fact it should not be surprising that motivation for cocaine can come to dominate motivation for more essential and health-promoting substances. Survival value has resulted from the fact that food, water, warmth, shelter, sex partners, and social and parental interactions have been subserved by the central circuits of reward and motivation. The refinement of substances such as cocaine and methods such as rewarding brain stimulation which can activate central reward circuitry directly, are unlikely to serve the further evolution of man so long as they provide shortcuts to the pleasures of reward and bypass the adaptive activities that have led to these pleasures over most of our evolutionary history.

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AUTHOR

Roy A. Wise, Ph.D.
Center for Studies in Behavioral Neurobiology
Department of Psychology
Concordia University, Montreal, Quebec
Canada

The Pharmacology of Cocaine

Reese T. Jones

As we approach the one hundredth anniversary of the use of cocaine in medicine, the reader might assume that scientific knowledge of cocaine is relatively complete. It is not. Much of what is known about cocaine, its local anesthetic properties, central nervous system stimulant actions, general subjective and cardiovascular effects when ingested by a variety of routes -- oral, nasal, by chewing, by injection -- was described 50 to 100 years ago. The "new" facts regarding the pharmacology of cocaine have mostly been collected and reported since 1975 when NIDA funded a series of research contracts to study the pharmacology of cocaine in humans. Those studies and ones evolving from them provide detailed descrip tions of acute, short-term cocaine effects and are reviewed elsewhere in this volume. The studies provide better documented information on relationship between dose and route of administration, blood levels of cocaine and limited physiologic or psychologic effects (Fischman et al. 1976,1983; Resnick et al. 1977; Van Dyke et al. 1978,1982; Fischman and Schuster 1980,1981,1982). However, many large gaps in what we should know about the pharmacology of cocaine remain. This chapter touches on some of the issues where more should be known, speculates on assumptions about what we do know, and suggests a few areas needing attention from researchers and from those sources that should support good research on the pharmacology of cocaine.

COCAINE AND BRAIN FUNCTION

Some of the most impressive and predictable consequences of cocaine are effects on brain function and the sought-after consequences of altered brain function -- euphoria, relief of fatigue and boredom, and other consequences of psychic stimulation. Hans Berger, in one of the earliest reports describing the human electroencephalogram (Berger 1931), mentioned that a 24-year-old man given a 30 mg dose of cocaine subcutaneously showed increased EEG; alpha frequency and amplitude 20 minutes after injection. Cocaine given during a second test session with this young man produced less EEG; change. A second subject demonstrated a similar alpha amplitude and frequency increase associated with the "stimulating

action of cocaine upon psychic processes." Berger gave a few more volunteers cocaine (Berger 1937). His new recording equipment allowed him also to measure EEG beta activity and he found increased beta activity along with the higher amplitude and higher frequency alpha 30 minutes after a 20 mg subcutaneous injection of cocaine. "We are confronted here with the graphic representation of the stimulating action exerted by cocaine upon mental processes," Berger said. Keep in mind Berger's papers were the first demonstrations of human EEGs and involved, among other things, comparisons of caffeine and cocaine.

Now, almost 50 years after Berger's auspicious demonstrations of cocaine effects on the electrical activity of the human brain, no further publications describing the effects of cocaine on the resting EEG in humans have appeared. One small study examined cocaine-induced sleep EEG; changes in depressed patients. Modest doses of cocaine (30 to 200 mg daily) given orally for ten days suppressed rapid eye movement sleep. When cocaine was stopped, a rebound of REM sleep quantity followed as it does after withdrawal of amphetamines and many other psychoactive drugs given for a few days (Post et al. 1974). The depressions did not improve.

In studies in our laboratories, we find substantial cocaine-induced changes in nonstimulated resting EEG and on the late components of auditory event-related potentials thought to be related to information processing. Intravenous doses of cocaine similar to those commonly used outside of the laboratory setting (0.2 mg/kg) produced increases in $beta_2$ activity like those described by Berger 50 years ago. However, no differences between cocaine and placebo on alpha activity have been found. Cocaine decreases the amplitude of the so-called P300 component of an auditory-evoked response recorded during a task that required the subject to evaluate each stimulus as to its task relevance. That the cocaine effect seems to be maximal at a 0.2 mg/kg dose with higher doses producing no greater decreases in amplitude suggests that even lower doses of cocaine may have measurable effects on brain function. Other laboratories report stimulants like methylphenidate increase the P300 component amplitudes. It is generally assumed that methylphenidate, amphetamine, and related stimulants have actions and many mechanisms similar to cocaine. The different pattern of evoked potential changes suggests that there may be some differences in actions or mechanisms as well.

Generalized convulsions were among the very earliest toxic effects of cocaine noted in the late 19th century (Van Dyke and Byck 1976; Eidelberg et al. 1963). The convulsions were generally considered to reflect cocaine's CNS stimulant effects. Early studies noting that at high doses the convulsive behavior was followed by death generally associated with respiratory depression, assumed that cocaine acted at the cortical level with "stimulation proceeding from above downward." When more precise neurophysiologic recording techniques were developed in the 19606, it was obvious that changes in limbic system function preceded the generalized motor convulsions. It was suggested that cocaine seizures originating in limbic structures might provide a useful model to investigate

temporal lobe epilepsy and psychoses that may be associated with psychomotor seizures (Eidelberg et al, 1963). Worth noting is that, in contrast to cocaine's propensity to induce seizures even after a single dose, amphetamines generally induce seizures only after repeated administration of high doses, suggesting possible differences between amphetamines and cocaine.

Ihe relative lack of interest in the human electrophysiology of cocaine is even more surprising since with animals one of the more dramatic consequences of chronic cocaine administration is a phenomenon referred to as 'kindling," manifest by increased sensitivity and responsivity of various neural and other systems (Post et al. 1976,1981; Stripling and Hendricks 1981; Ellinwood and Kilbey 1980). Hypothesized mechanisms accounting for kindling are related to enhanced propagation of electrical signals in the nervous system. That the locus of activity seems to be in the limbic system structures makes the phenomenon all the more interesting and clinically relevant because chronic cocaine and other stimulant administration mimics certain aspects of a schizophrenic-like process (Post 1975; Ellinwood and Kilbey 1980). It is plausible that the electrical and behavior changes seen in animals given cocaine repeatedly and some of the behaviors of people taking cocaine repeatedly could result frorm similar mechanisms. Such EEG phenomena as kindling have not been reported to occur in long-term, frequent cocaine users. On the other hand, such populations have not been studied systematically, if at all, in terms of this phenomenon observed in the laboratory.

Cocaine has complex actions on the central nervous system. Many effects on brain function are similar to those produced by other stimulants, for example, amphetamines or caffeine. Other cocaine effects are more similar to other local anesthetics, for example, potent membrane stabilizing properties. Since most local anesthetics do not produce the mental stimulation and other psychological effects of cocaine (Fischman et al. 1983), its local anesthetic properties are probably neither necessary nor sufficient explanations for cocaine's sought-after effects but could account for some of its untoward toxic effects. Cocaine alters the metabolism of norepinephrine, dopamine, serotonin, and acetylcholine. It is a potent convulsant, but under other circumstances has anticonvulsant properties. Some of the earliest studies with cocaine documented its delay in the inactivation of epinephrine and norepinephrine and blockade of norepinephrine reuptake. Subsequent neurochemical studies on the actions of cocaine on the brain focused on the catecholamine systems and generally reported effects similar to the more extensively studied amphetamines. However, some evidence has accumulated that cocaine also alters serotoninergic mechanisms, for example, blocking the synaptosomal uptake of tryptophan (Knapp and Mandell 19721. This would slow the conversion of tryptophan to serotonin even though tryptophan hydroxylase activity increases (Mandell and Knapp 1977). Turnover of 5-hydroxy tryptophan is slowed, suggesting possible differences in cocaine and amphetamine mechanisms (Friedman et al. 1975). Cocaine also decreases acetylcholine uptake (Liang and Questel 1969). Assuming that lithium diminishes cocaine effects (Cronson

and Flemenbaum 1981) and that endorphinergic mechanisms may be involved, then the whole story of cocaine mechanisms in the CNS is still incompletely understood and is probably complex.

ABSORTION AND METABOLISM

The availability of biochemical assays sufficiently sensitive to measure tissue levels of cocaine and its metabolites in humans now enables researchers to better assess the significance of clinical data and to more properly design research studies (Jatlow and Bailey 1975; Chinn et al. 1980; Lindgren 1981; Ambre et al. 1982; Miller et al. 1977; Johns et al. 1977; Hawks et al. 1974). In recent years, many of the laboratory studies with cocaine reporting data from humans have measured plasma levels of cocaine. Some rudimentary understanding has developed regarding relationships between cocaine dose, route of administration, and effects, but uncertainty remains.

Enzymes called esterases play an important role in the metabolism of cocaine. In humans and other mammals, plasma and liver have high levels of esterase activity. Moderate activity is present in other organs including brain (Foldes 1978). Cholinesterases, also referred to as plasma cholinesterase, serum cholinesterase, pseudocholinesterase, nonspecific cholinesterase, play an important role in the metabolism of cocaine (Stewart et al. 1979; Inaba et al. 1978). Individuals with low cholinesterase activity may have slower metabolism of cocaine and some of its metabolites (Jatlow et al. 1979). In vitro activity of these enzymes becomes an important consideration in cocaine assay procedures (and can make for considerable in vitro losses of cocaine unless inhibited by the addition of fluoride, physostigmine, or other esterase inhibitors) (Jatlow and Bailey 1975).

Plasma cholinesterase activity can vary greatly between individuals and between species. The genetics of plasma esterase inheritance are relatively well understood (Neitlich 1966; Foldes 1978). The percent inhibition of the esterase activity by dibucaine, known as the dibucaine number, is one common clinical measure used to screen for unusual sensitivity to the muscle relaxant succinylcholine. People with low dibucaine numbers seem to be not only slow metabolizers of succinylcholine but may also be slow metabolizers of cocaine, at least as judged by in vitro tests (Jatlow et al. 1979; Stewart et al. 1979). On the other hand, some individuals may have genetically determined increased cholinesterase activity and would be expected to metabolize cocaine more rapidly. A number of disorders including liver disease, the presence of carcinoma, and exposure to anticholinesterase drugs will lower cholinesterase activity (Foldes 1978).

Some inconsistencies in the cocaine literature, particularly in issues of tolerance and dependence, may result from species variations in cholinesterase activity and resulting cocaine metabolism. Cholinesterase activity is relatively high in humans, horses, and certain species of monkeys (for example, chimpanzees) but not others (for example, macaques). Cholinesterase activity is much

lower in other mammals (for example, dogs, cats, sheep, and rats) and very low in cows. Fourfold differences in cholinesterase activity can occur in various strains of mice. Cholinesterase activity is much lower in the fetus, infants, and aged males, and decreases to a lesser degree during pregnancy.

The pharmacologic significance of such variations in determining cocaine metabolism or toxicity is not entirely clear. Most cocaine studies in animals, particularly behavioral studies, have rarely even measured cocaine or cocaine metabolite levels, let alone determined kinetics. However, there is enough evidence from in vitro assays to indicate that variations in cholinesterase activity in the range commonly encountered clinically can have significant effect on the in vitro metabolism of cocaine and cocaine metabolites. Since there is both hepatic and nonhepatic metabolism of cocaine, the functional impact of very low or much higher than normal cholinesterase activity might depend on route of administration -- for example, it might be more important when the cocaine is given intravenously or perhaps smoked than with oral, intraperitoneal, or subcutaneous administration Rate and dose could interact as well.

METABOLITES

Cocaine is extensively metabolized in humans to water soluble metabolites that are mainly excreted in urine. The two major metabolites in urine are benzoylecgonine and ecgonine methyl ester (Fish and Wilson 1969; Inaba et al. 1978; Kogan et al. 1977). These hydrolysis products are generally assumed to result from the action of esterases in liver and in serum, though benzoylecgonine may be formed nonenzymatically in vivo (Stewart et al. 1979). The N-demethylated metabolites of each of the above may occur. Norcocaine has been identified in rat, monkey, and human (Inaba et al. 1978). Although the effects of norcocaine in humans are yet to be determined, norcocaine is biologically active as judged by inhibition of norepinephrine uptake in synaptosomes (Hawks et al. 1974), local anesthetic actions (Just and Hoyer 1977), and by effects on schedule controlled behavior (Spealman et al. 1979). Since norcocaine may have very similar kinetics to the parent compound, it may be less of a confounding variable than if its kinetics differed (Misra et al. 1975)

Benzoylecgonine is generally assumed to be without significant biological activity, though it occurs at substantial levels in plasma (Johns et al. 1977; Kogan et al. 1977). Even though it produces significantly less inhibition of norepinephrine uptake in synaptosomes that does cocaine (Hawks et al. 1974), Misra has speculated that benzoylecgonine could form molecular complexes with calcium ion and thus participate in a number of membrane level nerve functional changes (Misra 1976). Additional metabolites, hydroxycocaine and methylecgonidine, have been identified in the bile of a person dying of cocaine overdose (Lowry 1979). Cocaine blood levels in that case were substantial, 3700 ng/ml.

Assays of ecgonine methyl ester in urine (Ambre et al. 1982) or benzoylecgonine are useful as markers of cocaine use, although the pathways, particularly enzymatic versus nonenzymatic formation, are not yet completely worked out (Stewart et al. 1979). When considering the biological importance of cocaine metabolites, attention to possible species differences is important. For example, cocaine is a potent hepatotoxin in mice, probably due to the hepatic tissue binding of a metabolite of N-hydroxy-norcocaine (Rauckman et al. 1982; Smith et al. 1981). In humans and most other species, liver damage does not seem to be specifically associated with cocaine administration other than by speculative comments in some human studies where the general consequences of chronic intravenous drug use confound the issue. A relatively old report (Yamamoto et al. 1953) suggested decreased cocaine metabolism by rabbit livers after chronic administration, but the study did not specifically measure liver damage. Given some of the variability already alluded to in discussing plasma cholinesterase activity, it is particularly important when studying cocaine metabolites to keep in mind that there will be species selectivity and probably dose- and route-dependent interactions.

COCAINE RECEPTORS

Although a cocaine receptor has not yet been identified, specific binding characteristics have been suggested. In an appropriately speculative report, three lines of evidence were cited supporting the association of high affinity type cocaine binding in the cerebral cortex with serotonergic nerve terminals (Reith et al. 1983). There was a correlation between cocaine binding inhibition by various drugs and the inhibition of serotonin neuronal uptake in mouse cerebral cortex. In mice treated with various serotonin and catecholamine neurotoxins, only the serotonin neurotoxin decreased the high affinity binding of tritiated cocaine in rat cerebral cortex. Some reports have implicated serotonergic systems as important, particularly in increases in cocaine-induced locomotor activity that are not blocked by haloperidol or alpha methyl paratyrosine. Reith et al. (1983) remind us that the-array of effects produced by cocaine that include locomotor stimulation. mood changes, stereopy, and hallucinations are not likely to be due to a single mechanism. Thus, cocaine binding sites on serotonergic nerve terminals may mediate only some effects, but it is the mood elevating effects that are perhaps involved with these binding sites.

KINETICS

The pharmacokinetics of cocaine and its metabolites, that is, the mechanisms of absorption, metabolism, and excretion, have yet to be fully worked out. Some important parameters have not been determined in humans: for example, renal excretion pattern, protein binding, and blood/plasma partitioning. What has been published on the kinetics of cocaine and its metabolites reflects great unaccounted for variability, both within and between subjects in the same laboratory and between laboratories. For example, estimates of elimination half-life after intravenous

doses range from approximately 19 minutes (mean 41.4) (Javaid et al. 19831 to 168 minutes (Kogan et al, 1977). Some of the earlier studies offering kinetic data probably did not sample bloods long enough after cocaine administration to properly define the terminal phase of clearance, and numbers of subjects tested often were very small. Elimination half-life may be dose related but not to the extent that would account for the reported variability (Barnett et al. 1981). With a sample of 40 infrequent cocaine users, we found t-1/2 to range from a mean of 61 minutes at 0.2 mg/kg intravenously to 80 minutes at a dose of 0.6 mg/kg. However, at any given dose level there was great variability in the range of half-lives and equally great variability when subjects were tested on more than one occasion a week or two apart. Similar variability is evident even on such basic pharmacokinetic parameters as plasma versus time area under the curve, peak plasma levels, and times to peak plasma levels. It seems that one attribute of cocaine uptake, distribution, and metabolism is that it is variable.

ROUTE OF ADMINISTRATION

The availability of sensitive assays has led to a better understanding of the contribution of route of cocaine administration in determining effects. Although cocaine now is rarely taken orally, that is by swallowing or drinking, oral ingestion as an elixir was common in the late 19th century. Why has the nasal route become so popular? Relative bioavailability and intensity of many cocaine effects were similar after oral or nasal doses (Wilkinson et al. 1980; Van Dyke et al. 1978). we found similar patterns of effects after nasal and oral doses in a large number of subjects given oral, nasal, and intravenous cocaine. Bioavailability of both oral and nasal cocaine is about 30% to 40% when compared to intravenous doses given to the same person. The comparisons of oral, nasal, and intravenous routes suggest that the rate of change in plasma and presumably in brain drug levels and associated subjective effects may be very important considerations in determining preferred route of administration.

Similar oral and nasal cocaine doses produce similar peak blood levels and times to peak blood level (about 60 minutes), yet the onset and magnitude of both subjective effects and cardiovascular changes such as heart rate and blood pressure increase are much more rapid after intranasal administration. Effects begin within a minute or so after spraying the dose in the nasopharynx with a 18% cocaine solution and within a few minutes of administration of cocaine as a crystalline material. No one has done enough early plasma sampling after administration to properly define the earliest phase of uptake, but initial uptake appears to be faster when cocaine is taken nasally than when taken orally. For example, after 2 mg/kg doses; plasma levels at 15 minutes were 5.7 ng/ml with the oral route and 17.5 no/ml after nasal administration, yet the peak plasma levels at 1 hour were similar. It is likely that plasma concentrations do not adequately reflect brain levels of the drug, and that brain levels are important determinants of the sought-after effects. Regional distribution

and cocaine levels in various organs are not well characterized. In an autopsy case, brain cocaine levels were surprisingly high as compared to blood levels (Chinn et al. 1980). Given the vasculature of the nasopharnyx, it is plausible that cocaine brain levels at the earliest phase of nasal administration may exceed systemic plasma levels. Brain levels in rats given radiolabeled cocaine suggest cocaine is taken up rapidly by the brain (Misra et al, 1975). Perhaps the best illustration of the importance of rate of uptake is the intense but very transient subjective effect after smoking cocaine (Paly et al. 1982; Perez-Reyes et al. 1982; Siegel 1982). The initial effects after smoking seem more intense and more rapid in onset than comparable intravenous doses would produce.

NEUROCHEMICAL SUBSTRATES

As with most if not all psychoactive drugs, the neurochemical substrates of action are not completely understood. More precisely, the substrates seem to become more complicated as their interactions are better appreciated. It is important to consider neurochemical substrates following acute administration separately from those that follow chronic administration of cocaine. Single doses of cocaine (and other stimulants) may have quite different consequences than does chronic repeated administration. It traditionally has been said that the stimulating effects of cocaine could be attributed to its ability to block the reuptake of norepinephrine. This obviously is no longer considered to be a sufficient explanation, since many psychoactive drugs (for example, antidepressant drugs) in common use block the reuptake of neurotransmitters but are not stimulants and do not produce euphoria. Cocaine inhibits the reuptake of norepinephrine, and also dopamine and serotonin. Cocaine alters tryptophan hydroxylase and, thus, the drug-sensitive regulatory processes in the biosynthesis of serotonin. It may have direct effects on noradrenergic receptors. As do other stimulants, it interacts with the cholinergic system as well; for example, physostigmine, an acetylcholinesterase inhibitor, inhibits cocaine-induced hyperactivity and stereotypy in rats (Post et al. 1976). With repeated doses, neurochemical mechanisms can interact with conditioning or learning mechanisms, electrophysiologic changes, alterations in dopamine receptor binding sites, and possibly pharmacokinetic mechanisms (Ellinwood and Kilbey 1980).

ABSORPTION

Cocaine, when taken as the salt, is water and fat soluble and thus readily enters the body. When considering cocaine's pharmacology, particularly questions of absorption and metabolism, broad generalizations become risky because of the varied routes of administration available to the user or used by the scientist. Cocaine can be taken orally, i.e., swallowed; it can be taken nasally as a spray or a powder, much as tobacco snuff is taken; it can be taken buccally, either by chewing coca leaves or by placing it in the buccal pouch, much as one would do with tobacco snuff;

it can be smoked, injected intravenously or subcutaneously or intramuscularly. Since it is readily absorbed through mucous membranes or even abraded skin, those routes are available and have been utilized. Intraperitoneal injection is commonly used in studies with rodents.

Dose of any drug is, of course, of great importance in determining both acute and chronic toxicity. With cocaine, route of administration may be of equal and perhaps at times greater importance than dose, since metabolism and disposition are relatively rapid and involve mechanisms both in blood and liver and perhaps elsewhere. Since cocaine is a potent vasoconstrictor, its rate of absorption is altered by its effects on regional vasculature when given subcutaneously and perhaps by other routes. Most acute toxic reactions from cocaine are associated with the rapid onset of high plasma levels, usually after rapid absorption. Estimates of what is a lethal dose of cocaine vary greatly and depend very much on route of administration. Other aspects of toxicity, particularly chronic toxicity, may well vary with route of administration, possibly because of route-dependent metabolic differences.

ORAL INGESTION

Despite seemingly authoritative statements to the contrary, cocaine is readily absorbed when taken orally (Van Dyke et al. 1978; Wilkinson et al. 1980). This should not be surprising, since during the 19th century initial widespread use of cocaine in Europe and the United States was in the form of oral elixirs containing cocaine (Van Dyke and Byck 1982). The most common route by which cocaine is taken is still, of course, by chewing coca leaf or sucking on powdered coca leaves (Holmstedt et al. 1979; Paly et al. 1979; Holmstedt and Fredga 1981). When coca leaves are chewed, probably there is a combination of cocaine absorption from the mucous membranes of the mouth (and thus some avoidance of first pass liver metabolism) and also swallowing and absorption from the gastrointestinal tract. When coca leaves are chewed OK sucked on, measurable amounts of cocaine appear in the blood as soon as 5 minutes after chewing begins and, when swallowed, cocaine is measurable in blood within 15 minutes and perhaps earlier. The bioavailability of cocaine when taken orally has been estimated at about 20% (Mayerson and Perrier 1978). Currently in our laboratory, where more precise comparisons can be made to intravenous doses (thus taking into account metabolic processes other than hepatic metabolism), we find systemic absorption between 30% and 40% after oral doses.

The relative lack of popularity for oral dosing on the current drug-using scene is curious. Although peak subjective effects are slower in onset, they are not greatly different from those following dosage by the more popular intranasal route (Van Dyke et al. 1982, 1978). It has been argued that the toxicity of cocaine might be quite different, probably considerably less, if it were ingested orally by chewing coca leaves rather than by currently popular routes (Weil 1981). Most cocaine-using volunteers tested in our

San Francisco laboratories have never heard of or considered oral administration. Those few who are familiar with the oral route rarely have ever tried it. The precise sites of absorption, stomach versus duodenum, etc., and possible differences in metabolic profiles when taken by the oral route should be determined.

NASAL ADMINISTRATION

Cocaine produces excellent anesthesia and vasoconstriction of mucous membranes. For many years, cocaine was the anesthetic of choice for nasal surgery for that reason. When compared to oral administration, the absorption after nasal administration has a more rapid onset with correspondingly more rapid appearance of subjective effects. Even so, the peak plasma levels of cocaine, the time of peak plasma levels, and the bioavailability are similar with both nasal and oral administration Wilkinson et al. 1980; Van Dyke et al. 1982, 1978). The preference for the nasal route suggests that rate of increase in tissue levels is an important attribute to the cocaine user. The pattern and timing of effects suggest that there may well be more rapid increases in brain lwel of cocaine than in systemic levels reflected by venous blood samples. The vasculature of the nasopharnyx would allow for this possibility.

It should be kept in mind that plasma levels of cocaine do not necessarily indicate organ levels -- for example, brain levels. In an instance where cocaine blood levels were being measured in surgical patients (Miller et al, 1977), one patient developed restlessness, excitement, and bradycardia thought to represent early toxic symptoms from the cocaine within 2 minutes after cotton packs containing 5% cocaine solution were inserted in his nose. Even though the packs were removed immediately, his peak plasma cocaine levels 75 minutes later were 350 ng/ml, a threefold higher level than seen in other patients at that dose. At 20 minutes after the pack was removed, levels were 100 ng/ml. This single case illustrates that, for reasons not completely understood, the systemic uptake and perhaps more importantly the brain uptake of cocaine after nasal administration can be extremely rapid.

The factors determining rate of absorption of cocaine from nasal administration are not completely understood, Differences between the inhalation of crystals OK solution are small (Wilkinson et al. 1980). Variations in blood drug levels seem to be a function of total dose and not of the concentration of cocaine solution used (Cambell and Adriani 1958; Miller et al. 19771. Some of the relatively rare acute toxic reactions when cocaine is used for anesthesia may be due to the inhalation of cocaine mist which, if containing particles small enough to diffuse into alveoli, might be very quickly absorbed and, because of the very rapid uptake into brain, produce CNS levels that would otherwise not be attained through the slower absorption from nasal or pharyngeal mucosa or trachea (Campbell and Adriana 19581.

When the cocaine is instilled into the nasopharynx either as crystalline material or as a spray, surprisingly little of the delivered dose appears in saliva, suggesting relatively complete absorption from the nasopharynx rather than partial swallowing, The cocaine is very slowly cleared from nasal mucous membranes with measurable levels remaining 3 hours after administration (Van Dyke et al. 1982), probably due to paralysis of the cilia on the membranes of the nasal mucous blanket (Barton and Gray 1979). Since some studies reporting terminal half-lives for nasally administered cocaine only sample bloods for 2 or 3 hours, the validity of such kinetic measures must be considered in the context that absorption is still going on throughout the period when clearance is being measured.

PARENTERAL ADMINISTRATION

Cocaine can be injected subcutaneously or into muscle or vein. The former routes give relatively slow onset of effects, probably because of vasocontriction and thus relatively slowed absorption. The effects following intravenous injection are related to both dose and rate of administration (Javaid et al. 1978; Resnick et al. 1977; Fischman et al. 1976; Barnett et al. 1981). When injected rapidly, subjective and physiologic effects appear within 30 seconds, rapidly peak, and then decrease relatively rapidly over the next 30 minutes. Absorption, of course, is 100%. Rate of change, i.e., rapidity of injection, seems to be almost as important in determining subjective and physiologic effects as absolute blood levels. Rate and dose relationships have not been studied nor are the dose effect functions for most effects well worked out at cocaine dose levels much in excess of 0.6 mg/kg of body weight. A dose of that level injected over 1 minute will produce peak blood levels of between 300 and 400 ng/ml with brief but intense subjective effects. In contrast, a volunteer subject given four to five times that dose but distributing the injections over 60 minutes demonstrated peak cocaine levels of 1100 ng/ml but no greater subjective and cardiovascular measures than those produced by the much lower dose given over 1 minute (Fischman and Schuster 1982). Although the precise relationships between dose and rate of administration have not been investigated, one would expect that with a rapidly metabolized and rapidly redistributed drug like cocaine, rate might be as important as dose.

INHALATION: SMOKING

The very intense and relatively brief cocaine effects that follow the smoking of cocaine probably reflect the fact that the smoking of any drug is a very efficient way of delivering it in a very concentrated bolus to the brain (Jeri et al. 1978; Paly et al. 1982; Siegel 1982). The alveoli of the lung offer an enormous area for the absorption of the volatilized cocaine. More important perhaps in its appeal to certain users is that the circulation time from lungs to brain is about 8 seconds while from arm to brain it is at least 16 seconds. Even then an intravenous injection in an arm vein must first pass through the left heart, lungs, and right heart before reaching brain, with ample time for distri-

bution and metabolism by blood cholinesterases before brain is reached. The probable efficiency of smoking varies with the technique used (Jeri et al. 1978; Perez-Reyes et al. 1982). Most smoking techniques do not allow for precise temperature control, and variations from optimal pipe temperature may either make for low delivery or destroy most of the available cocaine.

The intense, pleasurable, and hence reinforcing, effects which sometimes lead to surprisingly frequent, compulsively repeated use should not be unexpected if similar patterns of tobacco use are considered. Although taking tobacco orally by chewing or by snuff will satisfy the nicotine craving of some tobacco-dependent individuals, most tobacco smokers would agree that the first few inhalations of the day are really quite different and are a special way of delivering nicotine to the brain. There is at least a partial analogy when comparing the various alternate routes of administration of cocaine. For smoking, the conversion of cocaine from its more common salt to the base is necessary because the physical chemical characteristics of the base, stability particularly, are more desirable. The toxicity that develops with smoked high-dose use is not well understood in terms of mechanisms (Siegel 1982).

Given that both liver and blood contain enzymes that metabolize cocaine, one might well expect differences in metabolism depending on route of administration. The metabolic profiles, particularly of benzoylecgonine and ecgonine methyl ester as they may differ by route, have not yet been determined, mainly because suitable plasma assays have only recently become available. The terminal half-life of cocaine, that is, the amount it takes for half of the material to be eliminated, is about 60 to 80 minutes no matter what the route, though there is tremendous variability both within and between subjects at any given route.

TOXICITY

Sometimes consideration of the acute and chronic toxicity of a drug will give insights into its modes of action. When cocaine is used for anesthesia, toxic reactions are not common. For example, a survey of American plastic surgeons found only five fatalities and 34 severe reactions out of a total of over 108,000 patients given topical cocaine. However, even under the relatively controlled conditions of the operating room, the mechanism of toxic reactions is still not well understood. Simple overdose does not seem to be the most common determinant and factors leading to rapid absorption may be more important (Campbell and Adriani 1958; Pearman 1979). Various authorities have estimated maximum safe doses of cocaine between 100 and 300 mg when administered topically (Pearman 1979). Doses in that range are in common use in experimental situations with normal volunteers without untoward effects, so those figures must be conservative ones.

The features of acute cocaine poisoning include profound central nervous system stimulation progressing to preconvulsive movements, then convulsions and cardiovascular and respiratory failure.

Although probably a more common sequelae after intravenous administration, deaths occur after cocaine taken by virtually any route if the dose is large enough (Bar-Or and Wahby 1982; Bednarczyk et al. 1980; Bettinger 1980; Dimaio and Garriott 1978; Fishbain 1982). Postmortem tissue levels, particularly blood levels, vary greatly because of cocaine metabolism postmortem, so the establishment of precise toxic doses is difficult (Fletcher and Hancock 1981; Jatlow et al. 1979; Lowry et al. 1979). The sudden death following cocaine administration may occur so rapidly that treatment is not available. In dogs (Catravas and Waters 1981) and in primates Guinn et al. 1980) chlorpromazine, possibly because of its antidopaminergic, antiadrenergic, sedative, and antihyperthermic effects, and diazepam, possibly because of anticonvulsant and sedative effects, appear useful in the treatment of acute cocaine intoxication. Symptomatic treatment of the respiratory and cardiovascular depression, of course, is important as well. Although beta blockers have been recommended in the treatment of early cocaine toxicity (Rappolt et al. 1978) in the animal studies, propranolol seemed to be of little use in modifying the consequences of high doses.

Because of the potentiation of catecholamine effects by cocaine, one might assume potentially toxic interactions with drugs or conditions where adrenergic activity plays a role (Smith 1973; Coleman et al. 1982). Curiously, although neuroleptics seem to diminish or block cocaine effects (Colpaert et al. 1978; Catravas and Waters 1981), tricyclic antidepressants, which might be expected to potentiate the effects of cocaine, seem to diminish some vasoconstrictor effects (Schecter et al. 1982), and diminish acute cardiac toxicity in rats (Antelman et al. 1981).

TOLERANCE AND DEPENDENCE

It is often said and written that tolerance to cocaine does not occur and that dependence as manifest by "physiologic" withdrawal signs does not occur. Both these beliefs are firmly reinforced by authoritative reviews and are probably incorrect. Discussions of cocaine tolerance usually start by citing the extensive evidence of seemingly increasing sensitivity to cocaine effects (Ellinwood and Kilbey 1980; Post 1975; Post et al. 1976, 1981; Stripling and Hendricks 1981; and many others). There has been less emphasis on data consistent with the development of more traditional tolerance, i.e., diminished effects with repeated doses (Branch and Dearing 1982; Teeters et al. 1963). Decreases in some cocaine effects with repeated doses are not necessarily inconsistent with the concomitant increased intensity in other effects, for example, kindling, indicating a sensitization to cocaine.

Tolerance must involve a variety of adaptive mechanisms and changes. It is reasonable to assume that some of these adaptive changes to the presence of the drug OK its metabolites might appear as increasing effects while at the same time other effects are decreasing. Only in the very special case where tolerance to a drug can be accounted for mainly by more rapid or complete metabolism is the coexistence of disappearing acute effects and

the gradual enhancement of other consequent effects not plausible. In the case of cocaine, dispositional changes or changes in the metabolism of the drug do not seem to be sufficient explanations for the phenomenon of tolerance when it appears.

Cocaine is a relatively short-acting drug. Optimal conditions to produce tolerance require a Constant presence of the drug in the body, particularly if the measures of tolerance are not sensitive ones, as may be the case in some animal studies. It may be that once daily or three times daily doses as have been used in animal studies are not always sufficient to produce tolerance. From the very earliest accounts of cocaine use in humans, in those instances where it was used frequently, diminished effects are commonly reported and are now being observed in controlled laboratory situations (Fischman and Schuster 1981).

In humans the progressive increases in irritability, restlessness, hypervigilance, paranoid and suspicious behavior associated with prolonged high-dose cocaine use may be the human correlate of the kindling phenomenon observed in some animal experiments. The psychoses Seen after sustained amphetamine use and after cocaine use are similar and thought to be a useful model in the study of naturally occurring schizophrenic psychoses (Post et al. 1976). such a state, i.e., Concurrent increasing and decreasing sensitivity to a drug, certainly does not fit the simplistic model of what tolerance to a drug should represent, On the other hand, if one conceives of tolerance as involving a number of mechanisms adaptive in one sense and perhaps maladaptive in another sense (if neurochemical changes produce a psychosis), then what is commonly observed clinically fits. Whether people with a genetic predisposition for schizophrenia are at more risk to cocaine-induced psychoses has not been determined. Whether metabolic explanations are relevant, likewise has not been determined. Curious inconsistencies appear-for example, the sustained and, at least as measured by plasma levels, relatively high dose yet relatively nontoxic use of cocaine by the Quechua Indians. Animal studies indicate that coca leaf contains constituents other than cocaine that alter its pharmacology (Bedford et al. 1982,1981). Does the whole leaf have something that serves as a protective device for the Quechua? Is it bioavailability? Is it a matter of cultural difference?

As clinical observations accumulate, the existence of a true withdrawal syndrome following cocaine use seems compelling. The depression, Social withdrawal, craving, tremor, muscle pain, eating disturbance, electroencephalographic changes, and changes in Sleep patterns must be more than simply the consequence of what traditionally has been termed "psychological dependence." When listening to descriptions of this state by cocaine-using patients, these dysphoric and often dramatic Symptoms must be viewed as negative reinforcers. For many patients it appears that the withdrawal symptoms are a major consideration that makes discontinuing cocaine almost impossible so long as the drug is available. Yet continuing the drug produces unacceptable irritability, paranoid and delusional thinking, and other unpleasant effects.

This cocaine-induced state becomes of theoretical importance in terms of model building as well as a practical consideration in treatment. Many of the current models, particularly those involving explanations for stimulant drug administration, tend to consider mainly positive reinforcement with only minimal attention to negative reinforcement because of what increasingly appears to be the inappropriate belief that tolerance does not develop and dependence does not follow the withdrawal of stimulant drugs. The differences between so-called physical dependence and so-called psychological dependence may be more a matter of semantics and sensitivity of measures than of neurochemistry. Most investigators would concede that psychological dependence certainly is a consequence of repeated cocaine use.

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AUTHOR

Reese T. Jones, M.D.
Drug Dependence Research Center
Langley Porter Psychiatric Institute
University of California, San Francisco
San Francisco, California 94143

Assessment of the Dependence Potential of Cocaine in Animals

Chris E. Johanson

INTRODUCTION

The illicit use of cocaine has increased dramatically over the last decade. The discussions, articles, and songs about cocaine in popular literature and the media are excessive, and few would disagree that cocaine is the most infamous drug of abuse in the United States today. Although actual use of other illicit drugs such as marijuana may exceed the use of cocaine, this is most likely due to cost and availability rather than preference. A myriad of factors are responsible for the meteoric rise in cocaine's popularity. One factor often cited is the association of cocaine with glamorous and highly successful segments of society such as movie stars, recording artists, and the ultra-rich. While such an association without a doubt contributes significantly to the popularity of cocaine, the drug itself, in the absence of these influences, has high dependence potential. In this paper, the experimental evaluation of cocaine's dependence potential will be reviewed, and it will be concluded that there is strong evidence demonstrating that cocaine is a drug of extremely high dependence potential. It is understandable that this characteristic of the drug coupled with social factors arising from its association with success and glamour would lead to the present disturbing level of abuse.

Two components are essential in the experimental assessment of the dependence potential of any drug. The first is the demonstration that the drug will be voluntarily self-administered by the experimental subject or, in the terminology of behavior analysis, that the drug has positive reinforcing properties. An event such as drug self-administration is considered a positive reinforcer if it increases behavior leading to its delivery or decreases behavior resulting in its withdrawal. More generally speaking, behavior is controlled by its consequences, including the administration of a drug. A variety of studies have shown that most drugs abused by humans also increase behavior leading to their self-administration in an experimental situation (Johanson and Balster 1978; Griffiths et al. 1980; Johanson and Schuster 1981). The reinforcing properties possessed by a drug are not a static pharmacological characteristic. They are the result of a dynamic interaction between the event and the environmental context of its administration. The dependence potential of a drug is directly related to the range of

conditions under which it functions as a reinforcer as well as the extent to which it controls behavior compared to other drug or nondrug reinforcers.

A second component in the assessment of the dependence potential of a drug is the demonstration that at doses which are voluntarily administered there are toxic consequences to the organism. This toxicity could include changes in morphology, biochemistry, sensory processes, or a vast array of behaviors, as well as the development of tolerance or physical dependence. All drugs produce toxicity but the important issue is the relationship and degree of overlap between reinforcing and toxic doses. In conclusion, the dependence potential of a drug such as cocaine can be assessed by measuring the range of conditions under which it functions as a positive reinforcer and the strength of its reinforcing properties relative to other drugs plus the degree of deleterious consequences produced by the self-administered drug at both individual and societal levels.

To assess these properties of a drug, it is essential to develop an experimental model capable of analyzing the variables controlling both excessive self-administration and its consequences in a simple enough situation that functional relationships between independent and dependent variables emerge clearly. Although more complex situations, which build upon and combine these relationships, can then be studied in order to understand their potential interactions, they can never reach the complexity of nonlaboratory settings and still produce unambiguous results. To a large degree, the experimental model which has been most extensively developed uses animal subjects, such as rats and rhesus monkeys, but it is desirable that the results are not species specific. The organism selected for a model of drug abuse would not have to be nonhuman. In fact, human self-administration studies in controlled laboratory settings have been increasing in number and are important for validating animal studies. However, using animals has several advantages. The range of manipulations possible with animals allows experiments to be done that would be impossible using human subjects. In addition, using animals in the study of behavioral influences on drug self-administration assists investigators in divesting themselves of psychological preconceptions and in being less prone to use vaguely defined hypothetical constructs as an explanation of drug self-administration (Schuster et al. 1979).

The continued use of the animal model which has been developed over the last 20 years is due to demonstrations of its validity (Johanson and Schuster 1981). Most important, drugs which are self-administered by animals in a laboratory situation are the same as those commonly abused by humans (Johanson and Balster 1978). These include psychomotor stimulants, opiates and opioids, sedative-hypnotics, alcohol, and some but not all hallucinogens (e.g., phencyclidine). In addition, the effects of environmental and pharmacological manipulations leading to changes in the degree of self-administration are similar in infra-humans and humans (Griffiths et al. 1980; Johanson and Schuster 1981). This concordance has led to the acceptance of the animal model as a valid predictor of dependence potential (Thompson and Unna 1977). In the

present paper, the use of this animal model to assess the dependence potential of cocaine will be reviewed.

METHODOLOGY

Prior to reviewing the experimental studies on the reinforcing properties and toxic consequences of cocaine in animals, a brief description of the methods is necessary. Cocaine is taken by humans by a variety of routes, including the oral, intranasal, and intravenous, as well as by inhalation (smoked as the base). Although cocaine is self-administered principally by the intranasal route in humans, the intravenous injection of cocaine is not uncommon. For technical reasons, however, this route has been more extensively utilized in experimental studies.

Techniques for the intravenous delivery of drugs to animals were originally described for rats by Weeks (1962) and for rhesus monkeys by Yanagita et al. (1965). Such systems have several fundamental aspects: (1) the chronic implantation of a venous catheter into the organism to allow immediate delivery of a drug; (2) an experimental arrangement that allows the organism relatively unrestricted movement, yet still protects the catheter; and (3) an automatic programming system for the delivery of drug, contingent upon some response by the animal. The salient feature of this type of system is that it is possible to deliver a drug with minimal delay into a vein without disturbing the animal.

Several designs incorporating these features have been used. In our laboratory, for instance, rhesus monkeys are fitted with a tubular steel harness which is connected to the wall of a large chamber by a metal spring. This arrangement allows the monkey to move relatively freely within the confines of the chamber. The catheter runs through the metal spring and is connected outside the chamber to a pump. The chamber is also equipped with response levers and lights signalling drug availability, all of which are controlled by electronic equipment.

THE REINFORCING PROPERTIES OF INTRAVENOUS COCAINE

In this section, the range of conditions under which cocaine has been shown to function as a positive reinforcer, i.e., to maintain responding, will be reviewed. The purpose of this review is to demonstrate that the number of experimental contexts where cocaine is self-administered is far ranging. It would be difficult to quantify the extent of this range simply by counting studies, but it is generally believed by researchers in the area that cocaine is one of the most reinforcing drugs. Although rigorous experimental proof of this contention is not easy to demonstrate, there is anecdotal evidence of cocaine's strength. For instance, most researchers use cocaine to train experimentally naive animals to self-administer drugs. Further, in most substitution studies, regardless of the drug(s) being evaluated, cocaine is used as the baseline drug because responding is so readily maintained (Johanson and Balster 1978). Finally, researchers embarking on a new area of behavioral research often select cocaine as the first drug to evaluate. For instance, except for alcohol, early studies on the effects of punishment on drug-taking behavior used cocaine (e.g., Grove and Schuster 1974).

In addition to demonstrating the ubiquitous quality of cocaine's reinforcing properties, this review will also show that behavioral variables such as schedule of presentation are exceedingly important in the way cocaine controls performance. Responding leading to cocaine delivery is controlled in much the same way as responding leading to the delivery of nondrug reinforcers. This qualitative similarity has important implications for understanding the behavioral mechanisms of action of drug reinforcement.

One of the first studies to investigate cocaine as a reinforcer was conducted by Wilson et al. (1971). Rhesus monkeys were given 4 hrs of daily access to cocaine during which each lever press resulted in drug delivery. Under these limited access conditions, animals regulated their drug intake to a remarkable degree. After animals were trained, they showed stability in their daily intake of cocaine over periods of months. There were no indications of changes in sensitivity to cocaine's reinforcing effects as would be indicated by an increase (tolerance) or a decrease (supersensitivity) in its rate of self-administration. Wilson et al. (1971) also demonstated the constancy of cocaine intake by changing the dose delivered for each lever press. As dose per delivery was increased, the number of infusions taken by the animals decreased, resulting in an almost constant intake of drug regardless of the dose per infusion. Regulation was also evident in the pattern of cocaine self-administration. Infusions were equally spaced throughout the session almost as if the drug were being delivered under the control of a clock. While most animals who administered cocaine showed clear signs of stimulation (e.g., piloerection, agitation), convulsions rarely occurred except in the beginning stages of training.

The results of this study by Wilson et al. (1971) have been replicated in a number of ways. What is impressive is the generality of the phenomenon. For instance, cocaine is self-administered by every species of animal tested, including rats (Pickens and Thompson 1968), squirrel monkeys (Goldberg 1973; Stretch 1977; Katz 1979), rhesus monkeys (Woods and Schuster 1968), pigtail macaques (Young and Woods 1980), and baboons (Griffiths et al. 1975), as well as dogs (Risner and Jones 1975; Risner and Silcox 1981; Risner and Goldberg 1983). This concordance across species is one type of evidence of the robustness of cocaine's ability to function as a reinforcer. A second type of evidence is that cocaine maintains responding regardless of its route of delivery. Allthough the i.v. route has been used most commonly, cocaine also maintains responding when delivered intragastrically (Altshuler and Phillips 1978; Woolverton and Schuster 1983), by chewing or smoking (Siegel et al. 1976), and even intramuscularly (Katz 1980; Goldberg et al. 1976). The failure to demonstrate that animals will snort cocaine is more likely a function of experimenter skills and absence of appropriate technology than of any difference across species.

Cocaine self-administration not only occurs with a variety of species and using several routes of administration but also under a variety of environmental circumstances. In the terminology of behavior analysis, this can be translated into schedule contingencies, i.e., the rule that governs the relationship between behavior and the delivery of the

reinforcer. As will be shown, the nature of that rule can have an overwhelming influence on the reinforcing properties of a drug. In the simplest schedule, continuous reinforcement (CRF), every response is followed by a reinforcer (e.g., Wilson et al. 1971). However, the relationship between responding and reinforcer may be more complex. A response may be reinforced on the basis of the number of responses emitted since the termination of the previous reinforcer delivery (a ratio schedule), or on the basis of the time elapsed since the last reinforcer delivery (an interval schedule). A ratio or interval schedule may either be fixed or vary in number or time. Four basic schedules, then, are fixed ratio (FR), variable ratio (VR), fixed interval (FI) and variable interval (VI). In addition to these, there exist numerous other possibilities for relating responding and the delivery of the reinforcer, i.e., schedules of reinforcement (Ferster and Skinner 1957).

Many studies have shown that cocaine maintains responding under fixed ratio schedules (Downs and Woods 1974; Balster and Schuster 1973a). The pattern of responding, typical of performance maintained by other events such as food and water (Ferster and Skinner 1957), is characterized by an initial pause followed by a high terminal rate of responding. Although the pattern of ratio responding maintained by cocaine is similar to that maintained by other events, the rates of responding typically found in drug self-administration studies have been low compared to rates maintained by food, and increases in dose/delivery further decrease rates (Kelleher 1975). In many studies, however, rates are higher at the beginning of the session (Downs and Woods 1974). This generally low or decreasing rate is most likely due to the dual actions of the drug (see Johanson and Schuster, 1981, p 233, for a complete discussion). On the one hand, cocaine serves as a reinforcer which increases rates of responding, but on the other hand the drug has the ability to temporarily disrupt ongoing behavior (Wilson and Schuster 1975; Spealman et al. 1977; Herling et al. 1979) and thus have a rate-decreasing effect. Since increased responding under ratio schedules results in increased rates of drug intake, the problem is particularly striking under this schedule. Several techniques have been used to avoid these effects while still using response-based, rather than time-based schedules. Goldberg and Kelleher (1976), for instance, limited the number of infusions available each session and, as well, imposed a time-out following infusions. These modifications resulted in much higher rates of responding.

Cocaine has also been demonstrated to maintain responding under fixed interval schedules. An important feature of interval schedules is that rates of responding can change considerably without affecting rate of reinforcement. One of the first studies using an interval schedule of drug delivery in monkeys was done by Balster and Schuster (1973b). They used a fixed interval 9-min schedule with responding maintained by cocaine infusions in one component and food delivery in the other. In addition, there was a 15-min time-out following the delivery of each reinforcer. Responding was well maintained and the pattern with cocaine was similar to that maintained by food. In contrast to ratio schedules, as dose per infusion increased, rate of responding increased. Similar results were found in a study by Goldberg and Kelleher (1976) using a

fixed interval 5-min schedule of cocaine delivery. However, response rates increased only up to a dose of 0.5 mg/kg and then decreased as dose was further increased. This difference was most likely due to the more frequent injections in the Goldberg and Kelleher (1976) study. Again despite the powerful nature of the contingencies governing reinforcer delivery in controlling responding, the nonspecific rate-modifying actions of cocaine also exerted an influence.

Several studies with cocaine as well as other drugs have used second-order schedules as a way of minimizing the direct effects of drug administration in order to get a less confounded estimate of a drug's reinforcing actions. In this type of schedule, responding specified by one particular schedule is treated as a unitary response that is itself reinforced by another schedule (Kelleher 1966). The responding treated as a unitary response can also be followed by the presentation of a brief stimulus paired with the delivery of the reinforcer. Goldberg, (1973) using squirrel monkeys, studied responding maintained by cocaine and d-amphetamine as well as food under a fixed ratio 30 schedule of stimulus presentations (2-sec yellow light), which itself was maintained under a fixed interval 5-min schedule of drug or food delivery. This schedule was designated a second-order (FI 5-min (FR 30:s)). When either drug was used to maintain responding, rates of responding were extremely high and performance was ratio-like between stimulus presentations. Furthermore, early in the interval, overall response rate was relatively low but accelerated as the interval progressed, which is the pattern of responding typical of fixed interval performance maintained by diverse reinforcing events. For instance, in the same study, responding maintained by food was virtually identical in both pattern and rate. Several additional studies have been conducted with this schedule using both squirrel and rhesus monkeys. Typical responding has been maintained under FI (FR) schedules by intravenous and intramuscular cocaine as well as with fixed ratio schedules of fixed interval components (Goldberg et al. 1981; Kelleher and Goldberg 1977; Goldberg and Kelleher 1977; Goldberg et al. 1975). Furthermore, in many studies, high rates of responding were maintained even when only one cocaine reinforcer was delivered at the end of the session (Goldberg et al. 1976; Katz 1979,198O).

Kelleher and Goldberg (1977) demonstrated the importance of the brief stimuli in maintaining responding under second-order schedules. When these stimuli were removed following the FR components but the drug was still delivered, rate declined and patterning was disrupted. If both drug delivery and the brief stimuli were removed, responding declined even further. However, when the brief stimuli were then reinstated without the drug, responding increased. Similar results have been found in other studies including ones with intramuscular cocaine (Katz 1979). Whether such rates would be maintained over long periods of time is not known. In order to determine whether the stimuli used in second-order schedules derive their ability to maintain responding from their association with drug, Goldberg et al. (1979) compared the response maintenance properties of drug-paired and unpaired stimuli. In this study both intravenous cocaine and morphine maintained typical responding under FI (FR) schedules in squirrel monkeys. Removing the

stimuli decreased rates and disrupted the pattern of responding. When new stimuli were presented at the completion of the FR components but never in association with the terminal ratio when drug was injected, response rate also declined. Therefore, it is not the presentation of a stimulus per se that maintains responding in these second-order schedules but rather the response-contingent presentation of a stimulus associated with the drug delivery. However, although Katz (1979) also showed that the substitution of unpaired stimuli decreased responding, the magnitude of the decrease was not so great as when stimuli were totally absent. The fact that both the drug and the stimuli are determinants of the rate of responding may explain the results when dose is manipulated with this schedule. Although there is some tendency for rate to increase with increases in dose, in general, dose-response functions are flat relative to those generated by other schedules. Therefore, the strength of cocaine's ability to control responding does not seem to change with its magnitude (dose) under second-order schedules. On the other hand, since rates are often high under such schedules, there are limits to the possible increases.

Two related procedures or schedules that have been used to compare different doses of cocaine in the absence of any confounding influence are concurrent schedules and preference procedures. In these procedures responding on different levers is maintained by different doses and the primary dependent variable is the relative frequency of occurrence of the alternative responses. These procedures have also been used with other reinforcers such as food and intracranial stimulation and have been found to be sensitive to differences in reinforcer magnitude.

With concurrent schedules, responding is maintained by two or more simultaneously operating schedules. In a study by Iglauer and Woods (1974), responding was maintained in rhesus monkeys under a concurrent two-lever VI schedule of cocaine injections with a 5-min time-out following each injection. In this study, relative reinforcing efficacy was evaluated by comparing relative response frequencies on the two levers. A standard dose of cocaine (0.05 or 0.1 mg/kg) was available under a variable interval 1-min schedule on one of two levers: the dose available under an identical schedule on the second lever (variable-dose lever) was varied to include both higher and lower doses of cocaine (0.013 to 0.8 mg/kg). The proportion of responses occurring on the variable-dose lever increased as the dose available on that lever increased; in all cases, the larger of the two doses presented for comparison was preferred.

Another method designed to compare reinforcing properties involves the use of discrete choice trials. In a study by Johanson and Schuster (1975), rhesus monkeys were given an opportunity to choose between two drug solutions, and injections were followed by a 15-min time-out period. The number of trials during which one option rather than the other one was selected was counted and used as the measure of reinforcing efficacy. As in the Iglauer and Woods (1974) study, higher doses of cocaine were preferred to lower doses. Similar results have been found by Brady and Griffiths in baboons (1977).

From this review two overall conclusions can be stressed. First of all, cocaine self-administration occurs under a variety of experimental situations and is not restricted to a narrow range of conditions. Unfortunately it is impossible in the absence of direct comparisons to conclude that the strength of cocaine's reinforcing properties is unique to cocaine. However, the ubiquitous use of cocaine in experimental studies reflects not only an interest in this drug but as well the ease of conditioning animals to self-administer it so that other variables can then be studied. The second point is that the pattern of cocaine self-administration and the circumstances under which it occurs are similar to behavior controlled by nondrug reinforcers, such as food and water. Although the direct or nonspecific actions of drugs can markedly affect absolute rates of drug-maintained responding, by manipulating schedule parameter values or using nonrate measures, dose-response functions indicate that response strength increases with dose. Of particular importance is the demonstration that persistent and excessive drug-seeking behavior is determined by an interaction between the drug's schedule of presentation and its specific pharmacological properties. This means that our general knowledge of how behavior is controlled may be useful in understanding the mechanisms of cocaine self-administration.

TOXICITY

Regardless of the nature of a drug's reinforcing properties and predicted dependence potential, there would be little public concern or action if the use of cocaine at the levels determined by the organism did not lead to toxicity. Deleterious consequences resulting from the drug self-administration of any drug can range from death to subtle changes in the ability of the person to cope with environmental demands. Any drug can cause serious damage if given in excessive doses over extended times, so the assessment of toxicity must include judgments of relative risks. Clearly, in the case of recreational drugs where there is not therapeutic justification, the safest option is to use no drug.

Despite the importance of toxicity studies, there have been only a few studies in which the toxic consequences of cocaine self-administration have been systematically evaluated (Deneau et al. 1969). Most of the studies reviewed in the previous section examined cocaine self-administration under conditions of limited access. Under these conditions intake is remarkably well regulated and signs of drug toxicity are seldom seen even when drug availability continues on a daily basis for years. However, these conditions of access are determined by the experimenter, not the organism. In contrast, in a study by Johanson et al. (1976), access to drug was not limited; regulation disappeared and extreme and somewhat unexpected toxicity was produced. More specifically, naive untrained rhesus monkeys were exposed to continuous around-the-clock access to one of a variety of psychomotor stimulant drugs in order to simulate conditions of availability in humans. In addition to measuring drug intake, food intake was monitored and behavioral observations were made. For two monkeys, each lever press resulted in the infusion of 0.2 mg/kg cocaine. Both monkeys began taking drug the very first day of its availablity and the number of infusions self-administered per day ranged from 100 to 500 (a total of 20 to 100 mg/kg). However, both

monkeys died following convulsions after 3 to 5 days of access. Food intake was almost totally suppressed during this period and behavioral changes including restlessness, stereotypic movements, dysmetria, tremors, mydriasis, piloerection, and ataxia were observed. Similar results were also noted with amphetamine and related drugs. Although there were indications that some amphetamine-like drugs had less toxicity than cocaine, the number of monkeys tested was too small to verify this conclusion. Furthermore, in a similar study by Downs et al. (1979), the authors claim that the toxicity of cocaine in amphetamine-experienced monkeys was not as great (2 of 3 died) and was less than that of methylphenidate (3 of 4 died). Unfortunately, except for weight loss, the condition of the surviving monkey on cocaine was not described, but its drug intake was low relative to the other monkeys. Taken as a whole, despite minor differences, these studies would indicate that under conditions where there are no outside restraints on drug availability, animals can suddenly increase their drug-taking behavior to the point of severe toxicity. In contrast, the intake of cocaine under other conditions (i.e., limited access) is surprisingly regulated. These differences may very well have implications for resolving the argument between those who claim that cocaine is a safe recreational drug and those who describe cases where users appear to "lose control" of their drug taking. Some people may regulate their cocaine use either by limiting their access or by a variety of other means and, like monkeys maintained on cocaine for years, remain healthy. Others, however, for reasons we do not understand, are described by clinicians as losing control. The toxicity which is then produced can be extreme.

OTHER FACTORS CONTRIBUTING TO DEPENDENCE POTENTIAL

Factors which contribute to the loss of regulation in an individual could either be internal (e.g., personality) or external. Although we may not understand all these factors, two lines of experimental evidence give us some clues. The first is that the reinforcing properties of cocaine, despite qualitative similarity to other reinforcers, are relatively powerful. The second is that some of the acute effects of cocaine in improving performance are seductive. That this indirect effect may wane with time and increased dose is not always appreciated.

In addition to the studies reviewed in the previous sections, there have also been numerous studies designed to directly compare the strength of the reinforcing properties of cocaine to other reinforcers, both drug and nondrug. It is assumed that there is a direct relationship between relative reinforcing properties and degree of dependence potential. Therefore, if experimental studies demonstrate that the strength of cocaine's reinforcing properties is extreme, it may be concluded that this property is one important factor contributing to its excessive illicit use. While there is a good deal of evidence that would lead to this conclusion, as will be described below, the assessment of relative reinforcing properties is difficult and time-consuming and only a few drugs have been evaluated. Many more studies would be required to show that cocaine is a uniquely powerful reinforcer, relative to others, particularly since it is unlikely that rankings are static. As emphasized before, reinforcing properties are a result of a dynamic interaction

between the drug and the environmental contingencies, and this is no less true when comparisons across reinforcers are made.

Two types of procedures have been used with animals to measure the reinforcing strength or efficacy of different drugs. One procedure which has been used extensively to compare drugs, including cocaine, is the progressive ratio schedule. In this schedule, responding is maintained by a drug under a ratio schedule. After responding is well established, the number of responses required for each drug infusion is systematically increased until responding declines to below some criterion, i.e., animals at these high ratios no longer continue to respond in order to get the drug. The ratio value which leads to this cessation in responding is called the breaking point. Although responding is maintained under a ratio schedule, the breaking point, not rate of responding, is used as the index of reinforcing efficacy. It does not matter how long an animal takes to complete the ratio (within limits) but simply whether or not it is finished. Using this procedure, Yanagita (1973) demonstrated that breaking point was a direct function of the dose of cocaine. At the highest dose of 0.48 mg/kg, animals continued responding even when 6,400 to 12,800 responses had to be made for each drug infusion. Cocaine's breaking point was 2 to 16 times higher than that for methamphetamine and amphetamine. Similar results were found by Bedford et al. (1978). Griffiths et al. (1975, 1978) determined that the breaking point for cocaine was higher than for other stimulant or anorectic drugs including methylphenidate, diethylpropion, chlorphentermine, and fenfluramine. However, secobarbital at the highest dose tested showed reinforcing properties comparable to cocaine. Studies using dogs have also demonstrated that cocaine sustains responding at higher FR values than. d-amphetamine, mazindol, fenfluramine (Risner and Silcox 1981), or nicotine (Risner and Goldberg 1983). It can be concluded from these studies that the reinforcing strength of cocaine is high.

Similar results have been found using a choice procedure (Johanson and Schuster 1975). In this procedure, described in a previous section, the number of trials during which one option rather than the other one is selected is used as the measure of reinforcing efficacy in much the same way as breaking point is used in the progressive ratio procedures. Similarly, this index is independent of rate of responding. It was found, as might be expected, that higher doses of cocaine were preferred to lower ones. In addition, while preference between cocaine and methylphenidate was dose dependent (Johanson and Schuster 1975), cocaine was generally preferred over diethylpropion (Johanson and Schuster 1977) and procaine (Johanson and Aigner 1981). Interestingly, in a choice procedure comparing cocaine to d,l-cathinone, these two drugs had similar efficacy (Woolverton and Johanson 1984). Cathinone, like cocaine, is the active alkaloid of a plant which is chewed recreationally by inhabitants of Africa and the Middle East. In many countries the chewing of the khat leaves has been a source of concern for years. However, unlike coca leaves, khat leaves must be chewed fresh, and the active alkaloid, cathinone, has only recently been isolated. Given the similarities between cathinone and cocaine and the results of

Woolverton and Johanson (1984), we would predict that cathinone, if it became available, would also be extensively abused.

In addition to comparisons between cocaine and other drugs, there have also been choice studies utilizing alternative nondrug reinforcers. For instance, monkeys preferred even low doses of cocaine to the opportunity to have visual contact with other monkeys (Woolverton, personal communication). Even more compelling, monkeys given a choice between food and cocaine preferred the latter and without experimenter intervention might have starved (Aigner and Balster 1978). Although clearly far more studies of this type are necessary, their implications are profound. Cocaine may be such a powerful reinforcer that the survival of the organism is threatened and therapeutic interventions designed to develop alternative life-styles (i.e., reinforcers) will have difficulty succeeding.

An alternative approach to assessing the strength of a reinforcer is to determine its resistance to the effects of punishment. The effects of punishment on behavior controlled by a variety of events other than drugs have been studied extensively. Punishment is a process of reducing the probability of a response as a consequence of: (1) the presentation of a stimulus or (2) the removal of a stimulus contingent on the response. In animal studies, the most frequently used punishing stimuli have been electric shock delivery and time-out from positive reinforcement. The degree of response suppression is dependent upon the intensity of the punishing event and its schedule of presentation, as well as the time delay between response and consequence. All else being equal, it could be assumed that the greater the difficulty in decreasing the self-administration of a particular drug, the greater is its reinforcing strength.

The effects of punishment of cocaine self-administration have been demonstrated in several studies. Grove and Schuster (1974) examined the ability of punishment to suppress responding maintained by cocaine injections in monkeys under a FR 1 schedule during daily 3-hr sessions. Punishment was accomplished by delivering a brief electric shock ranging from 1 to 8 mA at the onset of each injection. Responding maintained by both 0.1 and 0.2 mg/kg cocaine decreased as a function of the intensity of the shock. However, the degree of suppression expressed as a percent of control rates was the same for the two doses. That is, increasing the magnitude of reinforcement did not seem to attenuate the effects of punishment as might be expected if one assumes that higher doses of cocaine have greater reinforcing efficacy. This finding, however, is difficult to interpret because the baseline rates of responding maintained by the different doses of cocaine were not the same. Because responding was maintained under a ratio schedule, the rates maintained by the higher dose were lower.

In a study by Bergman and Johanson (1981), responding was maintained in rhesus monkeys by 0.1 mg/kg cocaine under a FR 10 schedule. During single test sessions, the onset of each infusion was accompanied by the delivery of electric shock. At intermediate intensity levels, the shock initially reduced, but did not eliminate, cocaine-maintained responding. Although test sessions with electric shock were separated by at least

three nonpunished sessions, adaptation to the suppressant effects of the shock occurred within five punishment test sessions for all monkeys. On the other hand, adaptation did not occur with higher intensity levels that had produced complete response suppression. This may imply that for punishment to be effective, it must be severe enough to initially eliminate all drug-taking behavior. It may also imply that cocaine self-administration is difficult to punish.

Further evidence of this is also shown in a study by Johanson (1977) using the discrete trial choice procedure previously described. Rhesus monkeys were given a choice between two alternatives of intravenous cocaine. These alternatives were initially equal in dose, but in subsequent comparisons they differed in magnitude. Electric shock was delivered at the onset of the delivery of one of the alternatives. When the two doses were equal, the nonshocked alternative was chosen. For some animals, the shocked alternative was preferred even when the dose of this alternative was only twice as high. Other animals continued to select the nonshocked alternative. However, as the dose of the shocked alternative further increased, all animals preferred the higher dose. It seems, therefore, that the effects of punishment can be overcome by increasing magnitude of reinforcement, and for some animals the necessary difference may be small.

The studies on the effects of punishment on cocaine self-administration lead to the conclusion that cocaine has strong and robust reinforcing properties. Unfortunately, comparable studies have not been done with other drugs so it is impossible to make any statements about relative strength in this context. While comparisons across drugs within the same class may be useful in the assessment of relative dependence potential, comparisons across drug classes may be difficult to interpret. This is because some drugs, delivered noncontingently, have differential effects on behavior that has been suppressed by punishment. For instance, certain drugs such as the barbiturates attenuate the suppressant effects of punishment, whereas other drugs such as the amphetamines generally do not. It would be interesting to determine whether these differential effects generalize to a situation where the drugs themselves also function as reinforcers. One might predict that under similar conditions, responding maintained by a barbiturate would be more difficult to suppress with punishment than responding maintained by cocaine.

Another demonstation that cocaine possesses strong positive reinforcing properties emerges from studies of conditioned taste aversions. If certain consequences (e.g., lithium chloride-induced illness) occur following the presentation of a novel fluid or food (e.g., saccharin solution) to an animal, the animal on subsequent presentations consumes less of that substance. This response has been termed conditioned taste aversion or gustatory avoidance conditioning. Initially, it was believed that only agents that induce illness could produce a gustatory avoidance response. However, subsequent studies have demonstrated that the administration of psychoactive substances including psychomotor stimulants can also induce this type of avoidance response (Cappell and LeBlanc 1978). Just as the valence of the reinforcing properties of electric shock can be

altered by environmental context (i.e., shock will maintain responding), even drugs which are positive reinforcers can have aversive properties under certain conditions (e.g., d-amphetamine). The effects of cocaine in this paradigm have been inconsistent. Some investigators report a weak efficacy (Booth et al. 1977; D'Mello et al. 1979; Goudie et al. 1978; Foltin et al. 1981; Foltin and Schuster 1982) while others report that cocaine produces no avoidance responses (Cappell and LeBlanc 1978). Although the reasons for the discrepancy are unclear, most investigators would agree that cocaine is a weak agent, at best, in inducing a gustatory avoidance response and its ability to do so is easily altered by minor changes in procedure (Foltin and Schuster 1982). In contrast, other drugs of abuse produce far greater aversions which are robust (Cappell and LeBlanc 1978). It is conceivable that the inability to modulate the positive reinforcing properties of cocaine may be another reason for its extreme dependence potential.

The studies that have been reviewed to assess the dependence potential of cocaine have evaluated the direct reinforcing properties of the drug. But drugs may also have dependence potential because of their indirect effects. For instance, if a drug improves performance necessary to the well-being of a person, the desire to use the drug regardless of its other effects may increase. A drug with both direct positive reinforcing properties and indirect ones may have the greatest dependence potential of all.

Since cocaine was first used experimentally, its ability to enhance performance has been extolled (Freud 1884). There are many anecdotal reports of enhancement, and the effects reported by cocaine users not only include feelings of euphoria but also include claims of greater skills across a variety of dimensions. Experimental evidence substantiating these anecdotal claims is limited, but it does lend some support to the hypothesis that "things go better with" cocaine. While many of these studies are with humans (see Fischman, this volume), animal studies also exist. In general, the effects of cocaine on operant performance are similar to those of other psychomotor stimulants (Kelleher and Morse 1968). Regardless of the event maintaining responding the effects of cocaine are rate-dependent, with low rates increased with low or intermediate doses and high rates decreased in a dose-dependent manner (Smith 1964; Spealman et al. 1977; Herling et al. 1979; Barrett 1976). This is true even when the effects of cocaine are evaluated using a self-administration paradigm (Spealman and Kelleher 1979). So although high doses may eliminate responding, there are lower doses which at least increase low-rate performance. Many other studies (e.g., Crow 1976; Schechel and Boff 1964; Torrelio and Izquierdo 1976) which have claimed that cocaine specifically enhances performance can also be interpreted within the context of rate dependency. Whether such increases in rate of responding can be used as evidence of enhanced performance is not clear. The use of other approaches not involving rate measures has received little attention in the animal literature. There is one report by Thompson (1977), however, showing that cocaine can increase breaking point maintained by food in pigeons.

Although the notion that cocaine enhances performance is widespread, particularly among users, it is clear that there is little experimental evidence in animals supporting it. To a large extent this is due to the fact that little research has been done in this area either in animals or humans (see Fischman, this volume). Additional studies will be required in this area to determine cocaine's effects on many types of performances, e.g., learning, motor, sensory, etc. Even if these studies were to demonstrate that acutely administered cocaine can improve performance, great care should be made in interpreting such findings. The effects of cocaine will always be dependent on dose and are likely to change with repeated exposure to the drug. Even if improved performance can be demonstrated with acutely administered cocaine, a deterioration in performance may be seen either with higher doses or when drug is repeatedly administered. But findings that acutely administered cocaine can have positive effects is important in understanding why humans use cocaine. That these enhancing effects may be transitory or dose-dependent does not negate their influence in producing subsequent drug use.

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AUTHOR

Chris E. Johanson, Ph.D.
The University of Chicago
Department of Psychiatry
950 East 59th Street
Chicago, IL 60637

The Behavioral Pharmacology of Cocaine in Humans

Marian W. Fischman

In 1977, in response to a perceived rise in the use of cocaine in this country, the National Institute on Drug Abuse presented an "...attempt to summarize our admittedly limited knowledge of cocaine through a series of reports by leading workers in the cocaine area" (Petersen and Stillman 1977, p. 1). One of the chapters in that monograph was entitled, "What are the Effects of Cocaine in Man?" (Byck and Van Dyke 1977). The most striking aspect of the response to that question was how little was actually known at that time. In fact, fewer than 10 laboratory studies investigating the effects of cocaine in humans were listed in the bibliography. Since then, the topic has received considerably more attention in several laboratories, allowing a more complete description of the behavioral pharmacology of cocaine in humans.

This paper reviews the available laboratory data on the behavioral and physiological effects of cocaine in humans. Since cocaine is self-administered via a number of different routes, wherever possible the effects of using this drug orally, intranasally, intravenously, and by smoking are described. A major theme in the self-reports of cocaine users is the insistence that they can do anything better under the influence of cocaine. The currently available data, reviewed in this paper, do not support this idea. In addition, since cocaine and amphetamine have very similar profiles of action, it is appropriate to use the laboratory data on amphetamine's effects to predict cocaine's effects. These, too, would not lead us to believe that cocaine is a good performance-enhancer. We would also predict that cocaine would have toxic and disruptive effects similar to those seen with amphetamine. Thus, the existence of a cocaine psychosis after repeated cocaine use is predictable on the basis of empirical laboratory evidence showing the development of an amphetamine psychosis after continuous amphetamine administration (Griffith et al. 1972). Although questions about the consequences of repeated cocaine use still remain, the

research reviewed here has provided the foundation on which these studies can be built.

ROUTES OF COCAINE ADMINISTRATION

Oral

Coca leaves have been harvested and chewed for more than 3000 years (Carroll 1977) by the Indians living in the area of the Andes Mountains in South America. They chew a combination of coca leaves and an alkaline substance to release the cocaine from the leaves. Paly et al. (1980a) measured plasma levels of cocaine in Peruvian Indians who were allowed to chew measured amounts of coca leaves under controlled laboratory conditions. Plasma levels reaching 95 ng/mg peaked shortly after cessation of chewing, and the levels achieved appeared to be related to the amount of cocaine in the chewed leaves. Despite elevated plasma levels, little "high" was reported in these chewers (Byck et al. 1980), perhaps due to the slow change in cocaine blood level. It was suggested that absorption occurred through the mucous membrane of the mouth as well as through the lower gastrointestinal tract since saliva containing the coca juice was swallowed as chewing continued. The correlation between dose and plasma level was also found by Holmstedt et al. (1978), who reported that the stimulating or energizing effect of the coca seemed to be well correlated with the rising concentrations of cocaine in the blood.

The most complete series of studies with oral cocaine was carried out by Sigmund Freud in the late 188Os, who described in some detail the results of his self-experimentation with pure cocaine. He described the onset of action as occurring within 10-20 minutes, with a stimulant effect which lasted for as long as 4-5 hours. Little has been added to his enthusiastic description of the stimulant and euphorigenic qualities of oral cocaine. Some of the other effects he hypothesized, however, such as its substitution for morphine, have not withstood the tests of time or further experimentation.

In an attempt to eliminate buccal absorption and determine whether or not cocaine was inactivated in the gastrointestinal tract, Van Dyke et al. (1978) administered cocaine-filled gelatin capsules. Under these conditions, peak plasma concentrations were reached at approximately 65 minutes after ingestion (Wilkinson et al. 1980) and dissipated about as rapidly as after intravenous administration.

Intravenous

Cocaine was first isolated from coca leaves in 1860 (Mortimer 1901), and, once available in a pure and considerably less cumbersome form, it was inevitable that it would be used by other routes of administration. The intravenous (i.v.) route of administration has remained a popular one with "serious," and perhaps more experienced drug users, since the drug goes rapidly to the brain; and subjective effects, including an intense "rush," are reported within 1 or 2 minutes (Resnick et al. 1977; Javaid et al. 1978). Estimates of dose made by laboratory subjects suggest that the average dose of cocaine injected intravenously by users in a recreational setting is approximately 16 mg/injection (Fischman et al. 1976). Cocaine plasma levels are correlated with dose of intravenous cocaine (Barnett et al. 1981; Javaid et al. 1983), and plasma levels of approximately 300 ng/ml have been recorded after single 32 mg doses (Javaid et al. 1978). It appears that the elimination half-life of cocaine by this route is approximately 40 minutes (Kogan et al. 1977; Javaid et al. 1983) although it has been suggested that this value is dose-related, increasing at very high doses (Barnett et al. 1981).

Intranasal

The most common nonmedical method of cocaine self-administration is "snorting," or inhaling. The crystalline substance is inhaled in its hydrochloride form, and is then absorbed through the nasal mucous membranes. A "line" of powder (20-30mg) is laid out and inhaled, and the user experiences approximately 20-40 minutes of stimulation, although no initial "rush." Repeated intranasal use of cocaine has potentially adverse physical consequences, including chronic rhinitis and, rarely, a perforated nasal septum. Peak plasma levels after intranasal crystalline cocaine occur at 30-40 minutes subsequent to inhalation (Javaid et al. 1978; Wilkinson et al. 1980) and not until 60 minutes after intranasal administration of the drug via cotton soaked with cocaine solution (Van Dyck et al. 1976). Peak plasma levels of 150-200 ng/ml are obtained after inhalation of 96 mg crystalline cocaine (Javaid et al. 1978). The half-life for intranasal cocaine administered as a powder or a 10% topically applied solution is approximately the same as after intravenous administration (Wilkinson et al. 1980; Javaid et al. 1983).

Smoked

The smoking of coca paste has been reported to be widespread in Peru, Ecuador, Colombia, and Bolivia (Jeri et al. 1980). The coca paste, containing solvents, is

mixed with tobacco or marijuana and smoked. Subjects tested in a research setting and allowed to smoke controlled amounts of coca paste on tobacco cigarettes showed peak plasma levels as high as 975 ng/ml within 5-10 minutes after smoking 0.5 g paste (Paly et al. 1980b). Plasma half life of cocaine was similar to that after other routes of administration. In subjects allowed to smoke ad libitum for 90 minutes, blood levels were fairly constant and similar during a second 90-minute session (Paly et al. 1982), indicating excellent dose regulation.

A more efficient method of self-administering cocaine via the smoking route has emerged in recent years. Cocaine is taken as the water-soluble hydrochloride when self-administered orally, intravenously, and intranasally. However, cocaine hydrochloride decomposes at the high temperatures necessary for smoking. Cocaine "free base," in which the cocaine alkaloid is "freed" from the hydrochloride salt (see Siegel 1982 for a review of this), has a melting point of 98°C and is volatile at temperatures above 90° , therefore providing an active drug for smoking. Extraction kits for converting the hydrochloride to the base are commercially available. Perez-Reyes et al. (1982) allowed subjects to smoke 50 mg cocaine free base and determined that no more than 32% could have been inhaled. Users interviewed by Siegel (1982) indicated that they generally began with approximately 81 mg of the base, and increased the amount of each "hit" to as high as 252 mg with the development of tolerance. Although no pharmacokinetic or blood level studies have been published, Siegel (1982) has reported that chronic cocaine free base smokers have shown plasma levels of 800-900 ng/ml 3 hours after smoking.

PHYSIOLOGICAL EFFECTS

The primary physiological parameters measured after cocaine administration have been cardiovascular functions. When administered intravenously in doses ranging from 8-32 mg, cocaine, like amphetamine, produces a dose-related increase in heart rate and blood pressure which begins 2-5 minutes after injection and peaks approximately 6-8 minutes later regardless of dose (Fischman et al. 1976; Resnick et al. 1977). These effects appear to parallel plasma levels, peaking early and showing decreases over the first 30 minutes after injection (Javaid et al. 1978). Cocaine has not been shown to have any effect on the electrocardiogram in i.v. doses of 4-32 mg (Fischman et al. 1976) nor, in doses of 10 and 25 mg, on respiratory rate and body temperature (Resnick et al. 1977). Intranasal cocaine administered in crystalline or in solution form has similar effects excepting that onset is delayed. Peak effects occur approximately 30 minutes after drug

administration (Resnick et al. 1977; Javaid et al. 1978), and the cardiovascular changes dissipate within the next 30 minutes, while blood levels are still elevated. Oral doses of 30-200 mg/day given in divided doses do not affect pulse, temperature, blood pressure, or respiration (Post et al. 1974b). These oral doses did, however, have a suppressive effect on both rapid eye movement (REM) sleep and total sleep. The effect of cocaine on REM sleep appears to be dose-related although this could be an artifact of the number of days of use as the drug was administered daily for 6 days in an ascending series. Cocaine's effects on sleep parallel those seen after amphetamine (e.g., Rechtschaffen and Maron 1964), an indication of the similarity of action of these drugs.

SUBJECTIVE EFFECTS

Cocaine's mood elevating properties were first described almost 100 years ago (Freud, in Donoghue and Hillman 1963), and the drug still retains its reputation as the euphoriant of choice among stimulant users. Experienced drug users, however, often cannot differentiate among cocaine, amphetamine, methamphetamine, and methylphenidate (Martin et al. 1970; Fischman et al. 1976), all of which appear to have similar profiles of action.

A consistent profile of cocaine's effects generally emerges when normal volunteers are administered the drug and answer standard drug effects questionnaires. When the Profile of Mood States (POMS), a five-point adjective checklist, was administered after intravenous cocaine, generally dose-related increases in a number of scale scores were obtained. These were: Confusion, Anxiety, Friendliness, Vigor, Elation, Arousal, and Positive Mood (Fischman et al. 1983a; 1983b). Scores on selected scales of the Addiction Research Center Inventory (ARCI), a true-false test measuring drug effects, have also consistently reflected the stimulant properties of cocaine. Increases, generally dose-related, were found in scores on the amphetamine (A) scale (Fischman et al. 1976; Resnick et al. 1977) as well as the morphine-benzedrine general scale (MBG, thought to be a measure of a drug's euphoric effects) and benzedrine general (BG) scale. Decreases were found on the pentobarbital-chlorpromazine-alcohol general (PCAG) scale which measures sedative effects (Fischman et al. 1976; 1983a; 1983b). Cocaine also resulted in increased scores on scales of "pleasantness" (Resnick et al. 1977), "high" (Fischman et al. 1983a; 1983b; Resnick et al. 1977), and "stimulated" (Fischman et al. 1983a; 1983b) as well as decreased scores on ratings of "hunger" (Resnick et al. 1977). Subjects who had substantial histories of i.v. cocaine use generally rated 16 mg i.v. cocaine as similar to the average dose

that they were self-injecting outside of the laboratory, and 24, 32, and 48 mg all as among the highest doses they had ever experienced (Fischman et al. 1976; 1983a; 1983b). The "high" obtained from i.v. cocaine began as an intense "rush," peaked approximately 3-5 minutes after injection, and was dissipated within 30-40 minutes, when subjects indicated that they would like another dose of drug (Javaid et al. 1978).

Subjects' reports of cocaine's effects after intranasal administration were quite similar to those after intravenous administration but less intense, slower in onset and without the initial "rush." Doses of 25-100 mg were followed by increases in "high" (Resnick et al. 1977; Van Dyke et al. 1979) and "pleasantness" (Resnick et al. 1977) scale scores, as well as the A (Resnick et al. 1977; Fischman and Schuster 1980) and MBG (Fischman and Schuster 1980) scales of the ARCI. Doses as high as 96 mg did not affect scores on any of the scales of the POMS. When cocaine was administered as a solution, peak "high" ratings occurred within 5-15 minutes and returned to baseline values between 2 and 4 hours after drug administration (Van Dyke et al. 1979). When the white powder was inhaled, subjects reported that their maximum "high" occurred 15-20 minutes after inhalation (Resnick et al. 1977; Javaid et al. 1978) and returned to baseline levels within 60-90 minutes (Javaid et al. 1978).

Cocaine given by the oral route appears to be effective in producing an increase in "high" ratings (Van Dyke et al. 1978). Subjects swallowed a gelatin capsule containing 2 mg/kg cocaine, and reported a "high" which peaked at 75 minutes and was dissipated approximately three hours after swallowing the drug. This effectiveness of cocaine via the oral route is expected in view of the reported use patterns of the Andean Indians since ancient times. Interestingly, until recently textbooks of pharmacology have stated that cocaine is rapidly hydrolyzed, and thereby rendered ineffective in the gastrointestinal tract (e.g., Ritchie and Cohen 1975). Clearly this is not so, although the delay in effect might indicate that the drug is not well absorbed until it reaches the small intestine.

When cocaine is smoked as the base, 37 mg of smoked base and 20 mg of i.v. cocainehave approximately comparable effects (Perez-Reyes et al. 1982) as measured by peak scores and duration of effect on the POMS. ARCI and "high" scales. Smoking caused significantly greater effects on the Vigor scale of the POMS and the "pleasantness" score. Degree of self-reported craving for another dose of cocaine at 30 minutes was greater after smoking the drug as compared with taking it intravenously.

The apparent acute stimulant and euphoriant properties of cocaine led to examination of its potential as an antidepressant in a group of depressed patients (Post et al. 1974). Oral doses ranging from 5 mg/day to 100 mg/day had no consistent effects on mood of the depressed patients studied. Intravenous doses of 2.5-25 mg often were effective in causing mood change, with doses associated with marked physiological effects usually resulting in intense mobilization of affect and tearfulness. Milder changes in vital signs were usually accompanied by more positive affective changes. Resnick et al. (1977) reported that one subject who received 25 mg i.v. cocaine showed marked crying in response to the drug. However, this subject had reported feeling depressed at the start of the experimental session. It thus seems that not all of cocaine's effects have been described as euphoria-producing. The baseline affective state of the subject may well play a role in the effect of cocaine on observed mood and verbal report of its effect.

Resnick et al. (1977) reported a biphasic response to cocaine beginning with a stimulant effect followed 30-60 minutes after drug by a "crashing" effect, "characterized by feelings of anxiety, depression, fatigue, and wanting more cocaine." This cocaine "crash" has been described by "street" users, but with the exception of Resnick et al. (1977) generally has not been described in laboratory studies. Fischman and Schuster (1980) reported that between 4 and 8 hours after intranasal self-administration of 96 mg, scores on the PCAG scale (a sedative scale) of the ARCI were substantially elevated and a composite stimulant score (A + MBG + BG) was substantially lower than after inhalation of placebo. This is somewhat longer than might be expected for a "crash" effect based on the data from) Resnick's laboratory.

TOLERANCE

There is anecdotal evidence that cocaine users can increase their intake of cocaine to levels that might be lethal to the cocaine-naive user. Although no long-term repeated dose studies have been carried out with cocaine in humans, Fischman et al. (in press) have demonstrated the development of an acute tolerance to the cardiovascular and subjective effects of intravenous cocainewhen it is given 1 hour after a 96 mg intranasal pretreatment as compared with the effects of the same intravenous dose given after a placebo intranasal pretreatment. In addition, when research subjects were allowed to self-administer 16 or 32 mg cocaine intravenously every 6-10 minutes for an hour, the initial injections of drug exerted maximal cardiovascular and subjective effects, with subsequent repeated injections within an hour having smaller

effects (Fischman and Schuster 1982). This apparent tachyphylaxis does not appear to be dispositional because blood levels rose at a rate consistent with the dose being administered repeatedly.

EFFECTS ON LEARNING

Most research on drug-behavior interactions has concentrated on studying the effects of drugs on previously learned tasks (i.e., on performance rather than on acquisition). However, behavior in transition might be more sensitive to a drug's effects than a well learned response would be. Fischman (1978) described a procedure adapted from the animal laboratory (Boren 1967; Thompson and Moersbacher 1979) for repeatedly measuring acquisition of behavior in individual research subjects.

Volunteer research subjects, working for points which could be exchanged for money, were required to learn a fixed sequence of 10 responses on 3 response keys. The sequence of 10 correct responses was changed for each 10-minute session. Within 10 sessions subjects showed stable acquisition curves from session to session as indicated by consistent within-session response rates and numbers of errors. This behavioral baseline on the repeated acquisition task was used to assess the effects of intravenous and intranasal cocaine. Seven subjects were tested with two determinations at each dose of drug (administered according to a modified Latin square design). Repeated acquisition tests were given pre-drug, in conjunction with drug administration, and 20 and 35 minutes after drug administration. Four different repeated acquisition tasks were thus studied within a 1-hour experimental session.

Response rate was generally unaffected by cocaine regardless of the dose administered (figure 1). The number of errors per 10-minute session, however, increased in a dose-related fashion following both intranasal and intravenous administration of cocaine and was highest after 32 mg intravenous cocaine, the largest i.v. dose administered. Verbal reports of cocaine's effects correlated with its other behavioral effects and with peak plasma level. Scores on both the POMS and the ARCI showed changes similar to those seen after administration of cocaine in other experimental situations (e.g., Fischman and Schuster 1980). Thus, both learning and verbal report of drug effect were maximally affected by intravenous cocaine immediately after injection, and by intranasal cocaine 20 minutes after inhalation. These data suggest that, at sufficient doses, cocaine interferes with tasks involving the acquisition of new behavior patterns, the first time that a cocaine-induced disruption in an operant task in humans has been demonstrated. This is

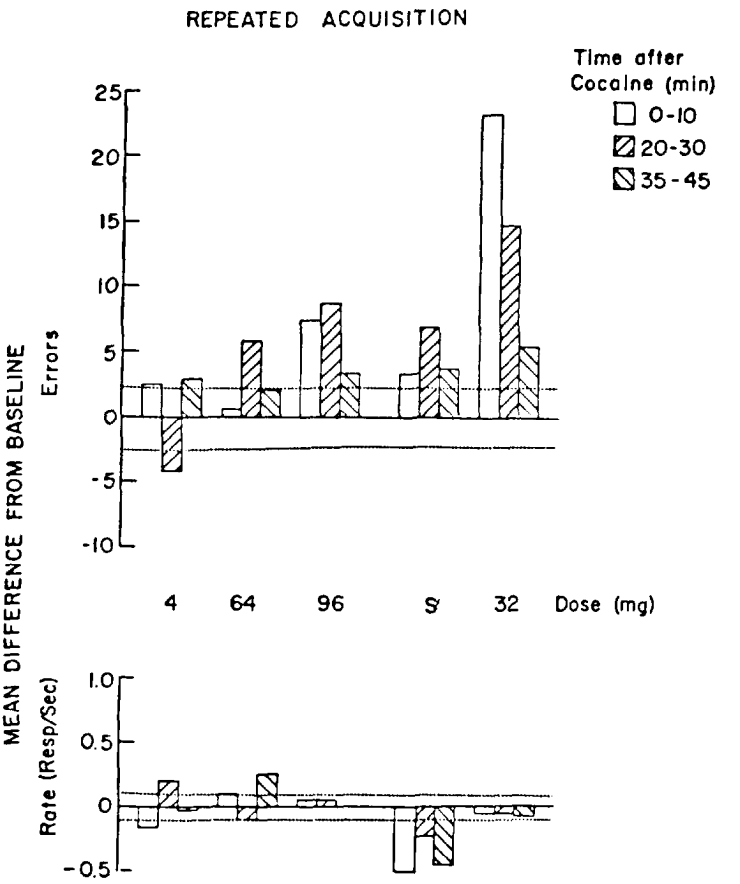

Figure 1. Effects of cocaine on learning new behavior patterns. Data collected during each pre-drug repeated acquisition task were averaged across subjects; the mean (± SEM indicated by broken horizontal lines) is used as the baseline score. Change from baseline is shown for number of errors and response rate during each of the three 10-minute post-drug tests. Cocaine was inhaled at doses of 4, 64, and 96 mg, and 32 mg was injected intravenously. S indicates an intravenous saline injection.

important since cocaine clearly has central nervous system effects as evidenced by the verbal reports of subjects describing its mood-altering effects. Despite such reliable effects on verbal report, it has been difficult to show other behavioral effects of this drug when it is administered in single doses in the dose range taken for recreational purposes.

EFFECTS ON PERFORMANCE

It has been suggested that the Andean Indians chew coca because it reduces hunger, produces a sensation of warmth, and enhances working ability (Hanna 1971). In fact, interviews with Indian coca-chewers yielded statements reflecting the belief that chewing enabled them to work harder: "Yes, I chew; I work hard." (Negrete and Murphy 1967, p. 14) In an initial study of the response of coca chewers to exercise (Hanna 1970) it was found that chewers, as compared to non-chewers, showed a lower exercise and recovery heart rate after using a bicycle ergometer, suggesting a slight advantage for the chewers. However, a more careful examination of the control group data indicated that the two groups were not well matched, and a second study using a bicycle ergometer and comparing matched groups of coca-chewers and non-chewers found no differences between the two groups in energy expenditure or efficiency over a range of work levels. Thus, the belief that coca use makes work easier was not supported.

There have been a number of suggestions that long-term regular ingestion of cocaine through the chewing of coca leaves causes deficits in such behaviors as attention, speed of responding, accuracy on tests, etc. (Cagliotti 1980; Zapata-Ortiz 1970). In an effort to investigate possible performance deficits of long-term coca chewers, Negrete and Murphy (1967) compared their performance to performance by a group of non-chewers using a battery of "intelligence" tests, auditory and visual memory tests, and attention tests. In general, controls scored better than chewers, although the differences were not substantial. A causal relationship between coca chewing and lower test scores was not demonstrated, and the results could have been due to variables other than coca chewing since groups were not well matched and testing was not blind. Further, the differences in test scores between the two groups was not reflected in their general social functioning or work behavior.

Cocaine users, as with coca chewers, frequently report that the drug enhances performance, but, with few exceptions this effect has never been investigated experimentally. Freud's self-experimentation led him to conclude that cocaine enhanced physical and mental capacity and restored the fatigued person to maximal alertness (in Donoghue and Hillman 1963). Resnick et al.

(1980), however, reported that neither 10 nor 25 mg cocaine administered intravenously or intranasally had an effect on hand-grip strength. Inhalation of 96 mg cocaine also had no effect on performance of a reaction time task in rested subjects (Fischman and Schuster 1980). However, when subjects were deprived of sleep for 24-48 hours, which resulted in a fatigue-induced decrement in performance, inhalation of 96 mg cocaine reversed (after 24 hours) or partially reversed (after 48 hours) the decrement. Freud also indicated that his cocaine-induced increase in physical capacity as measured by performance on a dynamometer was greatest when his condition was poor. No other research has been carried out investigating the effects of cocaine on performance in humans. Substantial data do exist, however, indicating that, in general, the amphetamines have minimal effects on performance in the non-sleep-deprived subject (see reviews by Weiss and Laties 1962; Weiss 1968) but are generally successful in returning to its pre-deprivation level performance which has deteriorated due to fatigue (Kornetsky et al. 1959). Laties and Weiss (1981) have recently pointed out, however, that the small changes induced by amphetamines can result in the one or two percent improvement which can make the difference in a close athletic competition. Such data are not available for cocaine, but its short duration of action argues against the usefulness of such an effect.

SELF-ADMINISTRATION

As indicated by another article in this monograph (see Johanson), cocaine is a potent reinforcer, readily self-administered by laboratory animals and often used as the training drug for drug-naive animals. In addition, reports of illicit cocaine use indicate substantial increases during the past 5 to 10 years, both in the drug-taking population as a whole and particularly in young adults (Richards 1981). Cocaine-related emergency room visits have also increased as indicated by the DAWN[1] survey data.

Only limited data are available describing cocaine self-administration by humans under controlled laboratory conditions (see Fischman and Schuster 1982). Subjects given a choice between injections of i.v. cocaine or saline approximately once every 6 minutes for 1 hour consistently chose cocaine (16 or 32 mg). As with laboratory animals, drug injections were fairly regularly spaced and intravenous cocaine intake reached 224 mg, with plasma levels of approximately 1200 ng/ml. This kind of regulation in intake was also seen with subjects allowed to smoke cocaine paste during a 90-minute limited access procedure (Paly et al. 1982). Subjects self-administering i.v. cocaine indicated that they felt high, stimulated, "weird; and anorexic for 2-3

hours after these sessions; several subjects indicated that they had difficulty sleeping 8-14 hours later. Cocaine, therefore, has been shown to serve as a positive reinforcer in humans and can maintain drug-taking behavior under limited access conditions daily for a two-week period.

SYNTHETIC LOCAL ANESTHETICS

Although the reinforcing properties of cocaine have been documented in the laboratory for both human and non-human research subjects, it is only recently that other local anesthetics have been similarly studied (Ford and Balster 1977; Hammerbeck and Mitchell 1978; Woolverton and Balster 1979; Johanson 1980). Drugs such as procaine, chloroprocaine, and dimethocaine are self-administered by rhesus monkeys, while lidocaine, proparacaine, and procainamide do not appear to serve as positive reinforcers in those animals. These data have been puzzling, since, in general, drugs which serve as reinforcers in animals do so in humans (Johanson and Balster 1978), and it is assumed that this property is an important factor in their dependence potential. Despite these reports of local anesthetic self-administration in non-humans, however, none of the drugs mentioned above appear to be commonly abused by humans.

A traditional approach to the evaluation of a drug's dependence potential is to compare its spectrum of action to that of a known drug of abuse (Fischman 1977; Jasinski 1977). Similarity to the prototype along several dimensions is then used to predict possible abuse liability. Two recently published studies have investigated the cardiovascular and subjective effects of synthetic local anesthetics using such an approach (Fischman et al. 1983a, 1983b). In both studies volunteer subjects were tested with a range of intravenous doses of cocaine and matched intravenous doses of either procaine or lidocaine. The effects of the two local anesthetics on verbal report of drug effect (as measured by the POMS, the ARCI, a series of visual analog scales evaluating drug effects, and a drug identification question), and measures of heart rate and blood pressure were compared to the effects of cocaine using the same measures.

In the preceding comparative studies, only cocaine had significant effects on heart rate and blood pressure, similar to those previously reported for this drug after intravenous administration. When the effects of 16, 32, and 48 mg cocaine on verbal report were compared with those of placebo, there was a dose-related increase in stimulant scale scores on the ARCI, POMS and Visual Analog Rating Scales. In contrast, matched doses of lidocaine or procaine did not produce any effects different from placebo except on the "high" and

"stimulated" scales of the Visual Analog Scale. The only measurable effect was a small but significant increase in "high" and "stimulated" scores after 96 mg procaine as compared with placebo. Subjects identified both 48 and 96 mg procaine as cocaine and were accurate in identifying saline as placebo and cocaine as cocaine. All doses of lidocaine and 16 and 32 mg procaine were identified as placebo.

There has, however, been one report of subjects giving similar ratings of "high" to cocaine and lidocaine when these two drugs were topically administered in solution intranasally in matched doses of 0.19, 0.38 and 0.75 mg/kg (Van Dyck et al. 1979). However, statistical tests were not applied to the data, making interpretation difficult. It seems likely that the two lower doses of cocaine were not discriminable from placebo. Although cocaine plasma levels were not reported by Van Dyck et al. in this study, levels after 1.5 mg/kg delivered by the same route in another study resulted in peak plasma levels of 130-165 ng/ml (Van Dyck et al. 1976). Extrapolating from this dose, we would expect 0.75 mg/kg to yield a peak plasma level of 65-80 ng/ml, with slow onset, and the lower doses to yield correspondingly lower plasma levels. Fischman et al. (unpublished) have found that doses of inhaled crystalline cocaine yielding peak plasma levels below 50-55 ng/ml do not appear to produce a response of "high" in volunteer subjects. Thus, the report of similar subjective effects of cocaine and lidocaine may be due to the very low doses of cocaine used.

The data from Fischman et al. (1983b) indicate that procaine and cocaine share some stimulus properties (i.e., procaine was identified as cocaine), and at the highest dose tested procaine caused increases in "high" and "stimulated" scores. To the extent that shared stimulus properties predict shared reinforcing properties, the obvious implication is that procaine might be expected to be a reinforcer in humans. In fact, preliminary data indicate that this is true (Fischman and Schuster, unpublished). Procaine, however, is not thought to be abused by humans. This descrepancy could be due to several factors. First of all, it may well be thatwhatpasses for cocaine "on the street" is, in fact, another local anesthetic such as procaine. Procaine is commonly misrepresented as cocaine or mixed with illegally sold cocaine, providing a less expensive substitute or filler in the sale of cocaine. Perhaps the "filler" is, in this case, not inactive but is being used for its own properties. Another factor to be considered in evaluating the abuse potential of procaine is its very short half-life. Procaine has been estimated to have a 7.7 minute elimination half-life in humans (Seifen et al. 1979), and that of cocaine is approximately 40 minutes after

intravenous injection (Javaid et al. 1978). Frequent injections of drug would thus be necessary to maintain intoxication. This is precisely what is seen with rhesus monkeys who self-administer large numbers of procaine injections rapidly (Ford and Balster 1977; Johanson 1980), but would generally be inconvenient for humans to arrange. Potency differences are also relevant. There appears to be a 6-to-10-fold potency difference between cocaine and procaine when the animal self-administration and discriminative stimulus property data are examined (Woolverton and Balster 1982). In rats, for example, cocaine was found to be 9 times more potent as a discriminative stimulus than procaine. Since 8 mg of i.v. cocaine has been found to be a strong reinforcer in humans, we would expect that 96 mg procaine should be a sufficient dose to be a reinforcer. Thus, the necessity of both frequent injections and substantial amounts of a drug might well be sufficient reason for its lack of "street" popularity except, perhaps, as an adjunct and component of cocaine mixtures.

TOXICITY

No laboratory studies have been carried out to investigate high-dose or repeated-dose cocaine toxicity. On the other hand, an increasing number of clinical reports have described the deleterious effects of repeated cocaine use via various routes of administration. Regardless of the route, the effects are similarly debilitating (Rappolt et al. 1978; Carbajal 1980; Siegel 1982). Gay et al. (1975) have described the "Advanced Stimulation 'Caine' Reactions" as divisible into three categories: (1) Early Stimulation is accompanied by excitement, apprehension, nausea, vomiting, and twitching of voluntary muscles; (2) Advanced Stimulation is characterized by hyperkinesis, convulsions, increases in pulse and blood pressure, and irregular respiration; and (3) Depression is accompanied by loss of reflexes, unconsciousness, circulatory and respiratory failure, and perhaps death. Siegel (1982) has pointed out that heavy chronic cocaine smokers often exhibit hallucinations and persecutory delusions and are generally incapable of regulating their drug intake. A recent report of iatrogenous cocaine psychosis (Lesko et al. 1983) described similar symptomatology in a young man given a topical anesthetic solution of dyclonine hydrochloride and cocaine which he was allowed to apply to the inside of his mouth as needed for pain due to oral ulcers. The hallucinations, paranoid ideation, hyperactivity, and repetitive behavior patterns disappeared within 60 hours of cessation of the cocaine.

These symptom descriptions appear to be indistinguishable from the toxic syndrome produced by the amphetamines. This latter effect has been produced

in human research subjects under controlled laboratory conditions (Angrist and Gershon 1969; Griffith et al. 1972) and indicates that in sufficient doses a toxic psychosis can develop in anyone regardless of pre-drug psychiatric status. Because of the similarity in action between cocaine and the amphetamines, there is no reason to believe that cocaine toxicity will be any less severe or general than that seen after amphetamine. The fact that the cocaine toxic psychosis has not been demonstrated under controlled laboratory conditions should not be taken to mean that it does not exist. This is a situation in which all of the other available data indicate that the similarities between cocaine and amphetamine are far more striking than their differences, and we can readily predict similar toxic effects. Clinical reports support this prediction.

CONCLUSION

Laboratory studies with human research subjects have indicated that cocaine's cardiovascular and subjective effects mimic those reported for other stimulant drugs such as the amphetamines, diethylpropion, and methylphenidate. Differences observed reside primarily in factors related to dosing regimens, duration of action, etc. Furthermore, these effects generally increase with increases in cocaine plasma level. In addition, as with nonhuman research subjects, cocaine clearly functions as a positive reinforcer.

When given concurrent alternative substances to self-administer (e.g., saline versus cocaine), subjects generally chose cocaine over saline and showed predictable increases in heart rate as well as verbal report of its stimulant effects early in the session. However, there does appear to be an acute tolerance to its effects.

The data collected in the laboratory have all been collected under limited access conditions. It has been pointed out in another paper in this monograph (Johanson) that rhesus monkeys allowed to self-administer cocaine under limited access conditions do so with well-regulated intake and few signs of toxicity. However, results from unlimited access procedures indicate substantial toxicity including convulsions and death. It is possible that with a less restricted drug-taking schedule for humans, other toxic effects would also emerge. The data indicating development of an amphetamine toxic psychosis provide the clues for what this toxicity might be, and point out the potentially serious consequences of repeated cocaine use.

FOOTNOTE

[1]DAWN, the Drug Abuse Warning Network, monitors drug-related emergency room visits and deaths. Now funded by the National Institute on Drug Abuse, it was funded jointly by NIDA and the Drug Enforcement Administration (DEA) from 1972 to 1980.

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AUTHOR

Marian W. Fischman, Ph.D., The University of Chicago, Department of Psychiatry, 950 East 59th Street, Chicago, Illinois 60637

Changing Patterns of Cocaine Use: Longitudinal Observations, Consequences, and Treatment

Ronald K. Siegel

INTRODUCTION

In 1858 the Austrian frigate Novara was sent to South America on a most unusual mission. The Novara was named after the city in which the Austrians had defeated the Italians, thereby stopping a threatening cultural and political renaissance. On board the Novara was a trade expert, Doctor Scherzer, who was intrigued by another Italian "renaissance" started by Milan neurolgist Paola Mantegazza. Mantegazza had published an 1857 paper proclaiming the medical importance of coca that he had chewed while a resident of Peru (Mantegazza 1857). The paper was the newest curiosity of the European medical community which even awarded Mantegazza a prize for this work in 1859 (Mortimer 1901). The Novara stopped in Peru and Scherzer took a quantity of coca leaves back to the great chemist Wohler at the University of Gottingen in Germany. Wohler's assistant, Albert Nieman, named the isolated alkaloid "cocaine" in 1859/1860 (Phillips and Wynne 1980). The isolation and naming of the alkaloid signalled the start of 125 years of changing patterns of cocaine use. Prior to that time, only coca products were available, and the patterns of their use had not changed substantially in over 4700 years.

For most of its early history, cocaine remained hidden and unidentified in the protective envelope of the coca leaf. The coca plant (Erthroxylum spp.) produces at least 14 different alkaloids as defensive agents to ward off foraging animals. The bitterness, numbing, and psychoactive properties of these alkaloids perform this defensive function effectively, teaching animals to avoid the plant and thus contributing to its evolutionary survival. Interestingly, compared with other tropical American crops, coca is relatively pest free. Herbivorous insects are rarely observed on plants and damage to the leaves is relatively minor.

Accidental encounters with ingestion of coca exposed early man to the effects of its alkaloids. From 3000 B.C. to the middle of the 16th century, coca was used by the indigenous peoples of

South America in religious, magical, medical, and recreational contexts. Little information is available on the psychopharmacological consequences of this use, but patterns changed very little during this period. The leaves were chewed whole or in powdered form , smoked with or without tobacco, or else swallowed in various infusions.

In 1580 coca was introduced to Europe, where it eventually, by the middle of the 19th century, found its way into widespread medical use. Coca products included preparations of leaves, extracts, wines, liquors, cordials, lozenges, cigars, cigarettes, and chewing gum, among many other forms. Patterns of use were largely confined to medical applications, although sane nonmedical uses were also reported.

After the isolation of cocaine in 1859/1860 by Nieman (a crude alkaloid, named "erythroxylon," was isolated by Gaedecke in 1855), early experimentation revealed stimulant and local anesthetic properties (Siegel and Hirscham 1983). The medical community became enthusiastic about this new wonder drug, the patent medicine manufacturers exploited it, and the nonmedical use of cocaine for pleasure began to grow rapidly. Fostered by glowing reports from the patent medicine advertisements, encouraged by the research and writings of Sigmund Freud (who was strongly influenced by Mantegazza), and pushed by the euphoria-enhancing techniques of intranasal and intravenous administration, the pattern of use began to change.

In addition to the numerous coca products, cocaine itself started to appear in flake crystals, tablets/ solutions for inject ion, ointments, and nasal sprays. Both coca and cocaine were also used in a variety of soft drinks and tonics, the most famous being Coca-Cola. Indeed, "during the seventeen years Coca-Cola contained cocaine [until 1903], the drink and drug became so closely identified that 'dope,' as in 'let's have a dope' became the established, common term for Coca-Cola" (Ashley 1975, p. 49).

Observations on these patterns of use were made in both the medical and lay press during the early 20th century. Many of these articles suggested that cocaine was associated with uncontrollable addiction, physical and psychological deterioration, demoralization, and criminal violence. Federal legislation, beginning with the Pure Food and Drug Act of 1906 and the Harrison Act of 1914, effectively launched a period of cocaine prohibition by restricting and controlling all aspects of its manufacture, possession, sale, distribution, and use. Both the medical and nonmedical use of cocaine gradually declined, and general interest in the drug all but disappeared between 1930 and the late 1960s.

Cocaine continued to be used, albeit by relatively few users, during this period of prohibition. The primary route of ministration was intranasal, although the intravenous route was also employed. In the early 1970s, cocaine was "rediscovered" as a recreational drug of choice. As with its initial introduction

a century before, contemporary users began to experiment with new preparations and patterns of use.

SHORT-TERM OBSERVATIONS OF USERS (1970-1983)

A number of studies have provided observations of contemporary patterns of cocaine use in the period 1970 to 1983. These studies have concentrated on selected populations of users that were seen at only a single point of time during this period. When reviewed chronologically, these observations suggest that patterns of cocaine use were changing rapidly throughout the period 1970 to 1983 and in particular for long-term users. For individuals engaged in continued use this change was characterized by increased dosage and frequency of use resulting in decreasing positive effects and increasing negative reactions including physical and psychological dysfunction. This changing pattern is also examined (see following sections) in a series of longitudinal observations made on a sample of users studied at multiple points of time during this sane period.

Users entered the 1970s with attitudes that supported their beliefs that cocaine was a "safe recreational drug." Gay and Inaba (1976) suggested that the rediscovery of cocaine in the 1970s was inevitable because its effect of euphoria and stimulation "reinforces and boosts what we recognize as the highest aspirations of American initiative, energy, frenetic achievement, and ebullient optimism" (p. 251).

Phillips and Wynne (1980) interviewed and observed a group of cocaine users and dealers in 1975 in a study of user beliefs and myths regarding cocaine. among the myths endorsed by users were: cocaine is an aphrodisiac; cocaine increases creative and physical performance; there are no bad effects associated with cocaine use; the cost of cocaine is related to its purity; and a cold shower is an antidote for cocaine intoxication. Widespread belief in these "street" myths appeared to support continued use of cocaine.

Gottlieb (1976) also interviewed and observed a number of cocaine users who expressed similar beliefs: cocaine is an aphrodisiac; cocaine facilitates the learning process; cocaine improves physical activity; and cocaine "is not addictive." While users preferred the intranasal route of administration, Gottlieb reported the growing experimentation with intrabuccal and sublingual routes of administration, the rediscovery of drinking cocaine in alcoholic beverges such as cordials, and the smoking of cocaine hydrochloride alone or in combination with marijuana or tobacco.

The consequences of this early use were repotted by Ashley (1975) who interviewed and observed 81 cocaine users, all of whom reported experiencing euphoria, sexual stimulation, increased energy, and reduced fatigue and appetite. His respondents also reported a wide range of other positive effects including increased mental lucidity and muscular strength. Not

surprisingly, these users agreed "that cocaine was a 'good' drug, and virtually all were certain it should be used in moderation" (p. 156). Reports of adverse effects were more variable and appeared to be dependent on the pattern of use. In this regard, Ashley observed three patterns of use: moderate, chronic moderate, and heavy. Sixty of his respondents were moderate users (0.25-0.50 grams/day for "a few" days) who reported minor adverse reactions such as lassitude. Fourteen were chronic moderate users (0.25-0.50 grams/day for prolonged periods) who reported mild insomnia, occasional impotency, irritability, and personality changes. The remaining four heavy users (chronic use of 2.0-4.0 grams/day) reported insomnia, impotency, irritability, personality changes, and paranoia. Importantly, Ashley's respondents noted a tendency to escalate dosages which resulted in increased adverse reactions. Consequently, they reported adjusting dosages or abstaining for brief periods in order to control use. Lassitude was the only withdrawal symptom noted by these users.

Using a more careful interview and questionnaire study, Resnick and Schuyten-Resnick (1976) described five profiles of typical cocaine-using behavior, based on the patterns of drug use established by the National Commission on Marihuana and Drug Abuse. These patterns included experimental (short-term and nonpatterned); recreational (use in social settings among friends); circumstantial (use for specific effect); intensified (daily use); and compulsive (high frequency and intensity). These researchers described intensified users as using from 3 to 20 times a day. Compulsive users were characterized as having a high degree of psychological dependence: "The most striking feature of this pattern is that the drug use dominates the individual's life and precludes other social functioning" (p. 221).

As Ashley had predicted, consequences of adverse reactions appeared dependent on the pattern of use. Users following the more intensified and compulsive patterns of use started to show up in treatment centers seeking clinical attention. Gay and Inaba (1976) traced an increase in cocaine users seekity clinical attention beginning in the middle of 1970. Chronic cocaine abuse was marked by psychological dependence, a withdrawal depression, and sleep disturbances.

In an interview study of 17 recreational users, Grinspoon and Bakalar (1976) found that even intranasal users experienced common psychological problems including insomnia, irritability, and anxiety. Physical problems included rhinitis and weight loss. Toxic eftects, psychosis, and loss of psychomotor control were considered rare reactions for these users.

However, with intravenous patterns of use, the problems appeared to escalate. In a series of in-depth case studies, Spotts and Shontz (1976, 1980) examined the lifestyles of nine American cocaine users. The users in their studies were primarily intravenous users with an average of 5 to 9 years of experience

with cocaine. They concluded that low levels of usage were associated with use of cocaine to enhance sensory pleasures, to make the real world seem like an imaginary paradise, and to help the user compensate for inability or unwillingness to accept responsibilities. Relatively higher levels of usage were associated with use of cocaine to provide necessary support for the self-concept, as a means to provide the drive and energy needed to succeed, or as a way of inducing a state of blissful oblivion to overwhelming life problems. These researchers found that at high levels of use the sensory pleasure is often counterbalanced by adverse react ions including tension, anxiety , paranoia, hallucinations, and fear of overdose and subsequent death. Interestingly, following completion of the study, Spotts and Shontz report that of the nine respondents "two of them are now dead, one is in prison, and one has been convicted of a felony involving cocaine. These chilling statistics highlight the danger and volatile nature of the world of the heavy cocaine user" (1980, p. 492).

Siegel (1979) cited the growing popularity of smoking cocaine free base and a concanitant increase in negative reactions:

> Free base parties have became increasingly popular, and the practice has spread, . . .Unlike intranasal users, cocaine smokers do not appear to titrate or adjust dosage. Consequently, both frequency and quantity of dosages escalate rapidly.. . This pattern of use is similar to that found with intravenous heroin and cocaine and has an associated high potential for dependency and overdose. (p. 373)

User beliefs, however, strongly supported the smoking of cocaine free base with attitudes that it was "the ultimate high," "the greatest thing since sex," "gives you the ecstatic illusion of a synthetic heaven," and is capable of producing mind-expanding experiences (Anvil 1979; Raye 1980; Davidson 1981). Smoking of cocaine free base continued throughout this period. Siegel (1982) studied 32 users seeking clinical attention for problems related to cocaine free base. Of the 32 users studied, 20 engaged exclusively in individual compulsive patterns of smoking, seven engaged in exclusively social compulsive patterns (usually with a single smoking partner), and five engaged equally often in both individual and social smoking. All users reporting initial periods of intensified use started with one gram per day (range 0.5-3.0) and escalated over the course of the intensified period to an average of 7.0 grams per day (range 2.0-28.0). All the users were diagnosed as having a Cocaine Smoking Disorder, an organic mental disorder with associated features of euphoria, dysphoria, and schizophreniform psychosis.

While these studies were being conducted on cocaine users in the United States, a series of reports began to emerge on abuse of coca paste in Peru and other countries in South America (Aramayo and Sanchez 1980; Jeri et al. 1978, 1980; Noya 1978; Valladolid 1979). Taken together, these reports suggested that the chronic

smoking of coca paste was associated with successive stages of psychopathology: euphoria, dysphoria, hallucinosis, and psychosis. Jeri and colleagues (1978) reported a characteristic profile of these coca paste users. Users experienced an initial euphoria followed almost immediately by compulsive anxiety to smoke more paste, depression, irritability, suspiciousness, paranoid thinking, excitement, and visual, auditory, and tactile hallucinations. In addition to toxic effects (e.g., convulsions and seizures) resulting from chronic or high dose usage, psychosocial dysfunction as well as psychological impairment was commonly reported.

Cocaine smokers were not the only users reporting such adverse reactions. As both the dosages and chronicity of cocaine use escalated, these adverse consequences became ubiquitous among all classes of users. Helfrich and coworkers (1983) found a profile similar to the coca paste users after examining a group of cocaine users who sought treatment. Examination of these patients revealed impairment in several areas: psychological, interpersonal, financial, physical, and vocational. The dysfunction appeared to be independent of the route of administration. This latter finding was consistent with a telephone interview study of users seeking help for cocaine-related problems (McConnell 1983). In the telephone study, users reported an average use of 8 grans per day, 6 days per week, with 56 percent reporting such use for 2 years. Symptoms included nosebleeds, exhaustion, headaches, seizures, paranoia, panic attacks, and violence towards others.

LONG-TERM OBSERVATIONS AND CHANGING LEGAL STATUS (1970-1983)

The period 1970 to 1983 was marked by a steady increase in virtually all aspects of cocaine use (Siegel 1982). Importation of cocaine, paraphernalia sales, cocaine-related stories in the media, samples of cocaine submitted by users for analysis, hospital and treatment center admissions for cocaine, cocaine-related deaths, seizures of illicit cocaine, cocaine-related crimes and arrests, among many other parameters, increased dramatically.

The changing patterns of cocaine use, as well as changing attitudes, have been reflected in the nature of legal defenses raised in cocaine-related crimes during 1970 to 1983 (Siegel 1983). Initially, cocaine was viewed as a "non-addictive" and non-narcotic recreational drug that was not as dangerous as the law maintained. The first evidentiary hearings on the scientific and medical nature of cocaine were held in Commonwealth v. Miller (366 Mass. 387,318 N.E.2d 909[D.Ct.1976]) in 1976. Here the constitutionality of cocaine's classification as a "narcotic" was successfully challenged and the judge issued 125 findings of fact regarding the state of knowledge about cocaine as a relatively safe drug in typical patterns of social-recreational use. Defenses from 1976 to 1981 attempted to educate the trier of fact about these opinions and thus, hopefully, to temper the judgment and disposition of the cases. These defenses met with

considerable success in lower courts, but higher courts have held that it is valid to classify cocaine as a narcotic for purposes of punishment. As cocaine use spread and effects of toxicity and dependency became recognized, defenses based on cocaine- induced diminished capacity or insanity started to emerge in courts. The effects of cocaine on criminal responsibility, on credibility of witnesses, and as a causative factor in accidental deaths or homicides were raised as mitigating factors in guilt or penalty phases of criminal trials. By 1983, cocaine appeared to be replacing phencyclidine as the novel drug defense of the decade.

The forensic issue that most clearly illustrates the changing patterns of cocaine use is the quantity necessary for charges of possession and sales. Some courts, particularly Federal courts, have permitted an inference of intent to sell to be drawn from the fact that a large quantity of a drug was involved, despite the absence of a statutory presumption. Thus, in the early 1970s possession of more than a gram of cocaine was often viewed as possession for sale. As users escalated their patterns and dosages, particularly with smoking cocaine free base, possession of larger amounts for personal use became more common. It was not unusual to find that intranasal users might possess a week's supply of several grams or a cocaine smoker might use as much as 1 ounce or more. Consequently, by 1980 many jurisdictions viewed 1 ounce of cocaine or less as simple possession for personal use.

One aspect of a changing pattern in cocaine use was clear: there were more users in general, more intensified and compulsive users in particular, and more cocaine-related psychological, physical, and legal problems. Another aspect of this changing pattern was less clear: did individual long-term users manifest parallel changing patterns of cocaine use? In other words, do the recreational and circumstantial users cited in the above studies escalate use to more intensified and compulsive patterns of use? Does increased use of cocaine increase the incidence of negative and toxic effects? Is long-term use of cocaine inevitably associated with an escalating dependency marked by more frequent use? If not, what factors control and maintain stable patterns of chronic use? A longitudinal study of a small sample of users was begun in 1975 to provide information on these questions as well as the consequences of long-term use dur iry this period. Preliminary findings from the first 4 years of this study have been reported elsewhere (Siegel 1977, 1980). Only those results relevant to the question of changing patterns of use will be discussed below.

LONGITUDINAL STUDY OF USERS (1975-83)

Methods

A total of 118 cocaine users were recruited for study in 1974. Of these, 19 were selected for interview and questionnaire study while 99 (85 males, 14 females) were selected for a more comprehensive longitudinal study. All 99 users (18-38 years old) were social-recreational users who met the initial requirement of

having used a minimum of 1 gram of cocaine per month for 12 months (range 1-4 grams). The majority of users were students (73 percent,) while others listed their occupations as housewives, business people, writers, attorneys, physicians, secretaries, teachers, or unemployed. Exaninations and tests were performed on each subject at 6-month intervals for 4 years (1975, 1976, 1977, 1978) and then at approximately 18-month intervals for another 5 years. Examination procedures included a personal history questionnaire, drug history questionnaire, subjective drug effects questionnaire, mental status exanination, the Minnesota Multiphasic Personality Inventory (MMPI), the Experiential World Inventory (EWI), in-depth interviews, and physical examinations (for most subjects). In addition, assays were performed on samples of cocaine used by these subjects. An important caveat is that a number of users dropped out of the study throughout the years or could not be located for followup examinations. Several followup examinations in the last 5 years of the study were conducted via telephone, and these were restricted to questionnaires and interviews. Nevertheless, a total of 61 users participated in all phases of the first 4 years of study and 50 users were available for followup in 1983. Eight additional users who refused followup examinations reported that they had stopped all cocaine use.

Preparations and Purity

All subjects used cocaine hydrochloride available through illicit markets. The average purity of their samples fluctuated throughout the years of the study: 43.2% in 1975; 56.2% in 1976; 52.1% in 1977; 60.8% in 1978; 25.0% in 1979; 13.9% in 1980; 48.7% in 1981: 58.0% in 1982; and 75.0% in 1983. When cocaine free base was prepared, the average purity of the final product was 95.0%. The most common adulterants and diluents were mannitol, lactose, inositol, lidocaine, and phenylpropanolanine.

Routes of Administration

All subjects employed the intranasal route at the start of the study period. By the end of the first year, 14 percent had experimented with smoking cocaine hydrochloride on tobacco or marijuana cigarettes. By 1978, 39 percent of the users had smoked cocaine as the hydrochloride or free base and 10 percent classifed themselves as primarily cocaine free base smokers. For the last 5 years of study, there were two distinct populations of users: intranasal users (90 percent) and cocaine free base smokers (10 percent). Throughout the study, users experimented with other routes including injection (n=5) and oral (n=11).

Dosages and Dose Regimes

Intranasal users administered cocaine in amounts (uncorrected for purity) of 20 g per &ministration if a "cokespoon" was employed or 50 g if “lines” were used. Throughout 1975-1978, intranasal users averaged between 1 and 4 grams (uncorrected weight) per month. From 1978 to 1983, intranasal users, approximately 90

percent of the sample, averaged between 1 and 3 grams per week. Cocaine free base smokers, approximately 10 percent of the sample, used approximately 100 mg of free base per "hit" or inhalation. Throughout 1975-1978, smokers averaged 1 gram per day during periods of use. From 1978 to 1983, smokers averaged 1.5 grams per day. The temporal spacing of hits and the total duration of a smoking episode varied considerably . Inhalations were repeated as often as every 5 minutes during binges ranging from 30 minutes to 96 hours. Individual consumption ranged from 1 gram to 30 grams per 24-hour period, although some users reported smoking up to 150 grams in 72 hours. Smoking episodes continued until supplies of cocaine were depleted or users became exhausted and fell asleep.

Patterns of Use

All 99 users were classified initially as social-recreational users, since use generally occurred in social settings among friends or acquaintances who wished to share an experience perceived by them as acceptable and pleasurable. Such use was primarily motivated by social factors and did not tend to escalate to more individually oriented patterns of use. Use tended to occur in weekly or biweekly episodes. From 1975 to 1978, 75 percent (n=46) of the users still in the study (N=61) engaged in episodes of more frequent use (see below) but remained primarily social users. From 1978 to 1983, 50 percent (n=25) of the users still in the study (N=50) remained social-recreational (with continuing episodes of increased use), 32 percent (n=16) of the users became primarily circumstantial-situational users, 8 percent (n=4) became intensified users, and 10 percent (n=5) became compulsive users. Importantly, this latter compulsive group consisted entirely of cocaine free base smokers.

An important caveat is that all users had episodes of decreased use or abstinence interposed between periods of use in their normal patterns. Thus, users reported abstaining from cocaine for periods ranging from a few days to several months. For example, from 1978 to 1983, four social-recreational users reported no use for 2 years. During this same period, all compulsive users reported periods of social use as well as brief periods of abstinence. And most users in all categories reported that supplies of cocaine were often unavailable, thus resulting in regular periods of nonuse. However abstinence also occurred during periods of cocaine availability.

Thus, 25 social-recreational users at the beginning of the study remained in this pattern of use after 9 years. Throughout this period, these users continued to report positive effects of intoxication including euphoria and stimulation, although they also reported negative effects including nasal problems, restlessness, and attentional difficulties. By restrictiting themselves to social patterns of use, they reported the ability to titrate their doses and thereby minimize these negative effects. Reliefs in cocaine as an "ideal safe drug" which facilitated social behavior, the economics of supply, and the

legal risks of use all seemed to contribute to maintaining stable patterns of use which did not change substantially for these people. The incompatibility of cocaine use with other activities (e.g., work) also served as controlling determinants.

Circumstantial-situational use was 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, Use tended to occur in four or five episodes per week. Sixteen of the social-recreational users adopted this pattern of use by 1983. The major motivations cited by users were to increase energy or performance at work and to enhance mood during periods of boredom or depression.

Four users became classified as intensified cocaine users by 1983. Intensified use is characterized by long-term patterned use 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. While sane social - recreational users referred to their periods of intensified use as short-term runs or binges, these four users reported that they were on repeated runs of several months' duration and did not return to social pat terns of use.

Compulsive use is characterized by high frequency and high intensity levels of relatively long duration, producing sane degree of dependence. The dependence is such that the individual user does not discontinue such use without experiencing physiological discanfort or psychological disruption. The five compulsive users found here were all cocaine free base snokers. Use tended to occur in episodes of continuous smoking for periods of several hours to 96 hours. These users were characterized by significantly reduced individual and social functioning. The motivation to continue compulsive levels of use was primarily related to a need to elicit the euphoria and stimulation of cocaine in the wake of increasing tolerance. Compulsive users were also motivated by the desire to avoid the discomfort and depression of withdrawal. Consequently, compulsive users were preoccupied with obtaining adequate and sufficient amounts of cocaine in order to forestall an abstinence-like syndrome. When compulsive users were sufficiently well supplied so that preoccupation with obtaining cocaine did not occur, it was common to find an equally intense preoccupation with using such supplies.

Acute and Chronic Effects

Users reported that a variety of acute intoxication effects were perceived as positive. These included: euphoria, stimulation, reduced fatigue, diminished appetite, garrulousness, sexual stimulation, increased mental ability, and increased sociability. Other acute effects were experienced as negative: restlessness,

anxiety, hyperexcitability, irritability, and paranoia. During 1975-1978 all users reported experiencing some positive effects in all intoxications and negative effects in only 3 percent of the intoxications. However, during 1979-1983 all users, except compulsive users, reported positive effects in all intoxications but negative effects in approximately 40 percent of the intoxications. Compulsive users reported the absence of positive effects in 15 percent of the intoxications and negative effects in 82 percent of the intoxications. The acute and chronic effects reported by these compulsive users, all of whan were smoking cocaine free base, did not differ substantially from those seeking clinical attention. These are discussed elsewhere (Siegel 1982).

Several positive and negative chronic effects were reported by users. The positive effects included: a generalized feeling of increased energy, increased sensitivity to cocaine, general mood elevation, and weight loss. Negative effects included restlessness or irritability, attentional or perceptual disturbances, nasal problems, and fatigue or lassitude. During 1975-1978, users reported a gradual reduction in the frequency of these chronic positive effects and a concomitant increase in the frequency of chronic negative effects such as fatigue (Siegel 1980, table 2). From 1979 to 1983, there appeared to be no further changes in the relative frequency of positive and negative effects for social-recreational users. Overall, these social users reported some chronic positive effects in all intoxications while negative effects were experienced in 11 percent of the intoxications. Conversely, the ratio of chronic positive to negative effects appeared to decrease with patterns of increased use. Thus, circumstantial users reported percentage ratios of 74 percent (positive effects) to 25 percent (negative effects) and intensified users reported 56 percent (postive effects) to 32 percent (negative effects). Compulsive users reported chronic positve effects in all intoxications and negative effects in 71 percent of the intoxications.

Toxic Crisis Reactions

In addition to the negative effects described above, users reported adverse physical and psychological toxic reactions. Toxic physical reactions were defined as acute crises consisting of at least one of the following symptoms: myoclonic jerking, chest pains, nausea or vomiting, respiration difficulties or failure, seizures or convulsions, or unconsciousness. More commonly experienced physical symptoms such as blurred vision, nasal problems, or insomnia were not classified as crisis reactions. Toxic psychological reactions were defined as acute crises with at least one of the following symptoms: hallucinations with delusions, violent loss of impulse control, or attempted suicide. More commonly experienced psychological symptoms such as psychomotor agitation, depression, paranoia, or situational impotency were not classified as crisis reactions here.

During 1975-1978, users reported no toxic physical or psychological crisis react ions. From 1979-1983, the social-recreational users continued to report no toxic physical or psychological crises. Also during 1979-1983, 18 percent of the circumstantial users reported an average of four physical crises and one psychological crisis, all instances of impulse dyscontrol. All intensified users reported an average of two physical crises and one psychological crisis. All compulsive users also reported experiencing adverse crises during this latter period. The incidence of these reactions was so frequent that canpulsive users could not accurately estimate their number. However, they reported that both physical and psychological crises developed in approximately 10 percent of their intoxications. The nature of these toxic crises for compulsive users has been discussed elsewhere (Siegel 1982).

Personality Profiles

During 1975-1978, retesting with the MMPI detected no pathological deviations from normal T-score means for adults. However, a slight but insignificant elevation in D scales (Depression) and Pa scales (Paranoia) was noted for 7 percent of the users on at least one retest during this period. Also during this period, the EWI retesting indicated that 38 percent of the users displayed elevated Euphoria scales. This suggests increased happiness and contentment with life. Concomitantly, 5 percent showed increased suspiciousness or paranoia, but this was usually directed at concern over their own bodies (hypochondriacal complaints, perceptual disturbances, rhinit is) rather than paranoid ideation concerning others.

From 1979 to 1983, retesting continued only with the EWI. The social-recreational and circumstantial-situational users showed no significant abnormal scores during this period. Most displayed elevated euphoria scales but these were not significant. The four intensified users did not show abnormal T-scores but all showed elevated scores on scales suggesting concern centering around their bodies, egocentricity, and disturbances in social adjustment and comnunication. The five compulsive users displayed marked elevations in almost all T-scores. The typical configuration of these scores suggested a paranoid profile with features of depression, reduced frustration tolerance, problems of social adjustment and communication, disturbances in sleep-wake rhythms, and difficulties in impulse regulation.

Multiple Drug Use

At the beginning of the study, all subjects had past and current (1975) histories of multiple drug use. Prior to their cocaine use, they reported experience with alcohol (100%), marijuana (100%), amphetamines (27%), barbiturates (20%), hallucinogens (10%), diazepam (10%), methaqualone (2%), and opiates (2%). During 1975-1978, the average percentage of subjects using other drugs were: alcohol-85%; marijuana-66%; amphetanines-8%;

hallucinogens-5%; diazepam-4%; opiates-4%; and methaqualone-4%. During 1978-1983, the following distribution was reported: alcohol-70%; methaqalone-30%; marijuana-24%; hallucinogens-18%; diazepam-13%; opiates-10%; and amphetanines-2.5%. An important caveat is that these drugs were not necessarily coadministered with cocaine. Many of these drugs were used to treat the hyperexcitability and stimulation produced during periods of excessive cocaine use.

Treatment

Since all users were monitored on a regular basis, few sought independent treatment for cocaine-related problems. Nonetheless, a number were given referrals for specific complaints: two users developed perforated septums; two developed skin problems associated with cocaine smoking: and six became involved in legal problems associated with possession of cocaine. Following toxic crisis reactions, two users summoned paramedics and one user want to the emergency room of a local hospital. One intensified and one compulsive user chose to enter a formal clinical treatment program.

Most users initiated self-control strategies in order to treat their own negative effects and crisis reactions. The most common strategy was to titrate or restrict the amount of cocaine used in a given period of time. This was usually accomplished by purchasing or carrying a limited anount of cocaine at a time. Social-recreational users reported success in this method. A few users attempted to control use by combining supplies of cocaine with cocaine substitutes, commercial products containing local anesthetics and stimulants that mimic the effects of cocaine.

Other users initiated strategies whereby they periodically abstained from cocaine in an effort to "detoxify" and/or "recover from cocaine effects" for periods ranging from a few days to a few months. The most common negative effects prompting abstinence were nasal problems and irritability. Three major strategies were employed. In avoidance strategies, users attempted to avoid all contact with cocaine, cocaine paraphernalia, and cocaine users. Some users reported that it was effective simply to avoid dealers or other social users. Others engaged in destruction of paraphernalia, and still others employed physical constraints by taking a vacation. In aversion strategies, users sought out and embraced information and stories containing aversive stimuli. Perhaps the most common stories were those that circulated about individuals suffering toxic reactions. These folklore stories told of frequent incidents of bizarre behavior, economic distress, casualties in the criminaljustice system, and toxic overdoses. The stories appeared to generate much concern and anxiety, prompting at least one intensified user to seek counseling and encouraging many others to return for periodic followup examinations throughout the study. In these exams, users would ask for verification of the folklore as well as explanations for cocaine-related effects. In self-initiated contingency contracting, which differs from

clinical models (Anker and Crowley 1982), users made a public pledge to family or peers and asked for support in maintaining abstinence. This support took the form of denial of cocaine supplies, tight controls over financial resources, and careful monitoring of behavior. Surprisingly, pledges were often made to dealers so that they would no longer supply cocaine, and many users reported such contracts were honored by their dealers. However, since the contracts were initiated and maintained verbally, they were easily broken after periods ranging from 1 week to 6 months.

Discussion

Considering the escalating toxicity and dependency associated with long-term use of stimulant drugs, the most apparent aspect of these findings is that many of the social-recreational cocaine users do not change their long-term pattern of use and do not appear to develop toxic crisis reactions that may warrant clinical attention. Thus, this population of users differs substantially from those "abusers" who experience physical or psychological dysfunction and seek clinical treatment (Helfrich et al. 1983; Kleber, this volume; Siegel 1982).

Fully 50 percent of the social users available for followup in 1983 retained this pattern of use from 1975-1983. One common factor cited for such controlled recreational use is the rate-limiting effect of cocaine's high financial cost. Fourteen of these users were students in 1975 and, throughout the study period, graduated and entered higher income levels. Yet only three escalated use from the initial social patterns. Two users, who were law students and became attorneys, developed circumstantial-situational patterns: the third, a medical student who became a physician, became a compulsive user. The 12 ex-students who remained social users, as well as the other users in this category, all reported stable patterns of cocaine use independent of increased income available for the drug. Thus, the notion that cocaine use is exclusively limited by cost is not supported in this group.

Surprisingly, social-recreational users maintained relatively stable patterns of use when supplies were available and when they were not purposely abstaining. These users ranked cocaine as their recreational drug of choice. It was viewed by users as a social drug which facilitated social behavior. When restricted to social situations, users reported that cocaine was "ideal" 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 minimal after effects. Users reported that this set and setting were the major factors controlling the pattern of use. In addition, they reported that the inconsistent quality of street cocaine, together with a rapidly developing tolerance to the euphoric effects, contributed to controlled use. Legal risks, supply, and cost were cited as minor factors.

The intranasal cocaine users averaged between 1 and 4 grams per month during 1975 to 1978. From 1979 to 1983, these users increased use to an average between 1 and 3 grams per week. The hypothesis that increased dosayes result in increased risks of negative effects and toxicity is partially supported by findings here. Social-recreational users averaged 1 gram per week during 1979-1983 and manifested significant increases in acute and chronic negative effects despite the absence of crisis reactions. Circumstantial-situational users averaged 2 grams per week during 1979-1983 and displayed increased chronic negative effects in 25 percent of the intoxications as well as some crisis reactions. Three of these users reported an average of four physical crises and one psychological crisis. Intensified users averaged 3 grams per week during the some period and reported chronic negative effects in 32 percent of the intoxications along with an average of two physical and one psychological crises. The relative reduction of crises in the intensified users may be partially related to behavioral tolerance that could be associated with daily patterns of use. Tolerance may also explain the reduction in positive effects reported by both circumstantial-situational and intensified users. However, such tolerance seems to have been easily overshadowed by the escalating dosages of compulsive use. Indeed, compulsive users, all of whom smoked cocaine free base, reported experiencing chronic positive effects in all intoxications, negative effects in 71 percent of the intoxications, and crises in 10 percent of the intoxications. Compulsive users also manifested profiles of a paranoid disorder, while most other users only displayed profiles of heightened euphoria.

The hypothesis that long-term use of cocaine is inevitably associated with an escalating dependency marked by more frequent patterns of use is not supported by these findings. While little is known about the 41 users who dropped out of the study at sane time during the 9 years, 8 social-recreational users who refused to report for followup examinations after 1979 explained that they had stopped all use of cocaine. During 1979-1983, several users reported abstaining for periods ranging from a few days to several months. Four social-recreational users stopped all use for 2 years in the middle of the study. Even compulsive users reported periods of social use or brief periods of abstinence. Thus, users periodically attempted to treat themselves with strategies of controlled use, forced abstinence, or even multiple drug use.

OVERVIEW

The year 1970 began with an increase in the nonmedical use of cocaine. Most users began as experimental users engaged in short-term, nonpatterned trials of cocaine with varying intensity. These users were primarily motivated by curiosity about cocaine and a desire to experience the anticipated drug effects of euphoria, stimulation, and enhanced sexual desire (Siegel 1977). Some users experienced little or no drug effect, which supported their belief that cocaine was a subtle,

over-priced drug undeserviry of continued use. Other users who experienced a “kick” or "rush" expressed a desire to continue use.

From 1970 to 1983 these users separated into various patterns of use and abuse. Short-term observations of these users suggested that intensified and compulsive patterns of use resulted in physical and psychological problems. Observations of users seeking clinical attention confirmed the presence of serious dependency, dysfunction, and toxicity. Longitudinal observations confirmed many of these findings but revealed that many users who adopt social-recreational patterns appear to control use with no escalation to more individual-oriented patterns, thus circumventing toxic crises.

Taken together, however, the increased frequency of negative effects and crisis reactions, the escalation of some users to canpulsive smoking of cocaine free base, the rising psychosocial and financial and legal costs, all indicate that the last 13 years of changing patterns of cocaine use have been the most unlucky of its 125 year history. Given the promise of cocaine as a "renaissance" of the 185Os, the "medical miracle" of the 187Os, and the "safe recreational drug" of the 197Os, these 13 years have also been disillusioning. As Mantegazza, who may have started it all, might have commented, as he did upon recovering from a coca intoxication full of blissful and fantastic images only to realize that they were mere hallucinations:

> One sighs deeply or laughs madly.
>
> (Mantegazza 1859, p. 39)

SUMMARY

The literature describing contemporary cocaine use from 1970 to 1983 has been reviewed. Short-term studies published on users observed an initial period of social-recreational use supported by the belief that cocaine was safe. By the end of this period, both dosages and chronicity of cocaine use showed an escalation marked by increased adverse reactions. A longitudinal study tracked 99 social-recreational users from 1975 to 1983. By 1983, 41 users had dropped out of the study while eight others had stopped all use. Of the 50 continuing users still in the study in 1983, 25 remained primarily social users with few negative effects and no toxic physical or psychological crises. The remaining 25 users, while engaged in some social use, were more frequently involved in other patterns. Sixteen users frequently escalated to circumstantial-situational patterns marked by some toxic physical effects but no psychological crises. Four users developed intensified (daily) patterns of use with episodes of both physical and psychological crisis reactions. Five users became compulsive users, smoking cocaine free base, and experienced crisis reactions in approximately 10 percent of their intoxications. The majority of users attempted to treat the

hyperexcitability and stimulation of excessive cocaine use with multiple drug use or self-initiated strategies of controlled use or short-term abstinence. It is concluded that many of the social users are capable of controlling use with no escalation to more individual-oriented patterns. Others, by escalating patterns of use, increase the risks of dependency and toxicity.

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AUTHOR

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

Mailing Address

P.O.B. 84358
Veterans ministration Branch
Los Angeles, California 90073

Cocaine Abuse: A Review of Current and Experimental Treatments

Herbert D. Kleber and Frank H. Gawin

Cocaine abuse is a rececntly revived drug problem that is again generating great popular concern. Unfortunately, scientitic evaluation of cocaine abuse treatment has been surprisingly sparse kind no consensus exists regarding optimal treatment strategies. This review summarizes current treatment issues and regimens. as well as preliminary data on new, approaches to cocaine abuse treatment.

Since this chapter will deal with treatment of the cocaine abuser, it is important from the outset to define what is meant by that term. Although in some settings any use of ilegal drugs equals abuse. such a definition is more legal than medical and will not he used here. Instead. the definition of drug abuse found elswhere in the field will be employed. namely..."the nonprescription use of psychoactive chemicals by an individual to alter his her psychological state in a situation in which the individiual or society incurs some harm" (Kleber 1974). The great majority of cocaine users applying for treatment fit into this definition. The most common exception is the individual who defines his use as recreational. controlled and nonharmful. but is brought to treatment by another (e.g. spouse, parent), while the significant other views the cocaine use as harmful and needing to be stopped at once. It can be argued. of course. that the existence of such a dispute is in itself evidence that "harm" is occurring. Alternatively, it may be argued that the legal definition is being imposed in such cases. These issues lead to the question of who "needs" treatment? A broad answer is: any cocaine user who finds that be cannot stop or significantly cut back his use in spite of the presence of problems arising from the use.

The above definitions approximate the DSM-III criteria for cocaine abuse: "a pattern of pathological use. impairment in social or occupational functioning due to cocaine use, and duration of disturbance of at least one month,"but are broader in their locus on the individual's self-perception of harm.

It should also he noted that the studies and impressions reviewed here are based only on patients who appear for treatment. It is probable that some cocaine abusers, like some alcohol and nicotine abusers, are able to stop use without treatment. No data is available indicating what proportion of those who want to cease cocaine use are able to do so without treatment. Similarly, the strategies employed and difficulties experienced by those who cease use without treatment have not been systematically studied. although Siegel has described longitudinal use patterns which include cessation and abstinence (this volume).

COCAINE, ABUSE AND CONCURRENT DISORDERS: DIAGNOSIS

Our clinical experience and the literature agree that individuals who abuse cocaine arc not a homogenous class. Distinctions in characterization of cocaine abusers with clear treatment relevance exist primarily along dimensions of psychiatric symptoms and behavioral-psychosocial disruption.

Greater variation in severity of use may exist in patients seeking treatment for cocaine abuse than in patients seeking treatment for abuse of other substances (Gawin and Kleber 1983a, Gold 1983). The typical cocaine user probably, begins his her use in a similar way to the typical marijuana user. albeit at a later age. Like marijuana. cocaine has been labelled by popular culture as "recreational," and most who try it do so with the firm belief that they will have no difficulty in controlling their consumption. Many people are successful in such an endeavor; some, however, increase their use and appear for treatment.

The point at which treatment is sought can vary dramatically. Because of cocaine's expense, significant psychosocial disruption leading to treatment can often occur without extreme abuse. The actual abuse in such cases is similar to that occurring with substances such as nicotine and marijuana. At the other end of the cocaine abuse spectrum lies very heavy intravenous (Gawin and Kleber 1983a) or freebase cocaine abuse (Siegel 1982), which is continuous for prolonged periods, in a pattern very similar to that observed in intravenous methamphetamine addicts (Kramer et al. 1967) over a decade ago. Treatment needs within this diverse population vary based on severity. Flexibility is therefore necessary in designing treatments for cocaine abusers.

Route of administration has been used as an indication of the probability that disruptive use patterns will develop. This has prompted recent controversy (Helfrich et al. 1983). Severe cocaine abuse has been considered a sequel of administration by routes that provide very rapid changes in plasma stimulant levels, such as intravenous use or cocaine freebase smoking (Siegel 1982; Van Dyke and Bach 1982). Intranasal use has been popularly considered comparatively mild abuse of a "nonaddicting," "safe" stimulant (Grinspoon and Bakalar 1976). Preliminary evaluations of patients appearing for treatment contradict the assumption that intranasal administration is not associated with severe cocaine abuse. Route of administration is not significantly related to psychosocial disruption (Gawin and Kleber 1983a: Helfrich et al. 1983), neuroendocrine abnormalities (Gawin and Kleber 1983b), or psychiatric diagnoses (Gawin and Kleber 1983a; Weiss et al. 1983). These data support the impression that severe cocaine abuse can develop with any route of administration. However. our experience and that of others is also that intravenous abusers or cocaine freebase smokers are more likely to develop significant distress requiring treatment. Epidemiologic study comparing distress and the need for treatment with mode of administration in the general population of cocaine users has not been done and should be extremely difficult to implement. Since severity of cocaine abuse cannot be determined simply on

the basis of route of administration, other factors, such as dosage. pattern and duration of use, degree of psychosocial disruption and impulse control, and medical and psychiatric characteristics. also require evaluation in assessing severity of cocaine usage and treatment needs. No research clearly: demarcating the contribution of each of these factors or of others to "severity" has been done; therefore. assessments remain based, at present. on clinical impressions and evaluation.

Variations also exist in the psychiatric characterization of cocaine abusers. Detailed modern psychiatric descriptions are limited. Past attempts have focused on nondiagnostic characterization using instruments such as the MMPI (Helfrich et al. 1983; Siegel 1977) or have focused on personality attributes or psychoanalytic formulations of cocaine abusers (Khantzian 1979; Wieder and Kaplan 1969; Wurmser 1974). and the relevance of such work to treatment decisions is unclear. Drug abusers, in general, have been observed to self-regulate painful feelings and psychiatric symptoms via their drug use (Khantzian 1981; Rounsaville et al. 1982). If cocaine use occurs as self-medication. conventional treatments modulating self-medicated symptoms would be indicated. The most important and clearly treatable disorders of this type correspond to DSM-III axis I categories. Only two studies of DSM-III axis I symptomatology in cocaine abusers exist. Weiss et al. (1983) recently presented DSM-III diagnostic data for 30 hospitalized cocaine abusers, and Gawin and Kleber (1983a) reported Axis 1 data on 17 outpatient cocaine abusers. These independent studies generated very similar results, with depressive disorders (Major depression, Dysthymic disorder. Atypical depression) appearing in 30 percent and bipolar disorders (including Cyclothymic disorder) in 20 percent of each sample. Also, a smaller hut possibly important sub-group of patients with Attention Deficit Disorder-Residual Type (ADD) existed in each sample. Thus a large proportion of cocaine abusers could be self-medicating. Since more and larger studies have not yet been done and methodologic problems require clarification (Gawin and Kleber 1983a). the actual prevalence, and therapeutic relevance. of Axis l-like psychiatric disorder in cocaine abusers requires further examination.

Accurate psychiatric and behavioral characterization of the cocaine abuser is important because symptomatology appearing during abstinence could theoretically provide important guides both to when and what pharmacological adjuncts are indicated (Gawin and Kleber 1983c). However, the meaning and importance of such symptoms are at present based only on the self-medication hypothesis. Two further issues confuse the interpretation of symptoms in cocaine abuse. First. definitive diagnoses of psychiatric illness other than substance abuse are difficult to make in the context of active drug abuse because symptoms may arise secondarily from the drug use itself, rather than preceding the drug abuse. Second, clarification between the acute depressive symptomatology occurring immediately after an episode of cocaine use (the post-cocaine "crash") and more enduring symptomatology independent of specific use episodes is also difficult. Thus investigators in the studies thus far have attempted to circumvent these issues by gathering extensive historical and

corroborating family history data, and by repeated longitudinal evaluations isolated from periods of acute cocaine use and post-cocaine symptomatology However, these "diagnostic" studies must be considered tentative in the absence of prospective study or more elaborate investigation because exclusinoary criteria based on substance abuse could not be applied

The “diagnoses” in the studies cited may nonetheless be useful as simple descriptions of the clinical state of cocaine abusers. Since symptoms in the cocaine abuser could indicate the presence of enduring cocaine-induced disorders which mimic psychiatric syndromes, or subclinical susceptibility to psychopathology aggravated by cocaine abuse. and both of these potential consequences of cocaine use could be responsive to conventional therapies, it is possible that distinctions between antecedent or consequent symptomatology would not determine initial pharmacological treatment choice. Such distinctions could. however, still affect issues such as duration of treatment or prophylactic treatment and require evaluation.

Two groups of pilot efforts that reflect diagnosis in the context of cocaine abuse treatment have been reported. These studies are all non-blind, non-placebo preliminary examinations. The first group consists of descriptions of a total of seven cocaine abusers with diagnoses of ADD by Khantzian et al. (1983a. l983b) and Weiss et al. (1983). Six responded to appropriate stimulant medications. The second study consists of a structured open trial of lithium and desipramine (Gawin and Kleber 1983c) in which lithium administration was associated with cessation of cocaine abuse and diminished cocaine craving in several cyclothymic patients, while non-cyclothymic cocaine abusers did not appear to benefit from lithium. Desipramine also appeared beneficial. but independently of diagnosis. This treatment is discussed more fully in the discussion of pharmacotherapy below. In all, these reports indicate that ADD-Residual Type and cyclothymic disorder bipolar disorder may comprise subgroups of cocaine abusers with distinct treatment needs. More definitive research is obviously needed to substantiate these studies. Future research would benefit from uniform attention to diagnostic issues and to non-homogeneity among cocaine abusers.

Treatment of thc acute complications sometimes associated with cocaine abuse is based on clinical experience rather than rigorous comparisons. Medical complications of acute cocaine use and their treatment are reviewed elsewhere (Gay 1982). Acute psychiatric complications occur in three areas. These include dysphoric agitation, psychotic symptoms, and acute, severe post-use depression. Gay (1982) and Rappolt et al. (1977) employ, diazepam for transient agitation and desribe dramatic amelioration of symptoms with addition of propranolol for more persistent cases. Neuroleptics are routinely used for brief periods for severe cocaine-associated psychotic symptoms. The present authors employ chlorpromazine because of its sedative properties and because evidence from primate studies indicates that a potential interaction between cocaine’s epileptogenic effects and decreased seizure threshold associated with neuroleplics does not occur. Instead chlorpromazine substantially antagonizes epileptogenic and lethal effects of cocaine (Guinn et

al. 1980). It should be noted that the same study reported increased seizure susceptibility and decreased mean lethal cocaine dose with propranolol. but the clinical significance of this is unclear, since Gay et al. (1982) have administered propranolol in several hundred cases without major untoward effects. Finally, suicidal ideation and other depressive symptomatology often occur during the post-cocaine "crash." Such symptoms are usually transient, require no acute treatment other than close observation, and resolve following sleep normalization (Gawin and Kleber 1983a). Prolonged severe depression was discussed earlier. Also, psychotic symptoms may be short-lived in cocaine abuse and usually remit following sleep normalization.

COCAINE ABUSE TREATMENT STRATEGIES

Strategies devised to treat cocaine abuse have existed since its intractable lure for some first became obvious almost a century ago. During this period no generally accepted or successful treatment has emerged. Chronic cocaine abuse has been assumed to cause no physiologic withdrawal state on discontinuation because of insufficient evidence for an abstinence syndrome of major physiological changes. like the classic sort characterizing sedative or opiate withdrawal (Glatt 1974; Grinspoon and Bakalar 1980; Woods and Downs 1973). Cocaine abuse has thus been assumed to be a "psychological dependence" rather than one involving neurophysiological adaptations, and currently used treatments consist of psychological strategies aimed at modifying addictive behaviors. Issues related to current psychological strategies will be discussed first, followed by a summary of evidence indicating cocaine abuse may cause neuroadaptation. The latter includes a review of pharmacological strategies, aimed at reversal of such adaptation, which may hold future potential as adjuncts in cocaine abuse treatment.

Current Treatments

Only two comprehensive efforts at cocaine abuse treatment are described in the modern literature. Both are nonpharmacological, but each involves a very different approach to treatment. Anker and Crowley (1982) have adapted the behavioral method of contingency contracting (Boudin 1972; Ross and Jones 1973) for cocaine abuse. The contract involves such contingencies as the therapist's holding letters of notification of cocaine abuse or resignation of professional licenses, written by the patient with content chosen specifically because of severe irrevocable personal effects, and mailing them to drug enforcement authorities, employers, or licensing boards upon finding evidence of cocaine use in urinalysis or after missed urinalysis. Such treatment appears to effectively induce abstinence in those willing to take part. Anker and Crowley report 48% of their sample were willing to engage in this treatment, with over 90% cocaine abstinence during the duration of the "contract." Over half of these patients relapsed following completion of the "contract"(Crowley 1982), however, even though the sample was a presumably well motivated and well educated group. The patients declining "contracts" (52%) were treated with supportive psychotherapy which was also used as an additional intervention in those accepting contracts. All noncontract patients nonetheless

dropped out and or resumed cocaine abuse within 2 to 4 weeks. In this case, the consequences used with the behavioral treatment technique may have been unnecessarily punitive and may reduce the clients' willingness to become involved in treatment. Anker and Crowley present no comparisons of severity of cocaine use and thus ignore the likely possibility that cocaine abusers with severe craving and problems of control recognize their inability to comply and consequently avoid what for them would simply become destructive treatment. In addition to problems of long-term efficacy and possible inapplicability to more severe cocaine abuse, obvious ethical problems exist in those cases where the procedure could have been based on positive reinforcement or on less aversive techniques. That is, when negative rather than positive reinforcement procedures arc applied, an obligation to use the least deleterious technique exists. Variations in "contract" design, such as employing contingencies graduated in severity. or a top contingency level with less drastic consequences, or applying positive contingencies for abstinence (e.g.. starting with a sum of money from the patient and giving part back each week for clean urines) could also circumvent the problems noted. Some cases might optimally need a combination of both positive and negative reinforcement. These variations have not yet been examined in cocaine abuse treatment. Thus, optimal ways of applying the promising approach of contingency contracting will become clear only after further investigation. Broader behavioral intervention techniques have been widely applied and studied in treatment of diverse forms of drug abuse (Grabowski et al. 1984) but other behavioral techniques have not been subject to outcome studies in cocaine abuse. Cocaine abusers are usually treated with more conventional psychotherapies. Except for one description, however. such treatments and their orientations have not been reported in the literature. In the one study reported, Siegel (1982) describes a treatment approach using frequent supportive psychotherapy sessions, self-control strategies, "exercise therapy," and liberal hospitalization during initial "detoxification." This treatment aims at initially separating the user from the use-fostering environment via external controls, and then gradually facilitating internalization of controls through psychotherapy. Half of Siegel's sample of 32 heavy cocaine smokers dropped out, but 80% of those remaining were cocaine-free at 9-month followup.

Almost all psychotherapeutic treatment of cocaine abusers can be organized around three dimensions (Rounsaville et al. 1983). These are: (1) To help the abuser recognize deleterious effects of cocaine use and accept the need to stop it. Anker et al.'s treatment approach emphasizes this area. (2) To help the abuser manage impulsive behavior in general. and cocaine use in particular; for example, exploring ways to disassociate the abuser from cocaine use situations and cocaine sources. Such supportive functions are emphasized in Siegel's treatment approach. (3) To bring the abuser to an understanding of the functions that cocaine has played in his life and to help him serve these functions without drugs. For example. cocaine can serve narcissistic needs through the glamor associated with its use (or by direct pharmacological effects). needs for identity via the social networks and drug-using subculture associated with it. and anaclitic needs via possible facilitation of intimate interpersonal interactions. among many others. These three dimensions are

present, in varying degrees. in virtually all cocaine abuse treatment programs. They correspond closely to behavioral, supportive, and psychodynamic orientations to psychotherapy. The authors feel all three orientations are necessary in the treatment of cocaine abusers, but their admixture is best determined by taking into account the needs of the individual cocaine abuser at the time of seeking treatment. rather than by simple program structure. For example, patients in Anker and Crowley's (1982) study who refused contingency contracts could be approached from psychodynamic or supportive perspectives. The authors' clinical impression is that severe cocaine abusers acutely attemptingabstinencedo not respond to psychodynamic interventions. while moderate abusers may be more readily able to utilize them. Hence choice of primary therapeutic orientation might shift from behavioral to psychodynamic to supportive as severity increases, The authors'approach to the psychotherapy of cocaine abusers is described more fully elsewhere (Rounsaville et al. 1983). These notions have not as yet received any empirical testing.

Whether inpatient or outpatient treatment is indicated, and for whom, is also somewhat controversial. Siegel's study and earlier work in stimulant abuse (AMA Council 1978; Connell 1970) both strongly advocate hospitaliration for initial detoxification. However, in Anker and Crowley's (1982) study and Gawin and Kleber's (1983c) study using pharmacological adjuncts, hositaliration was usually not indicated. It is likely that this also reflects severity. Siegel's subjects were very heavy cocaine smokers who were minimally treated with adjunctive pharmacotherapy and may have been incapable of combating cocaine craving without hospitalization and seclusion from cocaine sources. These circumstances can require hospitalization, as can the existence of severe acute depressive or psychotic symptoms, multiple drug dependence especially involving sedative drugs, and previous failure(s) of the outpatient approach. The question needs to be raised, however, of whether inpatient treatment for the initial treatment of cocaine abuse is not too uniformly employed. It is known that relapse following hospitalization is quite high. This is consistent with studies of animal behavior (Goldberg et al. 1979; Spealman et al. 1977) and clinical work (Maddux and Desmond 1982; Wikler 1973) with drug abusers that point out the importance of environment and conditioning in drug-taking behavior. Cocaine abusers ultimately have to maintain abstinence within the general setting where abuse developed. and our impression is that a period of abstinence within the context of everyday stimuli and stressors, akin to a period of "extinction," is a necessary prerequisite to consistent long-term reductions in craving. Hospitalization in many cases may thus simply delay confrontation with fundamental issues determining long-term outcome. Also, since many subjects in Gawin and Kleber's study were also severe abusers but did not require hospitalization, severity alone may not be an index of need for inpatient treatment. This area requires further attention and clarification. The current almost ubiquitous presence of cocaine in many areas of American life makes it unlikely that the former user will simply be able to avoid temptation. Like the former cigarette smoker or alcoholic, the person attempting to give up cocaine must make the drug "psychologically unavailable" since it is so hard to make it physically unavailable.

A final psychological approach to cocaine abuse is the self-help group modeled after A.A. Some former abusers have reported significant help either from A.A. or N.A. (Narcotics Anonymous). Structure. group support, a religious tenor, and availability of an around-the-clock helping network have been of important assistance for some abusers. Some inpatient programs combine the confrontation groups long in use at residential therapeutic communities for narcotic addicts such as Daytop Village with heavy N.A. emphasis. No outcome studies of these programs for cocaine abusers have been reported.

Treatment of chronic cocaine abuse as currently practiced is vaguely defined and difficult to evaluate. The more structured treatments of Anker and Crowley (1982) and Siegel (1982), which are both intensive efforts, can claim long-term effectiveness in 25% and 40% of the total number of patients initially seeking treatment. Most other cocaine abuse treatment presently heing conducted has received no systematic evaluation. is based on nonspecific psychological treatments for general substance misuse with no particular attention to the specific difficulties of cocaine abuse, and appears to be even less effective than the treatments reviewed above. Such treatment, focused on simple abstinence and psychotherapeutic management., has been recently characterized as "ineffective and idealistic" (Van Dyke and Byck, in press). Treatment strategies for abusers of other stimulants, such as amphetamine (AMA Council 1978; Connell 1970) have been similar to the treatment described by Siegel and provide no additional knowledge applicable to cocaine abuse treatment. There thus appears to be a substantial need for new and effective treatments of cocaine abuse.

Potential New Directions in Treatment

Despite the past assumption that cocaine abuse is a "psychological addiction," it is plausible that chronic cocaine abuse could lead to neurophysiologic adaptations which require more than psychological intervention. Cocaine exerts its effects neurochemically. The nervous system's usual response to persistent neurochemicat perturbation is compensatory adaptation. It is illogical to assume that this does not occur or is unimportant in cocaine abuse. This does not rnean a classic abstinence syndrome and tolerence uniformly occur; rather chronic high dose use may generate sustained neurophysiological modification whose clinical expression is psychological.

Neuroadaptation following extensive chronic cocaine use is suggested by presence of persistent post-cocaine symptomatology (Blum 1976; Ellinwood 1977; Jaffe 1980; Siegel 1982). evidence that enduring neurophysiologic changes occur in animals following chronic cocaine administration (Banerjee et al. 1979; Borison et al. 1979; Chanda et al. 1979; Pert et al. 1979; Taylor et at. 1979). preliminary data indicating neuroendocrine abnormalities may be associated with cocaine "withdrawal"(Gawin and Kleber 1983b). and reports that pharmacologic interventions (Cronson and Flemenbaum 1978; Ellinwood 1977; Gold and Byck 1978; Mandell and Knapp 1976; Resnick et al. 1977; Smith and Wesson 1980) may facilitate cocaine abstinence. Pharmacologic interventions in cocaine abuse could thus be useful, but pharmacotherapy

aimed at correcting presumably cocaine-altered neurophysiologic states has not been systematically examined.

The following review outlines evidence indicating that desipramine, lithium. and methylphenidate could each facilitate cocaine abstinence, by different mechanisms. Although these are the same treatments discussed earlier in relationship to diagnosis, we wish to make clear that the following discussion pertains to the possible use of these agents as general treatments, irrespective of distinctions in symptomatology. Some points at which "diagnosis" may interact with general treatments will. however, be noted.

Tricyclic Antidepressants (TCAs)

Animal research on neurotransmitter and receptor changes following chronic cocaine suggests long-term effects possibly reversible by treatment with TCAs. Studies of receptor changes in animals, measured by radioligand binding, report increased beta-adrenergic (Banerjee et al. 1979; Chanda et al. 1979; Pert et al. 1979), alpha-adrenergic (Pert et al. 1979), and dopaminergic (Borison et al. 1979; Taylor et al. 1979) receptor binding. Receptor supersensitivity (beta-adrenergic or dopaminergic) could be a neurochemical substrate for post-cocaine dysphoria or craving.

One study (Gawin and Kleber 1983b) also shows some human cocaine abusers have elevated plasma growth hormone and decreased plasma prolactin, findings that are consistent with the adrenergic and dopaminergic receptor changes in animals. Beta-adrenergic supersensitivity has been hypothesized to be a cause of depressive illness, and beta-adrenergic subsensitivity, which can be induced by different types of antidepressant treatments may explain antidepressant effectiveness (Charney et al. 1981; Maggi et al. 1980; Sulser et al. 1978). Dopaminergic receptor changes following antidepressant treatment (Koide and Matshushita 1981; Naber et al. 1980) also are in the opposite direction from those occurring following chronic cocaine use, and could be even more important, since dopamine may mediate acute cocaine euphoria (Wise 1980), and craving or dysphoria after chronic cocaine could be based on adaptations within dopaminergic systems (Gawin and Kleber 1983c).

Additional support comes from studies done on amphetamine. Evidence from acute experiments in humans (Fischman et al. 1976), observations of the post-use state (Cassems et al. 198 I; Kosman and Unna 1968; Leith and Barrett 1976; Schildkraut et al. 1971; Watson et al. 1972) as well as animal behavioral (Colpaert et al. 1979; Leith and Barrett 1976; Leith and Barrett 1981), electrophysiological (Colpaert et al. 1979; Kokinidis and Zacharko 1980; Leith and Barrett 1976; Leith and Barrett 1981; Simpson 1974; Simpson and Annau 1977), and neurochemical studies (Post et al. 1976; Schildkraut et al. 1971; Watson et al. 1972) indicate that generalization to cocaine from amphetamine data is appropriate. Reports indicate that treatment with TCAs reverses chronic amphetamine-induced decreases in self-stimulation (Simpson 1974), a possible model for stimulant craving and its treatment. TCAs also appear to have effects opposite to those of cocaine on urinary MHPG (Cobbin et al. 1979; Goodwin et al. 1975: Perry et al. 1981).

These data lend neurochemical plausibility to the clinical observation that TCA therapy can be helpful in treating the cocaine abuser (Blum 1976; Ellinwood 1977; Siegel 1982; Smith and Wesson 1980). However, little systematic evaluation of TCA treatment of cocaine abusers has been done. Tennant and Rawson (1983) reported anecdotal data that desipramine facilitated abstinence in 14 cocaine abusers, but their study was based on a rationale involving acute desipramine-induced decreases in noradrenalin reuptake rather than receptor changes, and consequently 11 of their subjects received desipramine less than 7 days. The other 3 subjects were not described. Also. several methodologic shortcomings (Gawin and Kleber 1983c) and limited followup make the meaning of this report unclear. Gawin and Kleber (1983c) report prolonged desipramine treatment in 6 subjects, systematically evaluating cocaine use, craving, and psychosocial function. All 6 demonstrated prolonged abstinence (> 12 weeks). and craving decrease followed a delayed time course consistent with desipramine's time course for neuroreceptor changes and its known clinical characteristics in depression. Unlike Tennant and Rawson's (1983) results, half of the patients continued cocaine use throughout the first week and until the third week of treatment. Two of the subjects had diagnoses of major depressive disorder, but the remainder did not, and displayed desipramine-associated craving decreases and abstinence-facilitating effects despite lack of neurovgetative symptoms and prior treatment failures. Although the above results are encouraging, the reports cited were both non-blind and uncontrolled. Further more rigorous studies with larger sample size are needed before any conclusions arc drawn regarding desipramine use in cocaine abuse treatment.

Lithium Carbonate

Lithium carbonate treatment has been advocated for stimulant abuse (Buchsbaum et al. 1977; Flemenbaum 1974; Gold and Byck 1978; Knapp and Mandell 1975; Mandell and Knapp 1976; Resnick et al. 1977; VanKammen and Murphy 1975) based on lithium's antagonism of multiple acute stimulant effects including euphoria. Lithium blocks behavioral (Berggren et al. 1978; Cox et al. 1971; Davies et al. 1974; Furukawa et al. 1975; Lal and Sourkes 1972; Poitou et al. l975), electrophysiologic (Cassems et al. 1973; Colpaert et al. 1979). and neurochemical (Cobbin et al. 1979; Scheel-Kruger et al. 1977; Simpson and Annau 1977) effects of acute cocaine and amphetamine. Case studies report blockade of amphetamine euphoria by lithium (Flemenbaum 1974), as does one doubleblind placebo-controlled study of 11 depressed patients (VanKammen and Murphy 1975). Lithium had more variable results on amphetamine euphoria in 8 patients with personality disorders (Angrist and Gershon 1979). In several case studies (Cronson and Flemenbaum 1978; Gold and Byck 1978; Mandell and Knapp 1976) lithium attenuated cocaine-induced euphoria. Decreasing cocaine usage during the lithium treatment was also reported. Lithium did not block i.v. cocaine euphoria in an experiment done on 6 methadone-treated opiate addicts with significant cocaine abuse (Resnick et al. 1977). In the latter study (not a direct treatment evaluation). lithium administration was associated with decreases in cocaine abuse. despite lack of euphoria-attenuating effects. Studies of other stimulants (Huey et al. 1981;

Jarbe 1978; Wald et al. 1978) report similar results. In both studies of stimulants reporting no lithium blockade (Resnick et al. 1977; Wald et al. 1978) the agents were administered intravenously in relatively large boluses. Studies using other routes of administration do report blockade. Lithium effects may thus be competitively antagonized by large abrupt increases in stimulant blood levels. Since much street cocaine use is intranasal, the practical impact of this possibility on treatment is unclear and merits examination.

Overall, neurochemical evidence clearly indicates lithium has multiple acute effects which counteract those of cocaine. Clinical evidence further indicates that such properties may be useful in the treatment of stimulant abusers; however placebo-controlled studies do not exist. In the study by Gawin and Kleber (1983c) cited in the discussion of diagnosis, the responding cyclothymic subjects did not use cocaine to test euphoria-blocking effects, but the nonresponding patients reported cocaine euphoria was unchanged in intensity. Some suggestion of decreased duration of euphoria was noted, but this did not appear to be therapeutically useful.

Although the theoretical focus in lithium treatment of cocaine abuse has been on blockade, another potential mechanism of action exists. Lithium is reported to modulate fluctuations in functional receptor activity (Bunney and Garland 1983). Lithium's effectiveness in bipolar patients could be due to damping of abnormal oscillations of select neuroreceptor populations (Bunney et al. 1977). Lithium might reverse cocaine-induced neurophysiologic changes in a manner similar to that postulated for desipramine. Further, if cocaine causes receptor changes, bipolar or cyclothymic patients might be more sensitive to both such cocaine effects and to opposite lithium effects. This could explain any diagnostic specificity found in lithium treatment of cocaine abuse. In all, lithium's efficacy, diagnostic specificity, and possible mechanisms of action in cocaine abuse treatment all require further study.

Methylphenidate (MPH)

There is experimental evidence logically supporting possible clinical usefulness of MPH as a general treatment for severe cocaine abuse. Stimulant "high" in humans appears to be related to both plasma stimulant level prior to an additive increment and to the characteristics of plasma level changes, rather than to simple absolute plasma level (Van Dyke et al. 1982; Zahler et al. 1982). Increases of plasma stimulant level in subjects with preexistent stimulant concentrations may correspond to less euphoric effect than identical increases in plasma level in subjects with a stimulant-free baseline. Similarly, increases occurring slowly may correspond to less subjective euphoria than increases occurring more rapidly. Self-administration data in animals also support this phenomenon (Balster and Schuster 1973; Brady and Griffiths 1977) which has been called "acute tolerance."

Since methylphenidate produces euphoria indistinguishable from amphetamine (Brown et al. 1978) and, presumably, cocaine, MPH could produce consistent tolerance-sustaining effects. Through such an acute "cross tolerance," a given dose of cocaine might be less euphorigenic and have less abuse liability.

This is similar to high dose methadone maintenance causing Longer term tolerance to opiates, thereby reducing heroin euphoria and abuse. Unlike methadone, however, MPH tolerance would end sooner, requiring more frequent administration, due to its shorter half life.

Although MPH is an abusable euphorigen, it has advantages parallel to methadone administration. The advantages of medical dispensation include controlled dosage, decreased legal risk, economic stabilization, and a breaking of "street" associations and secondary abuse reinforcers. In preliminary use, cocaine abusers considered MPH far less desirable than cocaine, decreasing compliance. Attenuated cocaine effects and decreased abuse were reported when compliance occurred (Gawin and Kleber 1983d) in three pilot non-ADD patients treated by the authors; but abstinence from cocaine was not sustained, and it is unclear whether methylphenidate has practical utility as a general treatment. In all, methylphenidate may be similar to lithium, with treatment response in the few reports available occurring only in one diagnostic subgroup (ADD-residual type) and not in other cocaine abusers.

The potential pharmacotherapies described simply represent the treatment rationales available given the state of current theory and research. Much is unknown, and other possibilities also exist.

Conclusions

Single focus approaches are generally ineffective in drug abuse treatment. A number of approaches to cocaine abuse are in current use and a number of issues require resolution. Preliminary data on pharmacologic treatments are beginning to appear and pharmacologic adjuncts may show promise in the future. However, it currently appears no more likely that any unimodal approach to cocaine abuse treatment will arise than it has for opiate abusers. Integration of various approaches based on the needs of the patients seems indicated instead. A possible schema illustrating this and utilizing the impressions and preliminary studies reviewed here is presented in figure I. Before any such schema is used in clinical practice, however, detailed comprehensive research will be needed.

FIGURE 1

Possible Future Guidelines for Cocaine Abuse Treatment

Cocaine Abuse Seveity	Psychotherapeutic Approach	Pharmacotherapeutic Approach
Mild	Behavioral with or without Psychodynamic	None
Moderate	Supportive and Psychodynamic with or without Behavioral	Only if psychiatric diagnosis is present. Choice of agent based on sysptoms. If no treatble diagnosis exists, general treatment (desipramine) may be usefully tried in difficult cases.
Severe	Supportive, with or without hospitalization for acute phase; then as in "moderate"	General treatment (desipramine) indicated unless diagnosis dictates another treatment choice

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AUTHORS

Herbert D. Kleber, M.D.
Department of Psychiatry
Yale University School of Medicine

Frank H. Gawin, M.D.
Departments of Pharmacology and Psychiatry
Yale University School of Medicine

Drug Dependence Unit
Connecticut Mental Health Center
34 Park Street
New Haven, Connecticut
06510

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