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The Pharmacology of Cocaine Related to Its Abuse*

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I. Introduction

VIEWS about cocaine have changed dramatically over time and with experience. The Peruvian Indians of ancient times believed that coca, the plant from which cocaine is extracted, was a gift from the gods. Coca was accorded a position of highest regard in that culture, and its use was restricted to the ruling Incan class. With time, use of this plant spread to other strata, and its religious significance declined as the dominance of the Incans deteriorated. When the Spaniards arrived in the New World, they pronounced coca sinful and attempted to eradicate its use among their Indian slaves. However, the Spaniards soon discovered that the Indians would work long and hard under perilous conditions if allowed to use coca. Coca's extraordinary effects were not appreciated by Europeans until its principal constituent was chemically isolated in the 1850s. Over the next 20 to 30 years, cocaine's use increased dramatically and virtually everyone who came into contact with the drug believed that it had special and powerful positive effects. The most famous of its proponents, Sigmund Freud, initially believed that use of cocaine could cure many of humanity's ills, both medical and psychological. However, Freud

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soon observed the tragic consequences of its chronic use, a discovery that is being remade today, a full century later. Growing concern about cocaine's toxicity at the turn of the century was one of the reasons for the passage of severe antidrug laws, culminating in the Harrison Narcotics Act of 1914. These measures resulted in a marked decline in cocaine abuse. Although certain segments of the population continued to use cocaine over the next 50 years, its popularity returned dramatically in the early 1970s. From that time, there has been an almost uncanny repetition of events that occurred a century earlier: exaltation followed by condemnation. That is, cocaine was initially extolled as a harmless recreational drug and was contrasted to the amphetamines that were believed particularly harmful drugs of abuse ("speed kills"). However, over the next 15 years, as cocaine use increased logarithmically, its ability to maintain drug taking which leads to severe psychological and medical problems was once again realized. Today, few people in the United States and elsewhere are not aware of the variety of problems that cocaine abuse has created. Cocaine use is undoubtedly a major factor in the increased efforts of the United States government to control drug abuse. Likewise, research interest in this drug has grown.

The present review summarizes research on the behavioral pharmacology of cocaine that has been conducted over the last few years. This review stresses those aspects of its pharmacological profile related to the initiation, maintenance, and consequences (i.e., toxicity) of its abuse. This research is placed into a context by briefly summarizing the history of cocaine abuse, the epidemiology of its present use, and treatment approaches for those who have abused it. Although the main purpose of this review is to summarize what is known about the dependence-producing properties of cocaine, the research conducted with cocaine has made a significant impact on our understanding of brain-behavior interactions. Cocaine has become an important pharmacological tool for researchers to investigate the control of human behavior. History suggests that the abuse of cocaine is likely to decrease in the near future. However, an understanding of the biobehavioral mechanisms which underlie cocaine's abuse potential will contribute to our understanding of a variety of behavioral problems.

II. Botany, History, and Medical Uses

A. Botany

Cocaine is the principal alkaloid of *Erythroxylon coca*, a shrub that grows abundantly in the Andean Highlands and northwestern parts of the Amazon in South America. There are over 200 known species of the genus *Erythroxylon* but only *E. coca* var. *ipadu*, *E. novogranatense*, and *E. novogranatense* var. *truxillense* contain appreciable amounts of cocaine (Evans, 1981). Interestingly, these cocaine-containing plants are not wild but are cultivated by Indians living in these areas, a practice that began in antiquity. The dried leaves of the shrub are used today by inhabitants of Peru and Bolivia, and to a limited extent by isolated Indian populations in Colombia and Ecuador (Plowman, 1981). In the highland areas, the dried leaves are chewed with lime or ash added to promote the release of cocaine by changing the alkalinity of saliva. In contrast, the Indian populations in the Amazonean areas pulverize the dried leaves and combine this powder with other types of alkaline materials (e.g., leaves, bark). This mixture is then placed into the mouth where it mixes with the saliva. Unlike the chewed coca leaves, this mixture is eventually swallowed (Schultes, 1981).

Regardless of the method of use, present-day Indians use coca both as a medicinal and a psychoactive substance. Further, the effects achieved are undoubtedly due to the actions of the principal constituent, cocaine. This is suggested by the findings that substantial cocaine plasma levels can be attained when cocaine is chewed in the typical manner (Holmstedt et al., 1979; Paly et al., 1980).

B. History

Cocaine itself has only been used for approximately 100 years. However, the coca leaf has probably been used for well over a millenium, since ancient Indian legends describe its origin and supernatural powers. How and when the practice of using coca began has been lost in antiquity, but there is archeological evidence from Peruvian burial sites that the use of coca had begun by the 6th century AD (Petersen, 1977). The Incas called the coca plant a "gift of the Sun God" and used it, like the highland Indians of today, by placing a wad of leaves along with some ash, into the mouth. This wad was masticated and sucked to extract the cocaine. Sixteenth century accounts stated that coca "satisfies the hungry, gives new strength to the weary and exhausted and makes the unhappy forget their sorrows" (de la Vega, reported in Grinspoon and Bakalar, 1981). In addition, there is evidence that coca was used as a medicine in ancient times (Grinspoon and Bakalar, 1981).

The Incas believed that coca was of divine origin, and therefore during the height of the Incan empire (11th to 15th centuries), its use was reserved for ceremonial or religious purposes. With the decline of this empire, coca use lost much of its religious significance, and its use became more widespread. When the Spanish conquered the Incas in the 16th century, coca use was banned as being idolatrous. However, the Spaniards soon realized that under the arduous working conditions they imposed, and with food scarce, their Incan slaves worked harder in the mines if they were allowed to chew coca leaves. In fact, in some cases, the Indians were paid for their labors with coca leaves. The Catholic Church, which had originally been opposed to coca use, began systematic culti-

vation of the plant and maintained coca plantations (Carroll, 1977).

Despite the recognized and publicized stimulant properties of coca leaves, they did not achieve the popularity in Europe of other stimulants such as coffee and tea. It has been suggested that although glowing reports of coca's effects were available, the coca leaves decayed during their long ocean voyage from South America and no longer produced any appreciable effects (Byck, 1974). In addition, the plant was difficult to grow in the European climate. However, cocaine became popular in Europe after isolation from the coca plant by Niemann in 1855 and the uncritical endorsement of coca and cocaine by a number of scientists of the time. Paulo Mantegazza wrote a monograph entitled "On the Hygienic and Medicinal Virtues of Coca," stating "I would rather have a life span of ten years with coca than one of 1,000,000. . . centuries without coca" (quoted in Petersen, 1977, p. 21).

Angelo Mariani, a Corsican chemist, developed a coca wine which was praised by such notables of the time as Auguste Rodin, President William McKinley, Thomas Edison, and the Czar of Russia, and Pope Leo XVIII awarded him a gold medal for his efforts. Mariani published 13 volumes of testimonials to his wine. All of the proponents quoted in these volumes were given a free case of wine by Mariani, a tribute to his marketing skills.

Sigmund Freud was no doubt influenced by such raptures and published "Uber Coca" in 1884 (translated, 1963), reviewing the history of cocaine and pointing out its therapeutic utility. He suggested its usefulness as a stimulant and aphrodisiac, in treating asthma, wasting diseases, and digestive disorders, as a local anesthetic, and, as well, in the treatment of alcohol and morphine addiction. He used cocaine to treat his friend, von Fleischl, who was dependent on morphine that had been prescribed for severe pain. To his dependence on morphine, von Fleischl added a dependence on cocaine, including sequelae such as paranoid hallucinations and delusions of bugs crawling underneath the skin. The idea that cocaine and morphine could substitute for each other has been suggested repeatedly in the history of drug abuse treatment, generally with disastrous consequences. A number of other adverse consequences of cocaine use were soon reported, and Albrecht Ehrlenmeyer accused Freud of having unleashed "the third scourge of humanity" (after alcohol and opiates; Jones, 1961, in Byck, 1974).

Freud's major contribution to the understanding of cocaine's actions was his research into its psychopharmacology, using himself, a trained observer, as subject. He evaluated dose-response relationships as well as the duration of cocaine's effects on mood, hand strength, and measures of perception. His results were published in 1885 in "A Contribution to the Knowledge of the Effect of Cocaine" (in Byck, 1974). Freud correctly identified cocaine as both a central nervous system stimulant and a euphoriant. For the next 90 years, the paper published by Freud was the only report available derived from controlled studies which documented cocaine's effects in humans.

One of Freud's colleagues, Karl Koller, experimented with cocaine as a possible local anesthetic for eye surgery. He appears to have been prompted in this endeavor by Freud's observation that cocaine seemed to have pain-relieving properties (Byck, 1974), although this suggestion was first made by Maiz, a Peruvian ex-surgeon, in 1868 (quoted in Holmstedt and Fredga, 1981), and was also published by von Anrep in 1880 (in Holmstedt and Fredga, 1981). After initial experimentation with laboratory animals, Koller experimented on himself and established the use of cocaine as a local anesthetic in eye surgery. A number of other physicians, exploring cocaine's medical usefulness, used themselves as subjects, often with disastrous effects. For instance, William Hammond, Surgeon General of the United States, carried out a dose-response evaluation of cocaine's effects and admitted that he "came very near taking a fatal dose" (Byck, 1974). William Halsted, a founding physician of The Johns Hopkins University School of Medicine, carried out research on cocaine as a nerve blocker and became heavily dependent on the drug (Heuer, 1952). He, like a number of other physicians, including Sigmund Freud, believed that morphine and cocaine could substitute for each other, and so took morphine to cure his cocaine "habit." Unfortunately, he soon developed a lifelong dependence on morphine.

Interest in cocaine in the United States continued and, since prohibitionist sentiment was strong, a nonalcoholic extract of coca leaves and the caffeine-rich kola bean was marketed as Coca Cola, with its beverage label advertising "the intellectual beverage and temperance drink." Physicians in the United States began prescribing coca and cocaine products for a variety of ills, including toothache, headache, dyspepsia, gastrointestinal disorders, neuralgia, and melancholy, and cocaine was an ingredient in many patent medicines. Increased use of cocaine was accompanied by increased concern about its harmful effects. The early 20th century marked a period in which the American Medical Association became increasingly concerned with maintaining higher standards of medical practice, including curbing patent medicine sales. In addition, deleterious publicity about cocaine's effects in the form of racial slurs and accounts of black people attaining unheard of powers after cocaine use were published repeatedly (e.g., *The New York Times*, reported by Petersen, 1977). Cocaine had become a feared drug, and the term "dope fiend" was initially coined to describe the uncontrolled cocaine user (Kleber, 1988). In response to this, the federal government began to regulate the manufacture and sale of patent medicines. The Pure Food and Drug Act of 1906 required that cocaine be listed on the labels of all cocaine-containing patent

medicines, and the Harrison Narcotic Act of 1914 forbade use of cocaine in proprietary medicines and required registration of those involved in the importation, manufacture, or distribution of opium or coca products. In 1914, just prior to the passage of the Harrison Narcotic Act, 46 of 48 states had laws restricting the distribution or sale of coca or cocaine, while only 29 had laws controlling the sale of opiates. Subsequent national legislation further increased penalties for violation and continued restrictions on cocaine's medical use. These laws also identified cocaine erroneously as a narcotic, adding to the confusion about its medical usefulness, an error that has been perpetuated to the present.

The combination of increased adverse publicity about cocaine's effects and legislation making it illegal was associated with a substantial reduction in its popularity. Although there are virtually no data on level of cocaine use between the 1920s and the 1960s, a relatively small subpopulation of jazz musicians, actors, and actresses, and other members of the "cultural avant garde" continued to use it (Petersen, 1977). Cocaine's cost and illegality also made it a status drug for the affluent.

C. Medical Uses

Cocaine has limited medical usefulness because of its substantial potential for abuse and possible toxicity (see section VI). Cocaine is currently placed in Schedule II, a category of the Comprehensive Drug Abuse Prevention and Control Act of 1970 for drugs with an acceptable medical use, but with a high potential for abuse as well. Its utility is based on the fact that it is the only drug capable of causing both intense vasoconstriction and local anesthesia (Barash, 1977). The most important local action of cocaine is its ability to block nerve conduction (Ritchie and Greene, 1985), and it was, therefore, initially used extensively in ophthalmology. However, because it causes sloughing of the corneal epithelium when applied to the eye, its use is now limited to topical application in the upper respiratory tract. Because cocaine has the additional advantage of producing vasoconstriction, it is useful in surgeries where shrinking of mucous membranes and the concomitant decreased bleeding and increased visualization of the surgical field are required. Peak anesthetic effect following topical application of cocaine occurs within 2 to 5 minutes and lasts for 30 to 45 minutes (Ritchie and Greene, 1985). When applied topically to mucous membranes, anesthesia is superficial and does not extend to underlying structures.

Barash (1977) has pointed out that although the suggested upper limit of cocaine dose varies, solutions greater than 20% should not be used. Ritchie and Greene (1985), in fact, suggest a 4% cocaine solution as appropriate for topical local anesthesia. In general, the size of the area to be anesthetized should be considered, with larger areas requiring more dilute solutions as rapid intravascular absorption can occur. Van Dyke and Byck (reported in Barash, 1977) were unable to find a single case report of an allergic reaction to cocaine, but adverse consequences have been reported when cocaine was employed as a local anesthetic in combination with other drugs such as thiopental (Orr and Jones, 1968) or tricyclic antidepressants (Davis and McNeil, 1973). A survey of 741 plastic surgeons (Feehan and Mancusi-Ungaro, 1976) reported that cocaine, used in approximately 93,000 operations, was associated with mild reactions in 224 patients and severe reactions in only 14 cases. There were no reports of fatalities. It would appear that in concentrations used clinically, and with adherence to the appropriate safeguards, cocaine is a useful local anesthetic—it has a short latency to onset, a duration of action suitable for many otolaryngological procedures, vasoconstriction, and no signs of permanent mucosal or nerve damage (Barash, 1977). However, cocaine is rapidly absorbed into the circulation following topical application to mucous membranes (Javaid et al., 1978), and risk of toxicity after such applications always exists (see section VI).

Cocaine has also been used in Canada and Great Britain, but not in the United States, as an ingredient along with alcohol and morphine, in Brompton's mixture, to treat chronic pain of terminal cancer (Grinspoon and Bakalar, 1981). A recent study comparing the effects of cocaine plus morphine with morphine alone, however, showed no added effectiveness of the cocaine in this combination (Twycross, 1977), bringing into question its usefulness.

III. Pharmacokinetics and Metabolism

Illicit cocaine is sold as a white crystalline powder, cocaine hydrochloride, a water-soluble salt, and is adulterated by a variety of ingredients. Some adulterants, such as sugars (e.g., lactose, mannitol), are added to give more volume to the final product. Others are simply cheaper stimulants (e.g., caffeine, amphetamine) or local anesthetics (e.g., procaine, lidocaine) added to help provide the "freezing" or numbing effect which most buyers mistakenly believe is an indication of the purity of the cocaine they are purchasing. The most common nonmedical route of cocaine self-administration is "snorting" or inhaling the drug as a white powder. Ninety-five percent of cocaine users reported, in 1985, taking cocaine by this route (National Institute on Drug Abuse, 1988a). Peak plasma levels after intranasal crystalline cocaine occur approximately 30 min subsequent to inhalation, with 96 mg resulting in peak plasma levels of 150 to 200 ng/ml (Javaid et al., 1978). Cocaine has a half-life of about 40–60 minutes via this route (Javaid et al., 1983). When the drug is taken by the intranasal route, it limits its own absorption by causing constriction of the nasal mucous membranes.

When cocaine is taken intravenously, it has a rapid onset of action, with an initial substantial effect or intense "rush" reported within 1 or 2 minutes. Eight

percent of cocaine users reported, in 1985, having taken it intravenously (National Institute on Drug Abuse, 1988a). Cocaine plasma levels are correlated with dose of intravenous cocaine, and plasma levels of approximately 300 ng/ml have been recorded after a single 32-mg dose (Javaid et al., 1978). Parallel dissipation of plasma level and subjective effects is seen, and subjects report that they are ready to take another dose of cocaine within 30 to 40 minutes (Javaid et al., 1978). Elimination half-life, as with all routes, is approximately 40 to 60 minutes except, perhaps, at very high doses (Javaid et al., 1983; Barnett et al., 1981).

An efficient method of smoking cocaine ("free base") has emerged in recent years. Since the hydrochloride form of cocaine decomposes if it is heated to a temperature that pyrolizes it, the cocaine alkaloid, or free base, is the form smoked. Cocaine base is soluble in alcohol, acetone, oils, and ether, but is almost insoluble in water. This form of cocaine is a colorless, odorless, transparent crystalline substance that is not destroyed by heating to the temperatures required for vaporization. Users can readily prepare free base from the cocaine hydrochloride they purchase on the street by mixing it with an alkaline solution and precipitating the alkaloidal cocaine. In addition, this form of cocaine is now "commerically" available from illicit dealers in the form of a cake-like solid that is "cracked" off larger pieces. Free base, or crack as the cake-like solid is called, is smoked in a pipe, or a marijuana or nicotine cigarette. Blood levels peak rapidly because of efficient respiratory absorption, and chronic free base smokers have shown plasma levels of 800 to 900 ng/ml 3 h after smoking (Perez-Reyes et al., 1982), suggesting that substantial levels would be present immediately after the drug was smoked. The effect, as with intravenous cocaine, is relatively short, but the route is an easy one to use for repeated dosing. When cocaine plasma levels are compared across different routes of administration, the intravenous and smoked routes of administration yield virtually indistinguishable curves in terms of time of peak effect and dissipation of plasma levels (Fischman, 1988). Thus, the cocaine smoker has a rapid onset of action with the potential for substantial plasma levels using a route of administration that is socially acceptable and requires none of the paraphernalia associated with illicit drug use (e.g., needles, syringes).

Cocaine is metabolized by plasma and liver cholinesterases to water-soluble metabolites that are excreted in the urine (Vitti and Boni, 1985). The two major metabolites are benzoylecgonine and ecgonine methyl ester. Smaller amounts of ecgonine, norcocaine, and various hydroxylated products are also found in the urine after cocaine administration. Oxidative pathways account for considerably smaller amounts of cocaine metabolism (Vitti and Boni, 1985). Plasma cholinesterase activity is much lower in fetuses, infants, elderly men, patients with liver disease, and pregnant women, all of whom would be expected to be more sensitive to cocaine. Some people have a congenital cholinesterase deficiency, and they, too, would be expected to be highly sensitive to small doses of cocaine. Cocaine may be present in the urine of an adult for 24 to 36 h, depending on the route of administration and cholinesterase activity. The metabolites of cocaine in urine are useful markers of cocaine use. Assays for these metabolites are frequently employed in treatment programs (see section VII).

IV. Epidemiology

Cocaine abuse continues to be a major public health problem in the United States. The abuse of stimulants in the United States has cycled during the past century with at least two cycles involving cocaine almost exclusively (see section II for a description of the initial cycle). The second cycle of cocaine abuse began in the 1970s with rapidly escalating trends in the number of people initiating use, which peaked in 1979 to 1980. As of 1988, it appears that this trend of increased incidence has either reached a stable plateau or is decelerating. Even with a stable rate of growth, substantial numbers of individuals are initiating cocaine use each year and prevalence rates are not decreasing. In addition, an increasing number of people are seeking treatment for cocaine-related problems.

Using self-report data, the 1972 National Survey on Drug Abuse (Fishburne et al., 1980) indicated that for individuals aged 12 to 17 years, 1.5% had used cocaine at least once in their lifetime. For those aged 18 to 25 years, this figure was 9.1% (Abelson and Miller, 1985). At that time, evaluation of the extent of cocaine's dangers conducted by U.S. government-appointed review panels concluded that they were minimal, and it was believed that there was little social cost related to cocaine's use (National Commission on Marijuana and Drug Abuse, 1973; Strategy Council on Drug Abuse, 1973). During the period between 1974 and 1976, the number of people trying cocaine at least once (lifetime prevalence) increased from 5.4 million to 6.5 million, with an additional increase over the next 2 years to 9.8 million. By 1985, it was estimated that lifetime prevalence of cocaine use had escalated to more than 22 million people (Adams et al., 1987). Table 1 presents prevalence data for 1977 through 1985, indicating a substantial rise in both current users (past 30 days) and those reporting having ever used cocaine.

The demographic characteristics of cocaine users have been summarized in several survey reports. For instance, every 2 or 3 years the National Institute on Drug Abuse

TABLE 1
Trends in prevalence of cocaine use (in millions)

	1977	1979	1982	1985
Ever used	9.8	15.2	21.5	22.2
Past 30 days	1.6	4.3	4.2	5.8

(NIDA) conducts a self-report household survey on drug use and abuse of a nationally representative sample of individuals living in the United States. Based on the 1982 and 1985 surveys, the profile of the "typical" cocaine user was an unmarried male or female over the age of 21, likely to have moved 3 or more times in the past 5 years and to have held 3 or more jobs during that period (Adams, 1988). In addition, the 1985 survey found that use is greatest among the unemployed, and prevalence is higher in the northeastern and western portions of the United States as compared with the northcentral and southern portions (Adams et al., 1987). Other studies (Kandel et al., 1985; Newcomb and Bentler, 1986) have reported similar findings.

Washton, Gold, and their colleagues reported on the characteristics of callers to a "Hotline" telephone number (800-COCAINE) advertised nationally for those seeking information, advice, or treatment referral for cocaine-related problems (Washton et al., 1984; Washton and Gold, 1987; Roehrich et al., 1988). Although the callers do not represent a random sample of cocaine users because they are self-selected, the three surveys conducted by these investigators from 1983 to 1987 represent the first major effort to characterize cocaine users seeking referral or treatment. The 1983 survey reported on a sample of 500 users randomly selected from 70,000 callers during the initial 3 months of operation of the hotline (Washton et al., 1984). The second survey, also based on a random sample of 500 cocaine users during a 3-month period, was carried out in 1985 (Washton and Gold, 1987). The third survey administered a 30-item structured interview to 987 consecutive callers to 800-COCAINE, and reported data on the 177 users who met DSM-III criteria for cocaine abuse and were seeking referral for treatment (Roehrich et al., 1988).

On the basis of the evidence gathered from 800-COCAINE callers, there appears to have been a striking change from 1983 to 1985 in the demographic characteristics of cocaine users. While the typical caller in 1983 was a white, middle-income male between 25 and 40 from the northeastern or western portion of the United States, by 1985 cocaine use had spread to virtually all areas of the United States, and a broader cross-section of the population was using cocaine. Use by females and minority groups had increased as had use by adolescents and lower income groups. Increased availability at reduced prices was also reported. Striking differences clearly emerged when the data from the first two surveys were compared with the data from the last survey (Table 2). However, these differences may be confounded by the fact that inclusion in the 1987 data set was contingent on questionnaire answers meeting DSM-III criteria for cocaine abuse. Thus, the data from the 1987 survey are from a group describing themselves as cocaine abusers and seeking, although not yet in, treatment. The data suggest that cocaine users seeking referral for treatment in 1987, as well as meeting criteria for DSM-III diagnosis of cocaine abuse, were younger, poorer, had less education, and were more likely to be unemployed than those telephoning for information or treatment referral in 1983 or 1985 (Table 2). In addition, in 1987, the authors reported that 20% of their female callers used cocaine during pregnancy and 24% of all callers stated that cocaine was the first drug they had abused. In contrast to the earlier surveys, the percentage of users that typically free-based cocaine had increased whereas intranasal use had dropped. Finally, only 53% of the callers in 1987 had begun using cocaine by the inhalation route. The remainder had begun use by the more dangerous intravenous or smoked route of administration.

TABLE 2
Cocaine hotline survey data compared across years

	1983–1985	1987
Mean age (yr)	28.5–31	27
Income >$25,000/yr (%)	52	20
College education (%)	50	16
Problems/unemployed (%)	16	54
Free base use (%)	21	56
Intranasal use (%)	61	34

Few descriptions of cocaine abusers in treatment have been published. Schnoll et al. (1985) described a population of 172 cocaine abusers requesting treatment at a large urban chemical dependency unit. Three groups of cocaine users could be differentiated: 1) patients with no previous drug abuse treatment experience but substantial experience with drugs of high abuse liability, 2) patients with previous drug abuse treatment histories, and 3) patients with minimal or no previous drug experience (other than their current cocaine experience). Patients in the latter group were older than the patients in the other two groups and were seeking treatment after a relatively short duration of abuse. The authors suggested that these differences have implications for treatment and prognosis. For example, those with minimal drug abuse histories seeking treatment after a short period of cocaine use may well respond to a short-term outpatient behavioral intervention while those who had experienced repeated treatment failures might be candidates for an inpatient intervention (see section VII).

Studies of cocaine abusers in treatment (Gawin and Kleber, 1985; Schnoll et al., 1985; Helfrich et al., 1983) report that the average age of patients requesting treatment for their cocaine abuse is the late 20s or early 30s. Most patients are males, with an educational level of high school or better, and at least 70% are employed. The cocaine abusers in these studies report using more than 6 g/wk. However, the route of administration most frequently employed by these cocaine abusers varied across the different studies. Helfrich et al. (1983) reported that intranasal cocaine was most frequently used by those requesting treatment in their programs while Schnoll et al. (1985) reported that more than 40% of

their patients used cocaine in its free-base form. Gawin and Kleber (1985) reported a similar proportion of intravenous users. These differences may be related to the years sampled or the geographical area covered by the different surveys.

In a sample of 473 patients seeking psychiatric but not drug abuse treatment at a metropolitan Veterans Administration (VA) medical center, 25% were current cocaine users and 46% had used cocaine at some time in the past (Brower et al., 1986). Cocaine was most commonly smoked by this population (56%), and current users spent an average of $850 dollars on 14 g of cocaine during the past 30 days. This VA psychiatric population had a similar profile to those in treatment for cocaine use at the VA, with the typical user being a 33-year-old black male blue collar worker with a high school education, using cocaine by the free-base route. These demographic characteristics describe a poorer, less educated cocaine user, reflecting perhaps a trend towards lower cocaine prices or a spread of cocaine use to lower socioeconomic levels related to year of survey or location of the sample. Although concurrent drug use was not always reported, in general, the majority of patients in treatment after 1985 were also using alcohol and marijuana (Schnoll et al., 1985; Brower et al., 1986).

Few data exist on the characteristics of cocaine users who are not seeking advice or treatment. Such information is important since this population represents the majority of users at any one time. Schuster and Fischman (1985) reported on 287 consecutive volunteers to a cocaine research project that did not involve treatment. Approximately two-thirds of the volunteers were male, predominantly white, between the ages of 21 and 35. About 40% of the applicants were unemployed and an additional 12% were students. Sixty percent of the volunteers were high school graduates, 35% had some college education, and 13% were college graduates. Most of the volunteers were polydrug users with marijuana, alcohol, and stimulants being the most popular drugs for this sample. The data reported for this sample of users who were not seeking treatment or referral are remarkably similar to those results reported in the early cocaine hotline survey (Washton et al., 1984).

Unlike heroin, which tends to be used on a daily basis, cocaine is used in a cyclic pattern, similar to the pattern of use described for methamphetamine 20 years earlier (Kramer et al., 1967). For instance, in a survey of patients in treatment, intravenous users reported taking cocaine in discrete episodes lasting an average of 10.4 h twice weekly. During each of these episodes, they consumed an average of 3.6 g (Gawin and Kleber, 1985). Intranasal users tended to use smaller amounts over longer time periods, but with 50% more episodes per week. Such binge use has also been reported by Siegel (1985). In contrast, a substantial percentage of the patients in the Schnoll et al. study (1985) reported daily cocaine use.

Data obtained from surveys have also been analyzed to determine the relationship between initiation of cocaine use and other variables. Based on analyses of the 1982 and 1985 National Household Survey data, Adams (1988) has advanced the hypothesis that the probability of cocaine use increases with the frequency of marijuana use. The survey data indicated that virtually all cocaine users have used marijuana, that its use generally precedes cocaine use, and that marijuana use remains the strongest predictor of cocaine use. In fact, the strongest association with cocaine use of any drug is the use of marijuana 50 or more times. Adams suggests that the use of marijuana may increase availability or the probability of being offered cocaine.

A second factor related to initiation of cocaine use is age. Although drug use initiation in general appears to occur during adolescence, peaking in the early 20s, the initiation of cocaine use increases through the mid-20s (Kandel et al., 1985; O'Malley et al., 1985) and peaks between age 24 and 25 (Raveis and Kandel, 1987). This peak may occur even later as these studies did not sample an older population. Such trends have also been found by Johnston et al. (1987) who tracked high school seniors for up to 10 years after graduation. They found that the prevalence rate of cocaine use was greater for 20 year olds than for 19 year olds whose prevalence rate was greater than that for 18 year olds (O'Malley et al., 1985). Adams (1988) reported that the majority of new users sampled in the 1982 National Household survey were 30 and older. Smart et al. (1984) also found a relatively large percentage (21%) of cocaine abusers who had initiated use at age 26 or older. The extent and recency of use of marijuana was also important in predicting cocaine use in this population.

Johnston et al. (1987) has surveyed a nationally representative sample of approximately 16,000 students graduating from high school in the United States each year since 1976. Cocaine and other stimulant use was a notable exception to a general pattern of decline of drug use which began in 1982. Thus, during the past 10 years, the percentage of seniors who ever used cocaine increased from a low of 9.7% in 1976, to 16.0% in 1982, peaking in 1985 at 17.3%, and decreasing only slightly in 1986 to 16.9% (Johnston et al., 1987). In contrast, current use of marijuana in this population dropped from a 1978 peak of 37% to 29% in 1982 and 23% in 1986. In 1986, 13% of the seniors admitted using cocaine in the previous year, and 6% in the previous month. In addition, the 1986 survey provided the first data on the prevalence of crack use, with 4.1% of seniors reporting having tried crack at least once in the past year (Johnston et al., 1987).

Although the trend of increased incidence has leveled off in both the general and high school populations, prevalence remains high and Adams et al. (1987) have published data collected by NIDA showing dramatic increases in emergency room and treatment admissions

related to cocaine use. The Drug Abuse Warning Network (DAWN), which tabulates drug-related emergency room visits as well as medical examiner cases, has shown increases in reports involving cocaine for several years, with an almost 9-fold increase between the first 6 months of 1981 and the last 6 months of 1986, when over 13,300 emergencies were related to cocaine use. More than two-thirds of all cocaine-related emergencies involved cocaine in combination with other drugs.

In parallel to the DAWN reports, the number of individuals seeking treatment has also risen. Prior to 1982, data on admission to drug abuse treatment were collected and reported to NIDA through the Client Oriented Data Acquisition Process (CODAP). Since then, treatment data have been reported on a voluntary basis, and currently 15 states participate in this reporting (Adams et al., 1987). In 1984, primary and secondary cocaine-related problems accounted for 29% of all the treatment clients reported to NIDA, with 57% inhaling the drug, 16% free basing, and 25% injecting it intravenously. These percentages are consistent with those reported by Washton and his colleagues (Washton and Gold, 1987) collected from telephone interviews, supporting the accuracy of the telephone interview data. Since the 1987 Cocaine Hotline survey (Roehrich et al., 1988) showed a substantial increase in those smoking cocaine, it is likely that this increase can be generalized to a larger population. In further support of that finding are preliminary data from DAWN reporting a rise from approximately 1 in 20 to 1 in 4 in the proportion of cocaine-related emergency room episodes involving smoking (Adams et al., reported in National Institute on Drug Abuse, 1988b).

Because information on the frequency of problems experienced by cocaine users comes from DAWN or treatment reports to NIDA, it is difficult to evaluate the extent of these problems in the population as a whole. Jaffe (1985a) pointed out that although we have good survey data over a number of years from which to make estimates of the number of people using cocaine, we do not have measures of the proportion of that group experiencing drug-related problems. In an effort to obtain such data, a section on problems experienced was included in the 1985 National Household Survey on Drug Use (see Adams, 1988). Among those who reported using cocaine 6 or more times, 11% reported a period of daily use of 2 weeks or more and 6% reported feeling dependent. Interference with psychological or emotional functioning during the past year was reported by 14% of this population with 7% reporting problems during that time period in social functioning and 2% reporting health problems associated with their cocaine use. The distribution of self-reported problems in the Household Survey indicated that trying to cut down (20%) and needing larger amounts to get the same effect (13%) were reported more than other problems. DSM-III criteria for either cocaine abuse or dependence were applied to these data, and the analyses suggest that of the 9,759,000 cocaine users surveyed who used the drug during the past year, approximately 1,639,000 met the criteria (Adams, 1988).

In summary, epidemiological data from a variety of sources indicate that the incidence of cocaine use, with the possible exception of free basing, has leveled off; prevalence may be decreasing, but the number of people abusing cocaine remains high. Furthermore, the increased reports of emergency room incidents and deaths related to cocaine use, as well as the greater numbers of cocaine abusers who are seeking treatment, indicate that those using it may be doing so in greater amounts. In addition, it is possible that the recent substantial reductions in price coupled with the readily accessible smoking route and its high potential for abuse might keep this endemic level of cocaine use relatively high. The extraordinary reinforcing properties of this drug (see section V) coupled with increasing reports of its toxicity (see section VI) indicate that a consistent and carefully focused program of cocaine abuse prevention is required to combat the many problems associated with cocaine use.

V. Behavioral Pharmacology

A. Motor Behavior

1. Acute effects. One of the defining behavioral characteristics of cocaine as a psychomotor stimulant is its ability to elicit increases in motor activity. These motor-increasing effects have been investigated in nonhuman organisms and are similar to those produced by other psychomotor stimulants, particularly amphetamine. At low doses, these drugs produce an alerting response consisting of increases in exploration, locomotion, grooming, and rearing (Scheel-Kruger et al., 1977; Snoddy and Tessel, 1985). As the dose is increased, locomotor activity decreases and the behavioral patterns become stereotyped, i.e., a continuous repetition of one or a few items of behavior (Randrup and Munkvad, 1967; Lewander, 1977; Tyler and Tessel, 1979). Although the specific behaviors exhibited differ across species, these behaviors are components of the species' normal repertoire, but are performed in an abnormal repetitive manner. In rats, the repetitive behaviors induced by amphetamine and cocaine include head bobbing, gnawing, sniffing, and licking (Scheel-Kruger, 1971; Scheel-Kruger et al., 1977). While the profiles of stereotypy are generally similar across psychomotor stimulants, Scheel-Kruger et al. (1977) showed that the stereotypies induced by cocaine were less pronounced and somewhat different in character than stereotypies seen following the administration of amphetamine when these drugs were given intraperitoneally. On the other hand, the stereotypies induced by cocaine were similar to those produced by amphetamine when cocaine was given subcutaneously (Scheel-Kruger et al., 1977).

Although stereotypies are generally regarded as uncon-

ditioned responses, their form can be influenced by ongoing learned behaviors. For instance, Collins et al. (1979) trained both rats and cats to respond on a lever under a conditional discrimination paradigm. Under one stimulus condition (S+), responding was maintained at relatively high rates by milk presentation. Under the other stimulus condition (S−), responding was not reinforced (extinction) and occurred at low rates. When cocaine was administered immediately prior to an S+ period, rate of responding increased dramatically, which the investigators interpreted as a form of stereotyped behavior. However, if cocaine was given prior to a S− period, no rate increases were seen, but the animal engaged in more typical forms of stereotypy, such as repetitive head turning.

The neurobiology of the motor-activating effects of cocaine and the amphetamines has been the subject of numerous investigations for over two decades. In fact, investigators of the neurochemical basis of cocaine's behavioral effects have tended to restrict their assays to changes in locomotor activity and stereotypy (e.g., Scheel-Kruger et al., 1977), so much of what is known concerning its central nervous system actions is limited to these behavioral repertoires and may not generalize to other behavioral actions.

A critical examination of cellular and molecular mechanisms is beyond the scope of the present review and the reader is referred to a recent monograph summarizing the work of some leading researchers in this area (Clouet et al., 1988). The majority of evidence indicates that the neurochemical effects of cocaine and amphetamine underlying their ability to increase motor activity involve dopaminergic systems (Costall and Naylor, 1977, 1979; Costa and Garattini, 1970; Scheel-Kruger et al., 1977; Beninger, 1983). Although the precise mechanism(s) and site of action are still unknown, and differences between amphetamine and cocaine are only now being defined, there is general agreement that cocaine's ability to block dopamine (DA) reuptake by binding to dopamine transporters plays a major role in its motor-activating effects (Reith et al., 1980, 1981, 1986; Reith, 1988). However, Snoddy and Tessel (1983, 1985) have shown that the locomotor activating effects of both amphetamine and cocaine are blocked by the noradrenergic antagonist, prazosin, in mice. There is also evidence that cocaine binds to multiple receptor sites and interacts with other neurochemical systems that could modulate any of its behavioral effects (e.g., Scheel-Kruger et al., 1977; Reith et al., 1983; Reith, 1988; Lakoski and Cunningham, 1988; Hanbauer, 1988). However, many of these cellular and molecular effects have not been related to any of cocaine's physiological or behavioral actions. An interesting recent finding is that metaphit, an analog of phencyclidine (PCP) that is believed to inactivate PCP receptors (Rafferty et al., 1985), is able to reverse the increases in locomotor activity produced by DA reuptake blockers, including cocaine, but not by amphetamine (Sershen et al., 1988). The mechanism of this antagonism is not clearly related to blockade of dopamine uptake mechanisms but may involve increased catabolism of dopamine (Sershen et al., 1988). In addition, PCP is reported to have an affinity for DA receptors (Kennedy and Hanbauer, 1983) and its stereotypic effects are blocked by metaphit in rats (Contreras et al., 1985). There is also evidence that locomotor effects and stereotypy produced by amphetamine and cocaine, although both involving DA systems, are mediated by different dopaminergic pathways within the central nervous system and that competition between these two classes of behavior can occur (Joyce and Iversen, 1984; Kelly et al., 1975; Lyon and Robbins, 1975; Creese and Iversen, 1974), although the evidence is not unequivocal (see review by Beninger, 1983). In support of separate neural sites, Bhattacharyya and Pradhan (1979) observed that cocaine increased both locomotor activity and stereotypic behaviors, but the time course of these two effects differed; when maximum increases in one of the behaviors were noted, the other behavior tended to decrease. This study also illustrates the importance of measuring behavioral changes at several time points following drug administration.

2. Sensitization and conditioning. One of the most interesting effects of psychomotor stimulants is that repeated administration of these drugs enhances many of their effects. Early studies with cocaine clearly demonstrated that chronic cocaine administration resulted in an augmentation in hyperactivity, stereotypy, and convulsions in several species (Tatum and Seevers, 1929; Downs and Eddy, 1932a, b). These studies have been replicated using more quantitative methods in recent years. In general, such studies have shown that with repeated administration, cocaine produces increased levels of locomotor activity (e.g., Shuster et al., 1977), increases in the intensity of stereotypies (e.g., Post and Rose, 1976; Kilbey and Ellinwood, 1977; Stripling and Ellinwood, 1977), enhancement of rotational behavior in animals with unilateral 6-hydroxydopamine (6-OHDA) lesions in the substantia nigra (Lin-Chu et al., 1985), an emergence of abnormal visual tracking behavior (Post et al., 1976), and increased susceptibility to drug-induced convulsions even with subthreshold doses (Stripling and Ellinwood, 1977; Post et al., 1976). Sensitization occurs in a variety of species including mice (Reith, 1986), rats (Post and Rose, 1976), cats (Ellinwood et al., 1977), and monkeys (Post et al., 1976). Increased responsivity to motor-activating effects has also been demonstrated using amphetamine (Klawans and Margolin, 1975; Segal and Mandell, 1974), but it is not clear whether cross-sensitization occurs to cocaine, which would indicate similar mechanisms (Shuster et al., 1977; Post and Weiss, 1988). Many investigators believe that sensitization is a model of psychosis or schizophrenia and as a result the phenomenon has received extensive experi-

mental attention (Post, 1975; Stripling and Ellinwood, 1977; Post and Contel, 1981, 1983; Jones, 1984). Furthermore, observations that there is an increased sensitivity to some of cocaine's effects may have important implications for understanding cocaine-induced paranoid psychoses and certain types of drug-related toxicities which appear to increase in probability with continued drug use (Post and Weiss, 1988).

Although repeated cocaine administration typically produces increases in its unconditioned behavioral effects, there have been exceptions. For instance, Castellani et al. (1978) administered cocaine intravenously to cats for 13 days either at the minimum dose that produced convulsions or at a lower, subthreshold dose. In both groups, tolerance was observed, as evidenced by an increase in the dose of cocaine required to produce convulsions. However, Castellani et al. (1978) also reported increases in the intensity of dystonic posturing and speed of stereotyped head movements with repeated administration of cocaine, which could be interpreted as an enhanced effect. Matsuzaki et al. (1976) administered cocaine intravenously to monkeys at the minimal convulsant dose (3.1 to 6 mg/kg) for several days and found that higher doses were required to produce convulsions after the repeated regimen, indicating the development of tolerance rather than sensitization. Tolerance also developed to cardiorespiratory effects of cocaine in that same study. Kokkinidis (1986), using the behavioral end point of enhanced startle response to an acoustic stimulus, found that chronic cocaine resulted in the development of tolerance to this effect in mice. Although amphetamine also initially increased the startle response to the same extent as cocaine, tolerance to its enhanced alerting effect did not develop with repeated administration.

Since it is not always clear whether repeated administration of cocaine will result in tolerance or sensitization, many investigators have attempted to identify variables that contribute to these different outcomes. Studies have shown that the dose of drug used to produce the behavioral effects is an important variable (e.g., Shuster et al., 1977). Reith (1986), for instance, demonstrated that the optimal dose of cocaine to produce sensitization in mice was 25 mg/kg, but at higher doses, tolerance, which was not attributable to increased stereotypy, developed to the locomotor effects of cocaine. Were this higher dose the only one tested, Reith (1986) would have incorrectly concluded that repeated cocaine administration leads only to the development of tolerance. This problem can be avoided by conducting complete dose-response determinations (e.g., Shuster et al., 1977; Reith, 1986).

The possibility that active metabolites, changes in the pharmacokinetics of cocaine, or its peripheral effects influence sensitization has also been explored. Generally, investigators have concluded that these are not factors with amphetamine (e.g., Browne and Segal, 1977; Kuczenski et al., 1982; Robinson and Becker, 1986), but there is some evidence that the pharmacokinetics of cocaine change with repeated administration in such a way as to account for increased effects (Reith et al., 1987). However, given that sensitization can occur after even a single injection (Lin-Chu et al., 1985) and is relatively long-lasting (Stripling and Ellinwood, 1977; Kilbey and Ellinwood, 1977; Shuster et al., 1977; Kalivas et al., 1988), it is not likely that kinetic changes play a major role.

Several studies have shown that classical conditioning and environmental context can often account for the enhancement of the motor effects of cocaine and other psychomotor stimulants. Tilson and Rech (1973) administered amphetamine to three groups of female rats for 14 days. One group received the drug before being placed in activity cages, one group received the drug after the testing session, and the third group served as a saline control. All rats received amphetamine before locomotor activity was measured on day 15, and it was found that only the group that had repeatedly received drug before placement in the activity cage showed an enhanced effect after the repeated regimen (i.e., effects were environment-specific). Furthermore, when saline was administered to all animals on day 16, the before-session group also showed an enhanced behavioral effect relative to the other groups. The investigators attributed the saline effect to classical conditioning since the rats showing enhanced effects were tested in the same environment (CS) where they had received cocaine (UCS) and experienced increased motor effects during the repeated regimen. It is not clear, however, why the development of conditioned effects, as evidenced when saline was administered, should account for the *enhanced* effects of repeated drug administration as observed on day 15. Presumably, the conditioned and unconditioned effects are additive in much the same way that postulated conditioned responses opposite in direction to drug-induced effects are additive to produce tolerance (Siegel, 1977).

Post et al. (1981a) conducted a study similar to that of Tilson and Rech (1973) with 10 mg/kg of cocaine administered for 10 days. As in the previous study, only those rats given cocaine before they were placed in the environment where locomotion and stereotypy were measured showed sensitization to cocaine after the chronic regimen. They also exhibited conditioned effects when saline was administered. Barr et al. (1983) found conditioned effects after 10 pairings of multiple stimuli with an injection of 15 mg/kg of cocaine in rats. Interestingly, while conditioned effects were seen with all four measures obtained (sniffing, head bobbing, rearing, and locomotion), the magnitude of the conditioned effects after saline alone was similar to the effects of cocaine on the 10th pairing for the first three measures, but was considerably smaller for crossings (200% increase with

saline alone versus 532% increase on the 10th pairing trial).

Hinson and Poulos (1981) used a differential conditioning paradigm which is a more powerful design for ruling out confounding factors (e.g., novelty during testing) to investigate the role of conditioning in sensitization. They administered 13 injections of 30 to 40 mg/kg of cocaine to rats intermixed with a similar number of saline injections over a 7-week period. Cocaine and saline were administered in distinctive experimental rooms and enhanced activity to cocaine during a subsequent test was only observed when the test was conducted in the experimental room associated with cocaine administration. These investigators also demonstrated that this conditioned effect could be extinguished after 36 daily extinction trials. Barr et al. (1983), on the other hand, were not successful in showing extinction following four daily extinction trials immediately after the termination of the chronic regimen. When three extinction trials were given over time on days 5, 10, and 15 following the termination of the chronic regimen, some (e.g., head bobbing) but not all of the components (e.g., crossing) of the conditioned response diminished. Thus, it appears that time rather than just number of trials was an important factor in extinction, which is not typical for classically conditioned responses.

The importance of behavioral factors in sensitization has also been demonstrated in a clever manner by Hirabayashi and Alam (1981) using methamphetamine. They showed that if animals were prevented from exhibiting motor activity (the UCR) because of restraint, sensitization did not occur. This was also true when motor activity was prevented by concurrent administration of pimozide, haloperidol, or diazepam (Weiss et al., submitted; Beninger and Hahn, 1983; Beninger and Herz, 1986), although other studies have demonstrated that antagonist treatment does not interfere with the development of sensitization (Gale, 1984). Interestingly, although concurrent antagonist treatment may prevent the development of sensitization, these agents are not capable of blocking its expression once it has developed (Beninger and Hahn, 1983; Beninger and Herz, 1986).

Despite demonstrations that conditioned effects contribute to the development of sensitization to cocaine and amphetamine, there have been negative reports as well. In many studies, for instance, although enhanced environment-specific motor effects have been observed, the administration of saline (CS) within the environmental context associated with drug administration has not resulted in increased locomotion and stereotypy (Shuster et al., 1977; Browne and Segal, 1977; Post and Rose, 1976; Weiss et al., submitted). In experiments designed to minimize the role of conditioning (e.g., administration of drug in the home cage), sensitization has still been shown to develop to amphetamine (Segal, 1975; Browne and Segal, 1977; Robinson, 1984). Furthermore, enhanced effects to cocaine have been shown to occur even after single injections, i.e., a single pairing (Lin-Chu et al., 1985), which is likely to be insufficient for conditioning to occur. On the other hand, Weiss et al. (submitted) found that enhanced locomotor activity that was dependent on testing in the same environment where drug had been administered, occurred even after a single pairing with 40 mg/kg of cocaine. Furthermore, the degree of enhanced activity was dependent upon the degree of similarity between the conditioning and testing environment. However, an injection of saline alone did not increase locomotor activity, making these results difficult to interpret.

Post et al. (1976) have shown that sensitization can involve the emergence of new behavioral patterns indicative of higher doses but which could not have been conditioned because they were not originally elicited. It is also difficult to explain sex differences in sensitization on the basis of conditioning. For instance, Robinson et al. (1982) using a single injection of 1.25 mg/kg amphetamine only observed sensitization 3 to 4 weeks later in intact females, ovariectomized females, and castrated males, but not intact males. Although classical conditioning and environmental context can account for sensitization in many studies, Post and Weiss (1988) have proposed that the role of conditioning decreases when higher doses are administered repeatedly. Further, sensitization produced by higher dose regimens is associated with neural pathways different than those involved in conditioning.

In addition to total dose administered, the schedule of drug administration can also influence sensitization (Post, 1980, 1981). When cocaine or amphetamine is administered using an implanted pellet which delivers a continuous level of drug, sensitization does not develop (Reith et al., 1987; Nelson and Ellison, 1978). Hirabayashi and Alam (1981) demonstrated that there was a trade-off between dose and interval between injections. At higher doses, for instance, greater augmentation was observed at longer interinjection intervals. However, given that sensitization also occurs after single injections of drug, the influence of intermittency is unclear. It may be that a constant drug level produced by pellet or frequent drug injections *prevents* sensitization, perhaps by interfering with behavioral determinants such as conditioning.

3. Neurobiology of sensitization. The neurobiology of sensitization to cocaine is complex since a variety of neurotransmitters change as a consequence of its chronic administration (e.g., Kalivas et al., 1988; Zahniser et al., 1988). Furthermore, although it is not clear whether cocaine produces neurotoxicity similar to that produced by the amphetamines (see review by Seiden and Kleven, 1988), care must be taken to distinguish between such toxic effects and neurochemical changes underlying the development of sensitization. Thus, the parameters of

cocaine administration that produce sensitization must be mimicked in studies assessing relevant neurochemical changes (Zahniser et al., 1988). Research primarily with amphetamine has concentrated on determining changes in dopaminergic systems and proposed mechanisms have included denervation supersensitivity, other postsynaptic alterations, and presysnaptic receptor sensitization (Post, 1981; Robinson and Becker, 1986). The enhanced effect of amphetamine after repeated drug administration in rats has been attributed to increased DA release in the striatum when amphetamine is readministered, although it is clear that changes in other brain areas and involving other neurotransmitters also occur with repeated drug administration (Robinson and Becker, 1986; Robinson et al., 1982).

The findings of increased dopamine release after chronic amphetamine administration has led others to examine whether this might also be the mechanism underlying cocaine's effects. These investigators reasoned that since sensitization develops even after a single injection (Lin-Chu et al., 1985), neurochemical changes should be detectable after a single injection. Thus, Peris and Zahniser (1987) showed that 24 h after a single injection of cocaine, there was an increase in DA release in the nigrostriatal pathway in response to amphetamine (Zahniser et al., 1988). If animals are treated with fluphenazine, or the more specific D-1 and D-2 antagonists, SCH 23390 and sulpiride, prior to the injection of cocaine, these changes in DA release are prevented. However, following more extended regimens of cocaine which are also known to produce even greater increases in responsivity, this enhancement of amphetamine-induced DA release was not evident (Zahniser et al., 1988). Additional studies have failed to find changes in DA uptake, synthesis, and metabolism, or changes in either presynaptic and postsynaptic receptor function in the nigrostriatal pathway consistent with sensitization. In fact, many changes that have been observed are more consistent with predicting the development of tolerance (Zahniser et al., 1986, 1988; Dwoskin et al., 1988).

More promising results have been found in studies which have examined changes in the mesolimbic DA pathway. For instance, Kalivas et al. (1988) have shown decreased levels of dopamine metabolites in mesolimbic neurons, indicating an increase in synaptic DA, following a 3-day repeated regimen of cocaine which produced behavioral sensitization to its locomotor effects. Alterations in D-2 autoreceptors and postsynaptic receptor sensitivity have also been reported although, taken as a whole, these changes in DA neurochemistry observed in the mesolimbic pathway are complex and difficult to interpret in terms of sensitization (Taylor et al., 1979; Taylor and Ho, 1977; Hanson et al., 1987; Hadfield and Nugent, 1983; Missale et al., 1985; Greene and White, 1986; Goeders and Kuhar, 1987; Dwoskin et al., 1988; Zahniser et al., 1986, 1988; Henry et al., 1987; Kalivas et al., 1988). Thus, at the present time, the precise neurochemical changes and their neuroanatomical localization occurring in response to the repeated administration of cocaine that are related to its enhanced locomotor and stereotypic effects still require additional study.

4. "Pharmacological kindling." In addition to changes in neurochemical systems, it has also been proposed that electrophysiological changes may account for the sensitization to some of the effects of cocaine and amphetamine. One of the effects of cocaine that becomes augmented with repeated administration is the production of clonic convulsions (Stripling and Ellinwood, 1977). The increased probability of seizures has been compared to a phenomenon called "kindling" because of their similar electrophysiological characteristics and temporal pattern.

Low-level electrical stimulation of limbic areas such as the amgydala initially produces no spread of activity or afterdischarge and few observable behavioral effects. With repeated daily exposure, however, electrical activity spreads after stimulation, eventually to the extent that clonic convulsions are produced. The threshold for this effect decreases and eventually convulsions can occur spontaneously (Goddard et al., 1969). As with sensitization to the effects of psychomotor stimulants, this effect is long-lasting and does not occur if the stimulation is applied continuously. Further, since high doses of cocaine which produce convulsions also elicit electrical activity in the limbic system that is similar to that produced by electrical stimulation (Ellinwood et al., 1977; Stripling and Ellinwood, 1977), several investigators have proposed that sensitization to the effects of drugs and kindling are related phenomena (Post and Kopanda, 1975; Post, 1977; Ellinwood et al., 1977; Stripling and Hendricks, 1981). It was reasoned that if the mechanisms underlying cocaine sensitization and kindling were similar, each could substitute for the other during development. In support of this hypothesis, Kilbey et al. (1979) and Stripling and Hendricks (1981) demonstrated that pretreatment with a dose of cocaine that produced convulsions increased the rate of development of electrical kindling in either the amygdala or olfactory bulb. However, many investigators have failed to observe any enhancement in the rate of the development of kindling after exposure to cocaine using doses that did not produce convulsions but which produced sensitization to locomotor effects (e.g., Rackham and Wise, 1979; Stripling and Ellinwood, 1977; Stripling, 1983). Sato et al. (1980) even showed that preexposure to cocaine inhibited the development of kindling and when Post et al. (1981b) determined the effect of prior kindling on sensitization to cocaine's effects, they found evidence of reduced effects, which the authors speculated were due to the possibility that amygdaloid kindling decreased concentrations of dopamine (Engel and Sharpless, 1977) or enhanced cholinergic activity. Therefore, while there are

intriguing similarities between sensitization to cocaine and kindling in terms of electrophysiological and temporal characteristics as well as neurochemical changes, it does not appear as if these two effects are identical, particularly when effects other than cocaine's convulsive actions are considered.

Recently, Post and Weiss (1988) have distinguished between behavioral sensitization to locomotor and stereotypic effects and increased probability of seizures and have attributed the latter to the local anesthetic properties of cocaine. In support of this notion, the repeated administration of other local anesthetics results in an increased probability of seizures, or "pharmacological kindling" (Post et al., 1975, 1984a, b; Racine et al., 1975; Post and Weiss, 1988). Furthermore, local anesthetics do not produce locomotor or stereotypic effects either acutely or chronically (Reith et al., 1985). It is not surprising, therefore, that preexposure to cocaine only at convulsive doses (e.g., Kilbey et al., 1979) results in the more rapid development of kindling. Post and Weiss (1988) have presented an interesting discussion of the clinical importance of "pharmacological kindling" related to the local anesthetic properties of cocaine in the development of toxic sequelae reported in cocaine abusers, such as panic attacks (e.g., Washton and Gold, 1984; Post et al., 1987), particularly in relation to the development of tolerance to mood-enhancing effects (Fischman et al., 1985).

B. Schedule-Controlled Behavior

1. Behavioral determinants. In addition to determining the effects of cocaine on unlearned or unconditioned behaviors, such as locomotion and stereotypy, its effects on behaviors that are conditioned have been extensively examined. These behaviors, typically generated using operant schedules of reinforcement, have distinct advantages over other approaches because the behavior which is conditioned is predictable and stable over long periods of time. This allows a powerful analysis of the behavior pattern before and after drug administration in the same organism. In addition, operant methods can generate a wide variety of behaviors differing in frequency, pattern, and complexity, which are useful for determining whether any aspect of the behavior itself influences cocaine's effects (see Ferster and Skinner, 1957, for definitions of operant terminology).

In general, the effects of cocaine on operant responding are similar to those of the amphetamines (Dews and Wenger, 1977; Fischman, 1987). The finding that rate of responding occurring under nondrug or control conditions influences the effects of a variety of drugs, particularly the psychomotor stimulants, under diverse conditions, led to the exposition of a unifying principle that behavioral effects of drugs are rate-dependent. The theory of rate dependency states in its simplest form that there is a systematic, mathematical relationship between rate of responding under control conditions and the subsequent effects of a drug. For instance, Dews (1958) showed that high rates of responding generated under a fixed-ratio (FR) or small valued fixed-interval (FI) schedule were decreased by the administration of the stimulant, methamphetamine, whereas low rates of responding generated under other schedules were increased by the same dose in the same animal. This dependency on rate of the behavioral effects of psychomotor stimulants has been replicated in many studies, largely with amphetamine, with much emphasis on ruling out the possible influence of other factors, e.g., schedule of reinforcement, frequency of reinforcer delivery, nature of the reinforcer, or degree of stimulus control (see reviews by Lyon and Robbins, 1975; Sanger and Blackman, 1976; Dews and Wenger, 1977; McKearney and Barrett, 1978; Thompson et al., 1981).

Although the majority of studies demonstrating the rate-dependent effects of psychomotor stimulants have involved amphetamine, there are studies with cocaine that have shown similar effects (e.g., Smith, 1964). For instance, Gonzalez and Goldberg (1977) determined dose-response functions for cocaine under three schedules of food reinforcement in squirrel monkeys: a FR schedule, a multiple FR-FI schedule, and a second-order FI schedule with FR components. These three schedules were selected because they produce a wide range of response rates and patterns of responding within a single session. The effects of cocaine were dependent upon the control rates of responding regardless of the schedule generating the responding. Similar results were found by Zuccarelli and Barrett (1980) in pigeons and Glowa (1986) in mice using procedures that extended the range of conditions under which the principle was shown to operate.

In a study with squirrel monkeys with responding maintained under FI schedules by food delivery or shock presentation, Barrett (1976) demonstrated that the effects of cocaine were rate-dependent and were not influenced by the nature of the reinforcer. Similar effects were found by Spealman et al. (1977) using multiple FI-FR schedules of food presentation or stimulus-shock termination with cocaine as well as two of its phenyltropane derivatives. Similarly, Katz (1982a, 1983) showed that changes in responding produced by cocaine under a complex schedule involving a conditional discrimination were also a function of rate-dependent changes rather than caused by changes in stimulus control. In contrast, pentobarbital did affect stimulus control under these same experimental conditions, demonstrating the sensitivity of the behavior maintained by this complex schedule. Finally, Valentine et al. (1983) showed that presession administration of cocaine had similar effects on responding maintained by food as well as cocaine itself (i.e., drug self-administration, see section (V D) and these effects were exclusively rate-dependent.

Although the rate dependency hypothesis is well ac-

cepted as a guiding principle in behavioral pharmacology, some have argued that a more parsimonious explanation of the effects of psychomotor stimulants, including cocaine, on schedule-controlled behavior is that these drugs produce a constant rate of responding under conditions that normally result in differences in rate (Gonzalez and Byrd, 1977; Byrd, 1979, 1981; Howell et al., 1988). Furthermore, while rate of responding appears to be a powerful and often sole determinant of the effects of cocaine on schedule-controlled responding, there are exceptions to rate dependency, i.e., there are other behavioral variables that influence the effects of cocaine. For instance, low rates of responding that occur under conditions where responding is not reinforced (e.g., during timeouts), or is punished, are not typically increased by cocaine or amphetamine (e.g., Katz, 1982a,b; Geller and Seifter, 1960; Spealman, 1979a).

Unlike Spealman et al. (1977), Johanson (1978a) found that the effects of cocaine as well as amphetamine could be influenced by the nature of the reinforcer maintaining responding under a multiple schedule in rhesus monkeys. More specifically, responding under a FR schedule of food delivery was decreased by doses of cocaine or amphetamine that either had no effect or increased comparable rates of responding generated under a FR schedule of shock avoidance. Katz and Barrett (1978) and Barrett and Katz (1981) have also found that FR responding generated under schedules of food presentation and stimulus-shock termination are differentially affected by amphetamine, although when the schedule of reinforcement was a FI (Barrett, 1976) or second-order FI(FR) schedule (Barrett et al., 1981), the effects of amphetamine were not influenced by the type of reinforcer maintaining responding but instead by the rate of ongoing responding.

In a study in pigeons where responding was maintained under a concurrent FI-FR schedule, Bacotti (1980) also showed that cocaine decreased FR responding at the same time that FI responding was increased. But this change in responding was not due to changes in rate of responding under the two schedules as has been shown using multiple schedules. Instead, it was shown that the animals simply spent increased time responding under the FI schedule and decreased time under the FR schedule with no change in rates. Therefore, while the changes produced by cocaine were related to baseline rate of responding, the mechanism of this change was influenced by the nature of the concurrent schedule which allowed the organism to control time spent under each schedule, an option not available under multiple schedules of reinforcement (e.g., Gonzalez and Goldberg, 1977).

The results of Bacotti (1980) can also be viewed as an example of the modification of acute drug effects as a function of other environmental events occurring under temporally (e.g., as in a multiple schedule) or situationally (e.g., as in a concurrent schedule) different circumstances. A further example is a study by McKearney and Barrett (1975) with amphetamine. These investigators used a multiple schedule where responding was maintained by food presentation under a FI 10-min schedule in one stimulus condition whereas a 10-min extinction component prevailed during a second stimulus condition. Subsequently, every 30th response in the FI component was punished by the delivery of an electric shock. Next, the schedule in the extinction component was changed to a continuous avoidance schedule. When responding in the alternate 10-min period had no consequences (i.e., extinction), lower doses of amphetamine had little or no effect on suppressed responding during the punishment component, as has been shown in previous studies. In contrast, when the punishment component alternated with shock avoidance, amphetamine produced large increases in punished responding. As Barrett and colleagues have pointed out (Barrett et al., in press), this drug effect on punished responding, i.e., rate increases, is similar to the effects that amphetamine (as well as cocaine) produces on avoidance responding.

In addition to contextual variables, there is intriguing evidence that previous behavioral experience can also modify the effects of drugs in a similar manner. Barrett (1977), for instance, demonstrated that the effects of amphetamine on punished responding of squirrel monkeys were markedly modified by an interpolated period during which the animals were trained to avoid electric shock. Initially, amphetamine only produced a decrease in the rate of food-maintained responding which was suppressed by electric shock punishment. Next, the monkeys were trained under different stimulus conditions to respond under a shock avoidance schedule but were then returned to the original behavioral contingencies (i.e., punishment schedule). The redetermination of the amphetamine dose-response function showed that after the history of avoidance responding, this drug now produced a large increase in rate of punished responding, just as had been shown when the avoidance schedule was operative concurrently (McKearney and Barrett, 1975). However, in this case, the animals had not experienced any rate-increasing effects with amphetamine since the drug had not been administered when responding was maintained under the avoidance schedule. Reversibility of the rate-increasing effects was demonstrated when amphetamine failed to increase rate of responding suppressed by punishment after these animals were again exposed to the avoidance schedule, but under extinction conditions. Although studies examining the influence of contextual and historical variables have not been conducted using cocaine, the general similarity between the behavioral effects of amphetamine and cocaine indicates that cocaine's effects are likely to be influenced by both of these categories of variables (see Barrett, 1985, 1986, 1987; Barrett and Witkin, 1986; Barret et al., in press, for general reviews).

The effects of cocaine on operant performance involving more complex stimulus control have also been assessed. One procedure involves chain schedules of food-maintained responding where different discriminative stimuli control differential responding. Thompson, Moerschbaecher, and their colleagues have developed a procedure in which the relationship between the stimuli and correct responding changes (acquisition component) or remains the same (performance component) from session to session. In a series of studies using both pigeons and monkeys, these investigators have shown that cocaine disrupted stimulus control and that responding in the acquisition component was disrupted at lower doses (Thompson and Moerschbaecher, 1979; Moerschbaecher et al., 1979). These results could not be attributed to rate effects and were interpreted as demonstrating that cocaine had greater effects on behavior under weaker stimulus control (as in the acquisition component). However, this differential effect, i.e., disruption on acquisition at lower doses, was not found when cocaine's effects were determined on acquisition and performance during separate sessions (Thompson, 1977). In that case, cocaine disrupted behavior at the same dose regardless of whether responding was maintained in an acquisition or performance paradigm. Although the implications of these studies for the assessment of the effects of cocaine on learning, i.e., the acquisition of a new sequence of responses, are not clear, they do illustrate once again the importance of behavioral factors in determining the effects of drugs.

2. *Behavioral tolerance.* In addition to behavioral history, the actions of amphetamines or cocaine can be modified by a history of drug administration. Sensitivity to a drug which is repeatedly administered may decrease (tolerance), increase (sensitization), or remain the same, depending on the response being studied as well as other pharmacological and behavioral variables. In general, the repeated administration of cocaine results in the development of tolerance to its effects on schedule-controlled responding (see section V A 2 on sensitization to motor effects), and this tolerance development is influenced by behavioral variables. Schuster et al. (1966) formulated a hypothesis stating that tolerance would develop to those behavioral actions of a drug which resulted in a decrease in the density of reinforcement. Conversely, where reinforcement density was increased or unchanged, tolerance would not develop. This hypothesis was generated on the basis of results of several studies with amphetamine using rats lever pressing for food under a variety of schedules or to avoid electric shock.

In those situations where drug administration resulted in a decrease in reinforcer delivery (decreased responding under FR schedules or increased responding under differential-reinforcement-of-low-rates (DRL) schedules), tolerance developed (Schuster and Zimmerman, 1961; Zimmerman and Schuster, 1962; Schuster et al., 1966). When reinforcer density was unaffected or increased, tolerance did not develop (Schuster et al., 1966). Smith and McKearney (1977) even demonstrated that tolerance developed to the rate-increasing effects of amphetamine on DRL performance with widely spaced drug administrations. Carlton and Wolgin (1971), as well as Campbell and Seiden (1973), showed that when amphetamine was administered before the experimental session and produced decreases in rate of responding and reinforcement, tolerance developed; however, if a second group of rats was given the same amount of amphetamine after the session, tolerance failed to develop. These studies showing behavioral or contingent tolerance to the amphetamines as well as other drugs have been replicated in a variety of studies under diverse conditions (see reviews by Demellweek and Goudie, 1983a,b; Goudie and Demellweek, 1986). However, in a study by Finnegan et al. (1982), tolerance developed to methamphetamine, given at neurotoxic dose levels, even in monkeys that received drug after the session and did not experience reinforcer loss during its development.

Although the vast majority of studies on behavioral tolerance have involved amphetamine, tolerance that is dependent upon behavioral variables has also been shown to develop when cocaine is administered repeatedly. For instance, Woolverton et al. (1978a,b) showed that when cocaine was given prior to experimental sessions where rats had access to sweetened condensed milk or were responding for food under either a FR 40 or DRL 20-sec schedule, the drug initially resulted in a decrease in reinforcer (milk or food) delivery. With repeated administration, tolerance developed, as evidenced by a shift to the right in the dose-response function. On the other hand, increased sensitivity was observed if cocaine was administered after the session (Woolverton et al., 1978a). These results are consistent with the hypothesis that decreased density of reinforcement results in the development of tolerance. Others have also reported results that can be interpreted as demonstrating that tolerance develops when cocaine decreases rate of reinforcement. For instance, Branch and Sizemore (1988) used a procedure in monkeys that varied the degree of complexity of the behavioral requirements (different length chain schedules) within the experimental session and found that complexity did not influence the development of tolerance to cocaine. However, since rate of reinforcement was decreased initially but increased over the course of the repeated regimen, it was postulated that this effect influenced tolerance. Likewise, Branch and Dearing (1982) used a match-to-sample paradigm with pigeons which varied the delay between the observation of the sample and the match. They found no difference in whether tolerance developed to cocaine as a function of delay, although at the longer delay interval, tolerance development was somewhat slower. However, since rate of reinforcement decreased and then recovered, the in-

vestigators postulated that reinforcement loss could have been an important determinant of tolerance development. Howell and Morse (1989) examined the effects of cocaine administered chronically using osmotic minipumps to squirrel monkeys that were responding under a FI schedule of stimulus-shock termination. When cocaine produced greater increases in FI responding during the chronic regimen which had no effect on ability to meet the behavioral contingencies, there was no evidence of tolerance. Conversely, when chronic cocaine completely suppressed responding, tolerance developed to this suppression. Tolerance was also reported in a study with rhesus monkeys that were exposed to constant levels of cocaine that initially suppressed responding under FR schedules for food (Woolverton and Kleven, 1988).

Other behavioral variables, in addition to loss of reinforcement, can influence the development of tolerance to cocaine and the amphetamines. For instance, in a study by Hoffman et al. (1987), the influence of schedule of reinforcement in tolerance development was examined. Pigeons were trained to respond under three FR schedules differing in the number of responses required for reinforcer delivery. When cocaine was administered repeatedly, tolerance developed to decreases in rate of responding (and rate of reinforcement) under the two schedules with the smallest and intermediate ratio requirements but did not develop in two of the three pigeons under the largest ratio requirement. This influence of schedule parameter is not consistent with the notion of behavioral tolerance described above since rate of reinforcement was decreased by cocaine under all three schedules. In addition, the mechanism of this tolerance is not clear since the higher ratio schedule not only required more responses per reinforcer but also resulted in a decreased rate of reinforcement under nondrug conditions.

Thompson (1977) also demonstrated the influence of schedule by comparing the development of tolerance to cocaine on responding during acquisition and performance schedules described previously. In his study, tolerance to cocaine developed more rapidly under the performance schedule. However, with time, tolerance also developed under the acquisition paradigm. Interestingly, time out responding which increased after the administration of cocaine, did not change with repeated administration, a finding in keeping with the idea that tolerance only develops when the drug produces decreases in reinforcer delivery. Similar results were found by Moerschbaecher et al. (1979) using a multiple schedule of acquisition and performance components. Smith (1986) showed differential tolerance development with amphetamine as a function of behavior occurring in the alternate component of a multiple schedule. That is, when responding was maintained under a random ratio (RR) schedule that was a component of a multiple schedule and responding was maintained under a DRL schedule in the alternate component, tolerance developed to the rate and reinforcement decreasing effects of amphetamine in the RR but not to the rate increases that decreased reinforcement in the DRL. However, if the RR component was eliminated and responding was just maintained under the single DRL schedule, repeated administration of amphetamine resulted in the development of tolerance which was then reversed when the RR schedule was reintroduced.

In addition to the type or context of the schedule maintaining responding, Branch (1979) has shown that the type of reinforcer maintaining responding can influence tolerance development, at least to amphetamine. In a multiple schedule with responding maintained under FI schedules of food, shock presentation, or stimulus shock termination in different components, repeated administration of amphetamine produced a shift to the right of the dose-response function only in the food and termination components but not under the shock presentation schedule.

In summary, cocaine as well as the amphetamines can clearly produce significant behavioral disruptions in repertoires that depend on learning and conditioning. These changes are not easy to predict because they are influenced by complex interactions among a variety of behavioral and pharmacological factors. The mechanisms underlying these disruptions undoubtedly are relevant for understanding the influence of cocaine on human performance. However, the complexity is heightened when one considers that under some conditions, but not others, tolerance may develop, both to effects considered desirable by human users as well as to detrimental effects that might otherwise serve to limit cocaine use.

C. Mood-Altering Properties

1. Subjective effects. One of the most important behavioral effects of cocaine is its mood-altering properties, particularly since it is generally believed that these effects are related to its abuse. In fact, in human studies aimed at determining the dependence potential of psychoactive drugs, their classification has been based, in part, on their subjective, or mood-altering effects. A variety of quantitative methods have been developed for assessing subjective effects including questionnaires such as the Addiction Research Center Inventory (ARCI; Haertzen, 1966) and the Profile of Mood States (POMS; McNair et al., 1971). The ARCI is a 550-item true-false questionnaire grouped into scales labeled by drug category, withdrawal state, personality assessment, etc. A shortened version of the ARCI (Martin et al., 1971) employs 49 items grouped into five scales. These scales were empirically derived based upon the pattern of responses of subjects after the administration or cessation of prototypic drugs of abuse (e.g., opiates, amphetamines, barbiturates). Each of the scales purportedly measures mood effects characteristic of these specific drugs or drug groups. The POMS is a list of adjectives describing

different moods and the subject indicates how he/she feels at the moment in relation to each adjective on a numerical scale from "not at all" to "extremely." The adjectives have been grouped using factor analysis into separate scales that are believed to be measures of unique mood states, such as Anxiety or Elation. Many studies have shown that this instrument is a reliable and sensitive indicator of changes in mood after the administration of drugs (e.g., Johanson and Uhlenhuth, 1980a,b; Fischman et al., 1985).

The approach for using measures of subjective effects to classify drugs has been to compare the mood-altering effects of an unknown drug with those of prototypic drugs. To the extent that two profiles are similar, i.e., that the subjective effects produced by the two compounds are the same, these two drugs are classified together. It has been assumed that drugs classified as similar based upon their subjective effects are also similar in other respects, such as molecular mechanisms of action or dependence potential. In addition, it is often believed that subjective effects may "explain" why drugs are abused, i.e., they are taken *because* they produce a certain type of subjective effect such as euphoria. However, this causal relationship has not been clearly established (see Johanson et al., 1987, for a discussion). Nevertheless, subjective drug effects are important indicators of both therapeutic efficacy and abuse potential.

The subjective effects of cocaine have been well characterized using a variety of measures including the POMS and ARCI. Fischman and colleagues demonstrated, not surprisingly, that cocaine produces typical psychomotor stimulant mood effects (Fischman et al., 1976; Fischman and Schuster, 1982). For instance, intravenous cocaine in doses ranging from 4 to 32 mg increased scores on the Benzedrine Group (BG) and Amphetamine scales of the ARCI in a dose-dependent manner. As the names of these scales imply, the changes produced by cocaine were similar to those produced by amphetamine (Martin et al., 1971). Cocaine, as well as amphetamine, also increased scores on the Morphine-Benzedrine Group scale, which is considered a measure of "euphoria," and decreased scores on the Pentobarbital-Chlorpromazine-Alcohol Group scale (sedative-like effects), and these changes were dose-dependent (Fischman et al., 1976). Over the same dose range, intravenous cocaine produced changes on many of the scales of the POMS, such as increases in Vigor and Friendliness (Fischman, 1984). Although there are differences in potency as well as in maximum effect, the subjective effects of cocaine administered by other routes (smoking, intranasal, oral) were similar (e.g., Perez-Reyes et al., 1982; Van Dyke et al., 1978; Javaid et al., 1978; Resnick et al., 1977). In addition, the effects of cocaine were indistinguishable from those of amphetamine and other psychomotor stimulants (Martin et al., 1971; Fischman et al., 1976).

The time course of the subjective effects of cocaine is dependent upon its route of administration and is generally correlated with cocaine plasma concentrations. After intravenous administration (16 and 32 mg), the highest plasma concentrations were seen at the first time sample, 5 min, and half-life ranged between 16 and 87 min across subjects (Javaid et al., 1978). Subjective effects (measures of "high") also peaked between 3 and 5 min and disappeared within 30 to 40 min, i.e., showed a decrease parallel to that of plasma concentrations. Plasma concentrations after intranasal cocaine (16 to 96 mg) peaked between 20 and 60 min after administration. These effects were also dose-related with substantial intersubject variability as was also evident after intravenous administration. The increase in reports of "high" after intranasal cocaine paralleled the increase in cocaine plasma levels but dissipated more rapidly.

The relationship between subjective effects and cocaine plasma levels with repeated dosing does not show the degree of correlation seen with acute administration. For instance, using a self-administration paradigm, Fischman and Schuster (1982) found that while plasma levels continued to increase after each injection of 32 mg of cocaine, separated by at least 8 to 10 min from the previous injection, large changes in subjective effects only occurred after the first injection, with smaller changes or no change recorded when the same dose was self-administered repeatedly.

Additional studies with multiple administrations of cocaine have shown even more clearly that the subjective effects produced by an injection of cocaine in the presence of already elevated cocaine blood levels were not comparable to those produced by an acute administration (Fischman et al., 1985; Fischman and Rachlinski, in press). This was true despite the fact that plasma levels continued to rise with the additional administrations, indicating an acute functional tolerance to the subjective effects produced by cocaine. Foltin et al. (1988) have shown that following repeated administrations of intranasal cocaine (96 mg), there is a tendency for the pressor effects of cocaine to continue to rise with blood level while the subjective effects show acute tolerance similar to that seen with intravenous cocaine. Since subjects under these conditions continued to request additional cocaine (but were denied additional drug to prevent toxicity), such differential tolerance could result in drug-induced toxicity, i.e., the self-administration of additional amounts of cocaine when the disruptions in cardiovascular function produced by cocaine have not disappeared (Foltin et al., 1988).

Ambre et al. (1988), using a 4-h infusion of cocaine in humans which maintained steady state cocaine plasma levels, reported the development of tolerance to self-reported ratings of "high" but incomplete tolerance to cocaine's chronotropic effects since heart rate remained steady but elevated above baseline levels. Kumor et al.

(in press), on the other hand, using a similar procedure to maintain stable cocaine plasma levels, reported little evidence of tolerance development to either cocaine's cardiovascular effects or self-reported effects. Despite the lack of tolerance to the subjective effects of cocaine in this study, the demonstration of tolerance in a number of other studies provides support for the idea that this differential tolerance is a possible reason for the cardiovascular toxicity reported for cocaine abusers (see section VI).

Because cocaine is a local anesthetic, the subjective effects of other local anesthetics delivered intravenously have been evaluated and compared to those of cocaine. Fischman and colleagues evaluated both procaine in doses up to 96 mg (Fischman et al., 1983b) and lidocaine in doses up to 48 mg (Fischman et al., 1983a) and found no evidence of any measurable subjective effects. However, procaine was identified as cocaine by some subjects (Fischman et al., 1983b). Interestingly, Kellner et al. (1987) have stated that the subjective effects of procaine range from euphoria to dysphoria in normal as well as depressed subjects, with bipolar patients most likely to experience euphoric effects. Similar results have been described by these investigators for cocaine and amphetamine (Post et al., 1974; Silberman et al., 1981).

The measurement of subjective effects of cocaine in humans could be used to evaluate the ability of medications to modify cocaine's actions in a way that might be useful in the treatment of cocaine dependence. Demonstrating that a drug can reverse the subjective effects of cocaine might also suggest possible mechanisms of action of these effects. For instance, early studies with amphetamine showed that depletion of catecholamines with α-methylparatyrosine or blocking dopamine receptors with chlorpromazine and pimozide diminished the euphoric effect of amphetamine. This antagonism did not occur with noradrenergic antagonists phentolamine and phenoxybenzamine (Jonsson, 1972; Jonsson et al., 1969, 1971).

While there are anecdotal reports that certain agents decrease the positive mood effects of cocaine, experimental studies in this area have been minimal and, in general, rigorous measurements of subjective effects have not been included in clinical research studies on the effectiveness of psychopharmacological agents for the treatment of cocaine abuse. A report by Gawin (1986a), while largely anecdotal, illustrates the potential of this approach. Gawin (1986a) interviewed individuals, who were abusing such high levels of cocaine that they experienced episodes of paranoia during binges. In an attempt to decrease abuse based upon cocaine's presumed effects on dopaminergic systems, the investigator prescribed haloperidol or chlorpromazine, both of which block dopamine receptors. Interestingly, these treatments had no effect on the frequency or level of cocaine abuse and the patients reported no decreases in cocaine-induced euphoria. On the other hand, delusional episodes during binges were found to decrease. These results may indicate that cocaine-induced psychotic-like episodes are not only a function of local anesthetic properties (Post and Weiss, 1988), but may also be related to dopaminergic function.

In one of the few examples of using changes in subjective effects to evaluate the utility of a pharmacological treatment for cocaine abuse, Fischman and Foltin (1988) assessed the effects of desipramine on cocaine's subjective effects in a laboratory study with subjects who were not seeking treatment. Their choice of desipramine was based upon a finding by Gawin and Kleber (1984) indicating that desipramine maintenance was efficacious as a treatment for cocaine abusers (see section VII). Gawin and Kleber (1984) assumed that desipramine was effective because it reversed neurochemical changes that had been produced by long-term administration of cocaine. However, Fischman and Foltin (1988) reasoned that this drug might alter cocaine's subjective effects as well. In fact, when the volunteer research subjects were treated with desipramine for 3 to 4 weeks at blood levels greater than 100 ng/ml, the profile of cocaine's self-reported effects shifted significantly, with decreases in cocaine's "euphorigenic" and stimulant-like effects (e.g., BG scores on the ARCI, Arousal and Positive Mood scores on the POMS) and decreases in scores on an "I want cocaine" scale (Fischman and Foltin, 1988). This study clearly illustrates the feasibility of assessing the effects of potential therapeutic agents on blocking cocaine's subjective effects.

2. Discriminative stimulus effects. The lack of studies on the subjective effects of cocaine within a treatment research context may be due, at least in part, to the risks of administering cocaine to patients seeking treatment. Therefore, alternative experimental approaches are needed to evaluate the influence of pharmacological agents on the subjective effects of cocaine. Until recently, it was felt that the approach of measuring subjective effects as indicators of dependence potential was only possible with humans because of their unique verbal abilities. However, at least a decade ago, it was suggested that the development of methods for establishing drugs as discriminative stimuli (DS) allows similar processes to be studied in animals (see Schuster et al., 1981 and Schuster and Johanson, 1988, for a discussion of the presumed relationship between subjective and DS effects).

Stimuli that are uniquely associated with the availability of a reinforcer are called DS when they acquire the ability to increase the frequency of the response reinforced in their presence. In a typical drug discrimination experiment, animals are randomly injected with drug or placebo on alternate sessions. Depending upon which solution is administered, responding on one of two levers or keys results in the delivery of a reinforcer, such as food, under a schedule of reinforcement. Responding on

the incorrect lever or key does not result in reinforcer delivery. With continued training, animals learn to make this discrimination and its accuracy is tested by administering the training drug and placebo during test sessions where either both responses are correct or extinction conditions are imposed. Sensitivity and specificity of the discrimination are evaluated by administering lower doses of the training drug and test drugs. Test drugs include those that are likely to be discriminated as the training drug (i.e., those from the same pharmacological class) as well as negative controls (i.e., drugs from other pharmacological classes).

A variety of drugs have been shown to serve as DS. The extensive literature in this area indicates that such discriminations have pharmacological specificity and are thus useful for classifying drugs and suggesting mechanisms of action that underlie their subjective effects in humans (see Schuster and Balster, 1977; Colpaert and Slangen, 1982; Colpaert and Balster, 1988). One of the drugs that has been extensively studied in this regard is cocaine. In 1976, Colpaert and his colleagues demonstrated that 10 mg/kg of cocaine could function as a DS in rats (Colpaert et al., 1976). Subsequent studies have shown that cocaine is capable of controlling differential responding in a variety of other species including pigeons (de la Garza and Johanson, 1985; Jarbe, 1981, 1984), squirrel monkeys (Woolverton and Trost, 1978), and rhesus monkeys (Ando and Yanagita, 1978; de la Garza and Johanson, 1983). Furthermore, this discrimination can be trained under a variety of schedule conditions and using different routes of administration. Finally, Wood et al. (1987) demonstrated that the DS properties of cocaine are mediated centrally by showing that intracerebroventricular (i.c.v.) injections also resulted in cocaine-appropriate responding in rats trained to discriminate intraperitoneal cocaine. Further evidence that cocaine's DS properties depend on central mechanisms is that quaternary cocaine, which does not cross the blood-brain barrier does not substitute for cocaine as a DS (Ho and McKenna, 1978).

The evaluation of the DS effects of cocaine has shown that this drug is similar in this respect to other psychomotor stimulants. For instance, in studies with animals trained with either cocaine or amphetamine, generalization tests have shown that the DS properties of these two drugs are similar. That is, if trained to discriminate cocaine from saline, animals respond on the cocaine-appropriate lever when given amphetamine, and vice versa (Jarbe, 1981, 1982; Huang and Ho, 1974; de la Garza and Johanson, 1983, 1985, 1986, 1987a; Kilbey and Ellinwood, 1979; McKenna and Ho, 1980; Emmett-Oglesby et al, 1983). In several studies, separate groups of rats have been trained to discriminate cocaine or amphetamine and the substitution of DS properties in crossover tests has been evaluated. In many of these studies (e.g., Colpaert et al., 1978a), amphetamine was more potent than cocaine but the relative ED50 values of the two drugs were the same in both groups of animals. However, D'Mello and Stolerman (1977) and Stolerman and D'Mello (1981) found that the potency difference between cocaine and amphetamine was exaggerated in amphetamine-trained rats relative to cocaine-trained rats, but the factors responsible for this difference are unclear (see Colpaert et al., 1978a, for a discussion).

In other studies, cocaine and amphetamine were similar in potency as DS in both pigeons (de la Garza and Johanson, 1985), rats (Emmett-Oglesby et al., 1983), and rhesus monkeys (de la Garza and Johanson, 1983). Using a different experimental paradigm, de la Garza and Johanson (1986) replicated their previous finding that cocaine and amphetamine were similar in potency as DS when delivered intramuscularly to rhesus monkeys. In addition, the potencies of both intravenous cocaine and intragastric amphetamine were similar to that of intramuscular cocaine. When intragastric cocaine was tested in these monkeys trained to discriminate intramuscular cocaine, it also substituted as a DS, but its onset of effect was considerably delayed and variable, and its potency was low relative to the other routes of administration. Despite earlier reports to the contrary (e.g., Ritchie and Cohen, 1975), it is clear from the results by de la Garza and Johanson (1986) that cocaine is active orally. These results also suggest that cocaine is capable of producing subjective effects in humans by this route, an inference experimentally verified by Van Dyke et al. (1978).

3. Tolerance. Although both tolerance and increased sensitivity have been shown to develop to certain of cocaine's behavioral actions, modified sensitivity to the DS effects of cocaine after repeated administration has not been extensively evaluated. Wood et al. (1984) trained rats to discriminate 20 mg/kg of cocaine and then suspended training for 6 days during which they administered 20 mg/kg/8-h of cocaine. After the repeated regimen, they found that the dose-response function for cocaine was shifted 2-fold to the right, indicating the development of tolerance. Similar results were found by McKenna and Ho (1977). Subsequent studies have indicated that this tolerance development is dose-related, but the maximum change in sensitivity is only a 2-fold shift in the dose-response function (Wood and Emmett-Oglesby, 1986). When the repeated regimen (i.e., 20 mg/kg/8-h) is terminated after 12 days, sensitivity returns after approximately 18 days (Wood and Emmett-Oglesby, 1986).

Cross-tolerance develops to other stimulants such as methamphetamine, amphetamine, diethylpropion, phenmetrazine, phentermine, and methylphenidate (Wood et al., 1984; Wood and Emmett-Oglesby, 1988). In addition, in rats trained to discriminate intraperitoneal cocaine from saline, there was cross-tolerance to cocaine administered i.c.v. and the degree of this tolerance was the same regardless of route (Wood et al., 1987). Fenflura-

mine did not substitute for cocaine either before or after the period of repeated cocaine administration (Wood and Emmett-Oglesby, 1988). These investigators have interpreted these data to indicate that the drugs which show cross-tolerance share mechanisms of action with cocaine whereas drugs such as fenfluramine do not. Although additional research may be necessary to verify the hypothesis, it is clear from these data that it is likely that tolerance can develop to the subjective effects of cocaine over a relatively short period of time, which may result in the abuse of greater amounts of cocaine (see also Fischman et al., 1985; Fischman and Rachlinski, in press). The extent of this tolerance development appears to be limited, i.e., the maximum change was a 2-fold shift but, in addition, it disappears relatively rapidly.

4. Central mediation of discriminative stimulus effects. A primary goal of many studies on the DS properties of cocaine has been to determine the central mediation of these effects. The approaches that have been used to investigate the underlying mechanisms of cocaine action include 1) substituting drugs with known agonist effects on specific CNS receptors to determine their similarity to cocaine as a DS; 2) concurrent administration (pretreatment) of drugs known to block specific receptors; and 3) lesions in specific areas within the CNS. The majority of these studies have indicated that the DS properties of cocaine, like many of its other behavioral effects, are mediated by dopaminergic systems. It is also clear, however, that dopaminergic systems alone do not completely mediate cocaine's DS properties. For instance, there is some evidence that noradrenergic mechanisms are involved and generalization studies with local anesthetics also provide evidence that this action of cocaine action may contribute to its DS properties.

Much of the evidence implicating dopamine as a mediator of cocaine's DS effects comes from studies in which other drugs known to have effects on dopamine systems have been shown to substitute for cocaine. For instance, as noted above, amphetamine substitutes for cocaine, and this is also true for a variety of other psychomotor stimulants such as cathinone, diethylpropion, phenmetrazine, and phentermine (Wood and Emmett-Oglesby, 1988; de la Garza and Johanson, 1987a). Drugs from other pharmacological classes (opiates, barbiturates, benzodiazepines, hallucinogens) do not substitute, which demonstrates that the discrimination has pharmacological specificity. Furthermore, drugs which have certain pharmacological properties in common with cocaine, but which do not share its effects on DA reuptake, do not substitute. Examples are the anorectic fenfluramine, whose actions are primarily mediated by serotonin systems, and strychnine (McKenna and Ho, 1980). However, drugs which have DS properties similar to cocaine also have effects on other neurochemical systems in the CNS just as cocaine itself does. Therefore, some studies have tested drugs that are believed to be more specific dopamine agonists. For instance, apomorphine has been shown to substitute for cocaine in rats (Colpaert et al., 1976; Colpaert and Jonssen, 1982; McKenna and Ho, 1980).

However, other studies have shown either no or only partial substitution of apomorphine in several different species (de la Garza and Johanson, 1983, 1985; Colpaert et al., 1979; Jarbe, 1981, 1984). Wood and Emmett-Oglesby (1987a) showed that initially apomorphine substituted for cocaine but after the development of tolerance to the DS properties of cocaine, there was no substitution even at higher doses. Furthermore, in monkeys trained to discriminate apomorphine, cocaine did not substitute whereas another directly acting dopamine agonist, piribedil, did substitute and the apomorphine discrimination was blocked by the DA antagonist, pimozide (Woolverton et al., 1987a). Colpaert et al. (1979) also showed that other directly acting DA agonists, namely piribedil, bromocriptine, and amantadine, only partially substituted for cocaine. Wood and Emmett-Oglesby (1987b) demonstrated that the D-1 agonist, SKF 38393, only partially substituted for cocaine. Partial substitution has also been shown with direct D-2 dopamine agonists (apomorphine, piribedil, bromocriptine) in monkeys when amphetamine was used as the training drug whereas SKF 38393 (a D-1 agonist) generated only saline-appropriate responding (Kamien and Woolverton, 1989).

Stolerman and D'Mello (1981) found that apomorphine only substituted for *l*-amphetamine when the discrimination was trained with a high dose. Nielsen and Jepsen (1985) suggested that low doses of amphetamine were acting via DA in mesolimbic areas of the CNS whereas the actions of high doses of amphetamine were mediated by the striatal dopamine systems. Since apomorphine may be a weak DA agonist in the mesolimbic area, it is not surprising that animals trained to a low dose of amphetamine did not respond on the drug lever when given apomorphine (Nielsen and Jepsen, 1985). On the other hand, with cocaine, Swedberg and Jarbe (1986) showed that in a three-lever discrimination among cocaine, morphine, and no-drug, apomorphine completely substituted for cocaine in animals trained with a low dose (3 mg/kg) but distributed their responses between the cocaine lever and the no-drug lever when trained with a high dose (5.6 mg/kg). Colpaert and Janssen (1982) found that apomorphine substituted for cocaine in rats trained with both 2.5 and 10 mg/kg of cocaine.

Taken as a whole, it is clear from the studies with doapmine agonists that dopamine is involved in the DS properties of cocaine and amphetamine but that it is likely that other neurochemical systems are involved as well. Preliminary evidence that noradrenergic mechanisms are involved comes from studies using amphetamine as a training drug that have shown that nisoxetine, a noradrenergic agonist, substitutes for amphetamine in

mice (Snoddy and Tessel, 1983), rhesus monkeys (Woolverton, 1984), and pigeons (Evans and Johanson, 1987). In addition, in mice trained to discriminate nisoxetine, cocaine substitutes as a DS (Snoddy and Tessel, 1983). Furthermore, prazosin, an α-1 adrenergic blocking agent, attenuates the DS effects of amphetamine as well as nisoxetine (Snoddy and Tessel, 1985). However, nisoxetine has not been tested in animals trained to discriminate cocaine, although it has been shown that prazosin blocks the locomotor-activating effects of cocaine (Snoddy and Tessel, 1985) as well as its effects on schedule-controlled responding (Tessel and Barrett, 1986).

Colpaert et al. (1980) showed that type B monoamine oxidase inhibitors (e.g., tranylcypromine) but not type A (clorgyline) inhibitors also substituted for cocaine as a DS and interpreted these results to indicate a possible role for β-phenylethylamines but not dopamine in mediating cocaine's DS effects. Thus, it appears that although dopamine may play a major role in the DS properties of cocaine, additional research is needed to determine whether other central systems also are involved.

One possibility is that the local anesthetic properties of cocaine contribute to its DS effects. To test this possibility, Woolverton and Balster (1982) trained rats to discriminate procaine from saline and found that cocaine as well as several other local anesthetics (e.g., lidocaine) substituted. de la Garza and Johanson (1985) showed partial substitution with procaine in pigeons trained to discriminate cocaine but lidocaine was not cocaine-like. Partial substitution for cocaine has also been seen with procaine in rhesus monkeys (de la Garza and Johanson, 1983) and lidocaine in rats (Huang and Wilson, 1982). It should be recalled that although procaine did not produce cocaine-like subjective effects in humans, some subjects did identify procaine as cocaine and 96 mg of intravenous procaine resulted in significant increases in reports of "high" (Fischman et al., 1983a; see also Kellner et al., 1987). Therefore, while cocaine and other local anesthetics do not have identical DS properties, there are some similarities which may indicate that the DS properties of cocaine have multiple determinants within the CNS (see Woods et al., 1987, for a discussion).

In addition to the strategy of using other agonist drugs to determine the neurochemical systems within the CNS that mediate cocaine's ability to function as a DS, receptor blockers have also been used. For instance, it has been shown that haloperidol, a dopamine receptor antagonist, disrupts but does not always completely block the stimulus control exerted by cocaine in several species (Jarbe, 1978; Colpaert et al., 1978a,b; McKenna and Ho, 1980). However, Colpaert et al. (1976) failed to demonstrate that haloperidol as well as pimozide disrupted cocaine's ability to function as a DS. On the other hand, in a recent study by this investigator that examined the entire dose-response function of cocaine, haloperidol produced a shift in the function to the right (Colpaert, 1987). Kleven et al. (1988a) have also shown that the D-1 receptor antagonist, SCH 23390, blocks the DS properties of cocaine. Attenuation of amphetamine's DS properties by haloperidol and SCH 23390 has also been reported (Woolverton et al., 1987b; Nielsen and Jepsen, 1985). The D-2 receptor blocker, pimozide, also antagonizes the DS effects of cocaine but this effect is only partial (McKenna and Ho, 1980; Jarbe, 1978, 1984; Colpaert et al., 1978a,b) and in one case, it had no effect (Colpaert et al., 1976).

α-Methylparatyrosine, which depletes newly formed dopamine, does not alter the DS effects of cocaine (Jarbe, 1978; McKenna and Ho, 1980) but does affect the ability of amphetamine to function as a DS (Kuhn et al., 1974; Ho and Huang, 1975; Schechter and Cook, 1975). In contrast, reserpine, which depletes dopamine from storage vesicles, blocks cocaine's DS properties but not amphetamine's. On the other hand, α- and β-noradrenergic postsynaptic receptor antagonists, as well as serotonin and cholinergic receptor blockers, do not affect the ability of cocaine to control differential responding (Jarbe, 1978; McKenna and Ho, 1980; Ho and Silverman, 1978; Colpaert et al., 1976).

As with the receptor agonist studies, the studies with receptor antagonists clearly indicate that a major determinant of cocaine's ability to function as a DS is due to its effects on dopamine. However, these effects are not a complete explanation and undoubtedly other systems as well as local anesthetic effects in some way modulate these effects of cocaine. Similar complexity is shown in studies which have used the neurotoxin, 6-OHDA, injected into the nucleus accumbens of rats, which results in the depletion of dopamine but not other neurotransmitters in that area. Although studies have demonstrated that 6-OHDA lesions disrupted the ability of amphetamine to function as a DS (Dworkin and Bimle, 1989; Woolverton and Cervo, 1986), results with cocaine have been contradictory (compare Woolverton and Cervo, 1986, and Dworkin and Smith, 1988).

D. Reinforcing Effects

1. Self-administration methods. A major reason for the present day interest in the pharmacology of cocaine relates to its widespread abuse by humans. Although incidence may be subsiding, the rapid escalation of cocaine abuse since the mid-1970s (see section IV) has resulted in renewed interest in the behavioral effects of this drug that are related to its abuse as well as the neurobiology of these actions. Because of the demonstrated relationship between the reinforcing effects and dependence potential of CNS drugs (Johanson and Balster, 1978; Johanson and Schuster, 1981a; Young and Herling, 1986), investigations of the reinforcing effects of cocaine using self-administration methods clearly have relevance for the etiology and treatment of cocaine abuse.

Such studies have not only elucidated behavioral and pharmacological variables which contribute to the ability of cocaine to control behavior but have also provided some evidence of underlying neurochemical mechanisms.

The positive reinforcing effects of cocaine as well as those of other stimulants have been investigated since the 1960s using drug self-administration techniques (Johanson, 1978b, 1984). Pickens and Thompson (1968) showed that rats with intravenous catheters would press a lever if that response was followed by an intravenous injection of cocaine. Because stimulant drugs such as cocaine were also known to produce increases in responding maintained by other events such as food, these investigators carefully demonstrated that lever pressing was a function of contingent cocaine injection, not just general behavioral activation. For instance, when saline replaced the active drug or when drug was automatically delivered simply on the basis of time, responding declined. When drug was available only for responding on the right lever, few responses were emitted on the left lever. When the experimenters reversed these contingencies, the rats modified their behavior appropriately, i.e., they switched their responding to the left lever.

In another early self-administration study (Wilson et al., 1971), rhesus monkeys were given 4 h of daily access to cocaine during which each lever press resulted in a drug injection. Interestingly, the monkeys regulated their drug intake to a remarkable degree. After training, 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 (sensitization) in its rate of self-administration. These investigators also demonstrated the constancy of cocaine intake by changing the dose injected after each lever press. As dose per injection was increased, the number of injections taken by the animals decreased, resulting in an almost constant intake of drug regardless of the dose per infusion.

Another type of regulation was also evident in the pattern of cocaine self-administration. Infusions of cocaine were equally spaced across the experimental session almost as if the drug were being injected under the control of a clock. This regularity in self-administration has also been observed in human research subjects (Paly et al., 1982; Fischman and Schuster, 1982). Stability of intake within sessions is not a characteristic shared by many other drug reinforcers. Even a drug such as amphetamine which shares many pharmacological properties with cocaine shows variation in intake; within sessions amphetamine is taken in bursts of infusions with long pauses between these bursts (Balster and Schuster, 1973a). On the other hand, a variety of other drugs which function as positive reinforcers and also have some properties in common with cocaine, including procaine (Johanson, 1980), cathinone (Johanson and Schuster, 1981b), and propylbutyldopamine (Woolverton et al., 1984), also show within-session regularity in intake.

Despite the stability of intake noted in these early studies, when access to cocaine is not limited to a few hours each day, this stability disappears (Deneau et al., 1969). In a study by Johanson et al. (1976a), untrained rhesus monkeys were exposed to continuous around-the-clock access to one of a variety of psychomotor stimulant drugs. Two monkeys given access to 0.2 mg/kg of cocaine began taking drug the very first day of its availability and immediately intake became erratic and excessive, resulting in severe toxicity that led to death. Similar results were noted with other psychomotor stimulants tested including amphetamine, methamphetamine, and diethylpropion. Therefore, it appears that if there are no outside constraints on the availability of psychomotor stimulant drugs, rhesus monkeys will suddenly increase their drug-taking behavior to the point of severe toxicity. In contrast, the intake of cocaine under conditions of limited access is surprisingly regulated. The mechanism underlying a loss of control is not understood, but it may be due to the ability of psychomotor stimulant drugs to produce stereotypic behavior, which may include the drug-taking response (Collins et al., 1979).

The results of the early behavioral experiments of Pickens and Thompson (1968) and Wilson et al. (1971) have been replicated in numerous studies. For instance, cocaine is self-administered by every species of animal tested, including rats (Pickens and Thompson, 1968), squirrel monkeys (Goldberg, 1973; Katz, 1979), rhesus monkeys (Woods and Schuster, 1968), pigtail macaques (Young and Woods, 1980), baboons (Griffiths et al., 1975), cats (Balster et al., 1976), dogs (Risner and Jones, 1975), and humans (Fischman, 1984; Henningfield et al., 1987). This concordance across species, both in terms of the ability of cocaine to function as a reinforcer as well as the characteristics of the maintained responding (see reviews by Griffiths et al., 1980; Johanson and Schuster, 1981a), is one type of evidence of cocaine's efficacy as a reinforcer. This also implies that similar molecular substrates are shared across species and that it is unlikely that cocaine abuse in humans is due to a specific type of psychopathology.

A second type of evidence that cocaine is an efficacious reinforcer is that it maintains responding regardless of its route of delivery. Although the i.v. route has been used most commonly in experimental studies, cocaine also maintains responding when delivered intragastrically (Woolverton and Schuster, 1983), by chewing or smoking (Siegel et al., 1976), intranasally (Foltin et al., 1988) and intramuscularly (Goldberg et al., 1976).

1. *Schedules of reinforcement.* 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 or schedule contingencies. Schedule of drug delivery has an important influ-

ence on the reinforcing effects of cocaine as evidenced by changes in the shape and position of its dose-response function. Many studies have shown that cocaine maintains responding under ratio schedules (e.g., Balster and Schuster, 1973a; Goldberg et al., 1971). The pattern of responding is characterized by an initial pause followed by a high terminal rate of responding. Although this pattern of ratio responding is similar to that maintained by other events, such as food and water, the rates of responding typically found in drug self-administration studies have been low compared to rates maintained by food and increases in dose per injection further decrease rates, i.e., the relationship between dose and rate of responding is inverse. These low rates are probably due to the dual actions of the drug. On the one hand, cocaine serves as a reinforcer that increases rate of responding, but on the other hand, the drug has the ability to disrupt ongoing behavior temporarily and thus have a rate-decreasing effect. As dose is increased, the latter effect predominates and responding becomes suppressed. Since increased responding under ratio schedules results in increased rates of drug intake, the problem is particularly striking under this schedule. Herling et al. (1979) provided evidence of this predominant effect by demonstrating that decreases in rate of responding under a multiple schedule of food and cocaine presentation were similar. That is, the noncontingent administration of cocaine decreased cocaine self-administration as well as the food-maintained responding that occurred in the subsequent component to exactly the same degree, such that Herling et al. (1979) claimed that rate of responding was under the influence of cocaine's nonspecific effects, not its reinforcing effects.

Further evidence that rate of responding is a reflection of cocaine's nonspecific effects is that imposing a time out after each injection, which presumably should have no effect on reinforcing effects but which allows time for the nonspecific effects to dissipate, results in a shift to the right in the cocaine dose-response function (Downs and Woods, 1974; Winger and Woods, 1985; Woods et al., 1987). Therefore, using ratio schedules to compare the potency of cocaine *as a reinforcer* to other drugs (e.g., Ritz et al., 1987) may be inadequate because the dependent variable itself, namely rate of responding, is not determined solely by reinforcing effects. This problem must be taken into consideration in interpreting studies designed to determine the underlying molecular mechanism of any specific behavioral effect such as reinforcing properties not only with cocaine but other drugs that serve as positive reinforcers as well (Johanson, 1988; Wise, 1987).

In an attempt to avoid a confounded measure of reinforcing effects, other schedules have been used in cocaine self-administration studies. These studies are also important in terms of further deomstrating the generality of cocaine's reinforcing effects. For instance, cocaine has been shown to maintain responding under 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 cocaine injections in monkeys was conducted by Balster and Schuster (1973b). Responding was maintained under a FI 9-min schedule of cocaine injections in one component and food delivery in the other. In addition, there was a 15-min time out following the presentation of each reinforcer. Responding was well maintained and the pattern of gradually accelerated responding over the interval with cocaine was similar to that maintained by food. As dose per injection increased, rate of responding increased, i.e., the dose-response function was direct. Similar results were found by Bradford and Griffiths (1980) in baboons when cocaine was administered only once every 24 h. However, in a study by Johanson (1982) using a FI 5-min schedule of cocaine injection without an intervening time-out period, the shape of the dose-response function was no longer a direct one but was an inverted U and the ascending limb of the curve was shifted to the left relative to that found in the Balster and Schuster (1973b) study. Similar results have been found in other species (Dougherty and Pickens, 1973; Goldberg and Kelleher, 1976). This difference is probably due to more frequent injections. Despite the powerful nature of the contingencies governing reinforcer presentation in controlling responding, the nonspecific rate-modifying actions of cocaine also exert an influence which can be minimized by more infrequent drug availability as in the Balster and Schuster (1973b) and Bradford and Griffiths (1980) studies.

Second-order schedules have also been used as a way of minimizing the direct effects of cocaine in order to get a less confounded estimate of the drug's reinforcing actions. Goldberg (1973), using squirrel monkeys, studied responding maintained by cocaine under a FR 30 schedule of stimulus presentations (2-s yellow light), which itself was maintained under a FI 5-min schedule of cocaine injection. This schedule is designated a second-order FI 5-min (FR 30:S). Under this schedule, rates of responding for cocaine were extremely high and similar to responding maintained by other events, such as food, under an identical schedule. Such high rates of responding have been maintained under FI (FR) schedules by i.v. and i.m. cocaine as well as with FR schedules of FI components in several primate species (Goldberg et al., 1981; Kelleher and Goldberg, 1977; Goldberg and Kelleher, 1977; Goldberg et al., 1975, 1976). High rates of responding have been maintained even when only a single reinforcer is delivered at the end of a session (Goldberg et al., 1976).

In addition to the importance of limiting overall rate of drug intake, Kelleher and Goldberg (1977) and Goldberg et al. (1979) also demonstrated the importance of the brief stimuli in maintaining high rates of responding

under second-order schedules. When these stimuli were removed after the FR components, but the drug was still injected, rate declined, and patterning was disrupted. If both drug injections 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 one with i.m. cocaine (Katz, 1979). The fact that both the drug and the stimuli are determinants of the rate of responding may explain the results when dose is manipulated under 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, if rate of responding reflects reinforcing effects, the strength of cocaine's ability to control responding does not seem to change with its magnitude under these schedule conditions. This is not the case under other schedules (e.g., Balster and Schuster, 1973b; Iglauer and Woods, 1974; Johanson and Schuster, 1975) and under second-order schedules with different parameters, the shape of the dose-response function is an inverted U-shape (Johanson, 1982).

The studies reviewed indicate that cocaine self-administration occurs under a variety of experimental circumstances and is not restricted to a narrow range of conditions. While this property is not unique to cocaine (see Johanson and Balster, 1978; Griffiths et al., 1980; Johanson and Schuster, 1981a; Young and Herling, 1986; Ator and Griffiths, 1987), most researchers believe that cocaine is a particularly efficacious reinforcer (Johanson, 1984, 1988). It is clear that persistent and excessive drug-seeking behavior is determined by an interaction between the drug's schedule of presentation and its specific pharmacological effects. As a comparison of the above studies reveals, the shape and position of cocaine's dose-response function can change dramatically as a function of the parameters of the experimental conditions (Woods et al., 1987). This dynamic quality is due to the multiple actions of cocaine (e.g., rate-suppressing, stereotypic, reinforcing) so it is important in studies that are focused on elucidating the underlying mechanism of cocaine's reinforcing effects to bear in mind possible confounds of the behavioral measure. In addition, however, the reinforcing effects of cocaine as well as those of other drugs are altered by a variety of behavioral factors (e.g., the influence of conditioned stimuli in second-order schedules).

One example of a variable that has an influence on cocaine self-administration is level of food deprivation. de la Garza et al. (1981) showed that rate of responding increased under both a ratio and an interval schedule of cocaine injection when rhesus monkeys were food restricted. Similar effects have been found in other studies as well (Carroll et al., 1979; Glick et al., 1987; de la Garza and Johanson, 1987b). The mechanism underlying this effect has not been completely elucidated. Carroll and Meisch (1984) have described the behavioral mechanism underlying this effect within a learning context which operates equally across drug classes. Glick et al. (1987), on the other hand, have proposed drug-specific mechanisms. For instance, they showed that food deprivation resulted in larger increases in cocaine self-administration relative to amphetamine in rats. Since Carlson et al. (1987) showed that food deprivation has selective effects on dopamine in the frontal cortex which has been proposed as the site of action of cocaine, but not amphetamine (Hoebel et al., 1983; Goeders and Smith, 1983; Goeders et al., 1986), they attributed this greater effect to the synergistic actions of cocaine and food deprivation in the frontal cortex. They suggested that the modification of self-administration by food deprivation can be used to elucidate neurochemical actions of drugs. The failure to replicate this differential sensitivity to the effects of food deprivation in rhesus monkeys (de la Garza and Johanson, 1987b), however, makes this proposal premature. But regardless of its relationship to neurochemical mechanisms, it is clear that food deprivation has profound effects on cocaine self-administration.

A second example of the powerful effects of behavioral conditions is illustrated by studies in which responding by squirrel monkeys was concurrently maintained under a variable interval schedule of cocaine delivery and a FI schedule where responding resulted in the *termination* of availability of cocaine (Spealman, 1979b). Responding was maintained over a 10-fold dose range under both schedules, resulting in a reduction in the number of cocaine injections self-administered. That is, relative to the frequency of cocaine delivery that was possible under the variable interval schedule alone, the addition of the FI schedule contingency resulted in a decrease in cocaine self-administration.

3. Measures of reinforcing efficacy. Because of the difficulty of using dependent variables such as rate of responding that can be influenced by effects other than cocaine's reinforcing properties, the development of rate-free indices has been vigorously pursued. Two other procedures that have been used to compare different doses of cocaine, hopefully in the absence of any confounding influence, are choice paradigms and concurrent schedules. 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. The actual rate at which either of these responses is made, which can be dramatically influenced by level of drug intake, is irrelevant and does not contribute to the assessment of reinforcing effects. 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 (Catania, 1963; Neuringer, 1967; Pliskoff and Hawkins, 1967).

With concurrent schedules, responding is maintained by two or more simultaneously operating schedules. In studies by Iglauer and her colleagues (Iglauer and Woods, 1974; Iglauer et al., 1975; Llewellyn et al., 1976), responding was maintained in rhesus monkeys under a concurrent two-lever variable-interval (VI) schedule of cocaine injections with a 5-min time out after 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 VI 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. 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.

The second procedure designed to compare reinforcing effects 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 doses of cocaine, and injections were followed by a 15-min time-out period. The number of trials during which one option rather than the other was selected was counted and used as the measure of reinforcing effects. As in the Iglauer and Woods (1974) study, actual rate of responding did not influence the measure of reinforcing effects and again it was found that higher doses of cocaine were preferred to lower doses. Similar results have been found by Brady and Griffiths (1977) in baboons and by Fischman and Rachlinski (in press) in humans.

The results obtained with both the concurrent schedule and choice paradigm have been encouraging. The assumption in studies of drug self-administration is that reinforcing strength or efficacy increases with dose. As indicated in the prior section, dose-response relationships with cocaine are rarely direct, and it has been assumed that this was due to rate-modifying effects of cocaine's action unrelated to reinforcing effects. To the extent that the influence of these other effects has been eliminated in studies using procedures that do not utilize rate as a measure of reinforcing efficacy, these procedures are likely to be useful in the elucidation of the molecular mechanisms underlying the reinforcing effects of cocaine, although to date their use has been quite limited.

In addition to the use of non-rate procedures, other approaches for evaluating the reinforcing efficacy of cocaine and other drug reinforcers have been developed to a limited extent. These approaches have in common the notion that the strength of a reinforcer can be measured in direct proportion to its ability to maintain responding even when that responding is challenged by some intervention (Nevin, 1974). The interventions that have been used in experimental studies include increasing the work required to obtain the reinforcer (increased response cost), imposing a delay between the required response and drug delivery, providing other mutually exclusive reinforcer alternatives, and punishment.

The influence of response cost on drug self-administration has been evaluated using progressive ratio schedules. 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 injection 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 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, studies have shown that breaking point is directly correlated with the magnitude of reinforcement for both sweetened condensed milk and intracranial stimulation (Hodos, 1961; Hodos and Kalman, 1963; Keesey and Goldstein, 1968). Likewise, 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 injection. Other stimulant drugs did not have breaking points that were as high.

Griffiths et al. (1975, 1978) and Bedford et al. (1978) also showed that breaking points were dose related at doses below 0.4 mg/kg. Above that dose, breaking point did not increase with dose and in some animals even decreased (Bedford et al., 1978). Similar results were found by Winger and Woods (1985) in rhesus monkeys, i.e., maximum breaking point occurred at a dose of 0.32 mg/kg whereas a higher dose yielded a decrease in this measure. Interestingly, Winger and Woods (1985) also found that the function generated under the progressive ratio schedule was not radically different than the function generated under a fixed-ratio schedule and differences were largely a function of the time between injections, not the nature of the dependent measure.

Johanson (1975) used a combination of the previously described choice procedure and a progressive ratio schedule. Under the initial condition, animals given a choice between a low and a high dose selected the high dose. Next the FR requirement necessary to produce the preferred dose was systematically increased while the behavioral requirements for the alternative (FR 5), but less preferred dose of cocaine, remained the same. It was reasoned that although animals prefer higher doses of cocaine over lower doses, if the behavioral requirements for the preferred dose were great enough, the animals would choose the alternative. In addition, the greater the difference between the size of the doses of the two

alternatives, the greater the increase in ratio necessary to alter preference. In two of the four monkeys tested, the results were as predicted. For instance, in one monkey, when both doses were 0.05 mg/kg cocaine, the ratio had to be increased to 40 before the monkey exclusively chose the option requiring only 5 responses. When the alternative was a higher dose of 0.1 mg/kg, this ratio was 65. Similar results were obtained with the second monkey. However, for the remaining two monkeys, the high dose continued to be selected even when ratios were increased to above 300 responses per injection. Given the results by Yanagita (1973), it is likely that higher ratios would have been required to alter preference in these two monkeys.

In an adaptation of Johanson's choice procedure, Fischman and Rachlinski (in press) found that human subjects given a choice between 8 mg of i.v. cocaine and i.v. saline showed no systematic preference for either solution when the requirement for injection was a FR 10. However, when the FR was increased to 200, there was a clear preference for the 8 mg-cocaine dose.

Progressive ratio schedules have also been used to compare the reinforcing effects of cocaine to other drug reinforcers. For instance, Yanagita (1973) found that 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 that for other stimulant or anorectic drugs including methylphenidate, diethylpropion, chlorphentermine, and fenfluramine. Studies using dogs have also demonstrated that cocaine sustains responding at higher ratio values than *d*-amphetamine, mazindol, fenfluramine (Risner and Silcox, 1981), or nicotine (Risner and Goldberg, 1983). The important point of these studies is that cocaine is a more efficacious reinforcer than these other drugs and the extent of the difference can be expressed numerically by comparing maximum breaking points.

When a delay is imposed between the response required for reinforcer delivery and its presentation, responding is typically decreased. Stretch et al. (1976) showed that delay can also reduce rate of responding maintained by cocaine, particularly if animals are punished for making responses during the delay interval. Similar results have been found by P. M. Beardsley, J. A. Salay, and R. L. Bolster (Personal communication) for both cocaine and procaine, but Johanson (1975) reported negative results using a choice paradigm. Another type of intervention that has been postulated to decrease the efficacy of a reinforcer is the availability of alternatives, the selection of which eliminates the opportunity for cocaine self-administration. The choice procedure developed by Johanson and Schuster (1975) has been used in this regard to compare different drugs to cocaine. When differences in potency are taken into account, cocaine was found to be more efficacious as a reinforcer than methylphenidate (Johanson and Schuster, 1975), diethylpropion (Johanson and Schuster, 1977), and procaine (Johanson and Aigner, 1981). Interestingly, in a choice procedure comparing cocaine to *dl*-cathinone, the active alkaloid of a plant which is chewed by inhabitants of Africa and the Middle East, these two drugs had similar efficacy (Woolverton and Johanson, 1984).

In addition to comparisons between cocaine and other drugs, there have 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 (W. L. 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). As with the progressive ratio and drug-drug choice studies, these results clearly indicate that cocaine is a powerful reinforcer, i.e., its reinforcing efficacy exceeds most other reinforcers. On the other hand, when Carroll et al. (1989) examined the effects of the concurrent availability of a highly preferred glucose and saccharin solution on cocaine self-administration in rats, they found that this alternative reinforcer effectively interfered with acquisition and maintenance of cocaine self-administration.

The third approach to assessing the strength of a reinforcer is to determine its resistance to the effects of punishment. The effects of punishment, such as electric shock and time out from positive reinforcement, on behavior controlled by a variety of events other than drugs have been studied extensively (Azrin and Holz, 1966). The degree of response suppression is dependent upon the intensity of the punishing event and its schedule of presentation, as well as the time between response and consequence. All else being equal, it would be assumed that the greater the difficulty in decreasing the self-administration of a particular drug using punishment, the greater its reinforcing efficacy.

The effects of punishment on 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-h sessions. Punishment was accomplished by delivering a brief electric shock at the onset of each injection. Responding maintained by both 0.1 and 0.2 mg/kg of cocaine decreased as a function of the intensity of the shock. However, the degree of suppression expressed as a percentage of control rates was the same for the two doses of cocaine. 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 two 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 an attempt to eliminate the problem of rate differences, Johanson (1977) used the discrete trial choice procedure previously described with added punishment contingencies. Rhesus monkeys were given a choice between two alternatives of i.v. 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 injection 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 eventually preferred the higher dose.

All of the studies reviewed in the preceding sections clearly lead to the conclusion that cocaine has strong and robust reinforcing effects as indicated by its ability to continue to maintain responding even when response cost is high, even at the expense of refusing alternative reinforcers as important as food and even when self-administering cocaine is punished. All of these approaches can be utilized to compare cocaine's reinforcing efficacy to that of other drugs but, to date, not enough data have been generated to indicate unequivocally that any of these approaches will be successful in quantitatively differentiating reinforcing efficacy across drugs and conditions.

4. Neurobiology of cocaine reinforcement. In general, the more sophisticated behavioral approaches described above have rarely been used in studies designed to assess the neurochemical mechanisms of cocaine's reinforcing effects (Johanson, 1988; Roberts and Zito, 1987). Despite this, a great deal has been learned over the last 20 years about the neurochemical and neuroanatomical events which mediate cocaine's ability to function as a positive reinforcer utilizing simple schedules of drug self-administration. The strategies for determining the neurochemical mediation of cocaine's reinforcing effects with self-administration procedures are similar to those used to determine mediation of its other behavioral effects. These strategies, which have been more thoroughly reviewed by Dworkin and Smith (1987), include the determination of the reinforcing effects of other drugs which are presumed direct agonists at specific receptors, blockade of the reinforcing effects by receptor antagonists or neurotransmitter depletion, and lesions in areas of the CNS with known receptor systems. These latter studies, as well as those involving the direct administration of drugs into the CNS, are also useful for determining site of action. While there are debates involving the precise localization and specificity of cocaine's reinforcing effects (e.g., Koob, 1987; Wise, 1987; Wise and Bozarth, 1984; Dworkin and Smith, 1987; Ettenberg et al., 1982; Goeders et al., 1985; Koob and Bloom, 1988; Bain and Kornetsky, 1987), there appears to be general agreement that cocaine's ability to initiate and/or maintain responding is related to its actions on mesolimbic/mesocortical dopaminergic neuronal systems.

Presumptive evidence that dopamine systems *can* be involved in the maintenance of responding by drugs comes from studies that demonstrate that direct dopamine agonists can maintain responding leading to their delivery. For instance, the dopamine receptor agonists, apomorphine and piribedil, have been shown to be self-administered by rats (Baxter et al., 1974; Yokel and Wise, 1978). Woolverton et al. (1984) demonstrated that apomorphine, piribedil, propylbutyldopamine, and bromocriptine, all of which are D-2 receptor agonists, were generally self-administered by rhesus monkeys whereas the D-1 receptor agonist, SKF 38393, was not. In addition, nisoxetine, which is a selective noradrenergic uptake blocker, was not self-administered by rhesus monkeys (Woolverton, 1987), and Risner and Jones (1976) also showed that the noradrenergic agonist, methoxamine, did not maintain responding in dogs.

Although the characteristics of the responding maintained by the D-2 agonists in the Woolverton et al. (1984) study were similar to responding maintained by cocaine (constant intake across dose, pattern of responding), the finding that direct dopamine agonists can function as reinforcers does not prove that this is the mechanism by which cocaine is functioning as a reinforcer, particularly since these other compounds have other neurochemical effects as well. As many reviews have pointed out (e.g., Johanson and Balster, 1978), many drugs including opiates and barbiturates function as positive reinforcers, undoubtedly by other neurochemical mechanisms. Interestingly, local anesthetics, such as procaine (Ford and Balster, 1977; Hammerbeck and Mitchell, 1978; Johanson, 1980; Fischman, in press), chloroprocaine (Johanson, 1980; Woolverton and Balster, 1982), dimethylprocaine, and dimethocaine (Woolverton and Balster, 1982) also maintain responding. On the other hand, there are local anesthetics that do not maintain responding (Woolverton and Balster, 1979, 1982).

Nevertheless, the studies with other drugs that have dopamine agonist effects do support the notion that this action of drugs can support self-administration behavior. These results have been utilized by Ritz et al. (1987) to provide evidence that the blockade of dopamine reuptake mediates the reinforcing effects of cocaine and some other dopamine agonists. In their study, they showed a significant correlation between the potencies of cocaine and cocaine-like drugs in self-administration studies and their potencies in inhibiting [^{3}H]mazindol binding to dopamine transporter sites in the striatum of the rat. On the other hand, there were no significant correlations

with a wide range of other pre- and postsynaptic binding sites. Although these results are provocative, the use of rate of self-administration to determine potencies across studies with widely different parameters, the inclusion of local anesthetics in the correlation, and using mazindol, which does not support self-administration behavior in humans (Chait et al., 1987), as the ligand, require caution in interpreting the correlation.

An alternative strategy for determining the neurochemical basis of cocaine's reinforcing effects involves the use of receptor blockers of specific neurotransmitters. However, again there are problems of interpretation with this approach if rate of responding is used as an indicator of modifications in reinforcing effects. First, since under the types of schedules that have been used in these studies, there is usually an inverse relationship between rate and dose of the reinforcer, partially blocking the reinforcing effects of a dose of the drug on the descending limb of the dose-response function may produce an increase in rate comparable to the effect of lowering the dose. A complete blockade of the drug's effects, on the other hand, is equivalent to extinction, which initially results in increased rates followed only later by response suppression. Furthermore, since rate of responding is also determined by the nonspecific effects of the drug, as reviewed above, changes may also be due to the blockade of these rate-suppressing effects (Woods et al., 1987).

Several studies have shown that drugs which block dopamine receptors, including chlorpromazine (Wilson and Schuster, 1972; Roberts and Vickers, 1984), perphenazine (Johanson et al., 1976b), haloperidol (de la Garza and Johanson, 1982; Roberts and Vickers, 1984; Woods et al., 1978), sulpiride (Roberts and Vickers, 1984), and α-flupenthixol (Ettenberg et al., 1982), all increase rate of responding maintained by cocaine. de Wit and Wise (1977) used longer sessions and demonstrated in rats that after high doses of pimozide, there was first an increase and then a cessation in responding over time, similar to patterns of responding seen when saline was substituted for drug, i.e., extinction. Woolverton (1986), using rhesus monkeys, has also shown that pimozide increased cocaine as well as piribedil self-administration whereas the D-1 receptor blocker, SCH 23390, did not. However, Koob et al. (1987a) showed that SCH 23390 did increase cocaine self-administration in a study conducted with rats. These discrepant results require further study. Other studies have shown that neither α-adrenergic nor β-adrenergic blocking agents affect cocaine self-administration (de Wit and Wise, 1977; Wilson and Schuster, 1974; Goldberg and Gonzalez, 1976; Woolverton, 1987). However, Wilson and Schuster (1975) did show that atropine increased the rate of cocaine self-administration, a finding that has not been systematically explored.

As previously discussed, the ability of receptor blockers to modify cocaine self-administration could also be a function of antagonism of the rate-reducing effects of cocaine, with no change in reinforcing effects. In fact, Woods et al. (1987) concluded that there is a mutual antagonism of the rate-reducing effects of cocaine and neuroleptics, such that increases in cocaine self-administration after the administration of neuroleptics is not related to changes in reinforcing effects. Herling and Woods (1980) provided evidence suggesting this hypothesis by showing that responding maintained by low doses of cocaine that presumably did not produce rate-decreasing effects was decreased by chlorpromazine to the same extent as responding maintained by food.

Valentine et al. (1983), using second-order schedules of cocaine and food delivery where only a single reinforcer was available each day so that rate-decreasing effects were not produced, also showed that chlorpromazine only decreased responding and this decrease was similar regardless of the event, food or cocaine, that was maintaining responding. Woolverton and Virus (1989) attempted to circumvent the problem of a mutual antagonism by using a multiple schedule of reinforcement that minimized the nonspecific rate-reducing effects of cocaine. Under this schedule, rate of responding was directly related to drug dose. However, neither moderate doses of pimozide nor SCH 23390 affected rate of responding for cocaine. At higher doses of the antagonists, cocaine self-administration decreased in a manner comparable to decreasing its dose. However, rate of responding maintained by food in the other component of the multiple schedule also decreased, suggesting a nonspecific rate-reducing effect of the antagonist. Likewise, using a food-drug choice procedure similar to that employed by Aigner and Balster (1978), Woolverton and Balster (1981) were not able to show that chlorpromazine or haloperidol decreased cocaine's reinforcing effects. In summary, as a whole, the results of several studies that have used different approaches to the assessment of cocaine's reinforcing effects (Woolverton and Virus, 1989; Woolverton and Balster, 1981) lend support to the contention of Woods et al. (1987) that dopamine antagonists exert their effect by antagonizing effects of cocaine unrelated to its reinforcement.

In addition to attempts to determine the neurotransmitters involved in cocaine's reinforcing effects using agonists and antagonists, several groups of researchers have also attempted to determine which catecholaminergic pathways are involved, i.e., its site of action. One strategy in these studies has been to train rats to self-administer cocaine, make specific lesions in different areas of the brain, and then assess whether the reinforcing effects of cocaine have been altered. A second strategy involves the direct administration of cocaine into discrete brain areas and determining its ability to maintain responding. These two strategies have been combined in studies that determine the ability of i.c.v. cocaine into

certain sites to maintain responding before and after its lesioning.

None of these approaches is without methodological problems (Dworkin and Smith, 1987). For instance, as with antagonist studies, lesion studies suffer from the use of rate of self-administration as the measure of alterations in cocaine's reinforcing effects, since any change produced in rate of responding by the lesions could as well be due to a modification of the general effects of cocaine, not just its reinforcing properties. Furthermore, given the U-shaped or inverse function relating dose and rate of responding for drug, it is not clear whether changes in rate of cocaine self-administration following a lesion when only a single dose is tested represent a decrease or increase in reinforcing effects (see Roberts and Zito, 1987; Wise, 1987). Clearly, studies involving complete dose-response functions or using nonrate measures of reinforcing efficacy would be desirable for verifying the specific role of brain amines in particular neuroanatomical regions in mediating the reinforcing effects of cocaine. On the other hand, when lesions result in the *total* suppression of responding, a qualitative rather than quantitative change, this may indicate an elimination of the substrate mediating cocaine's reinforcing effects. When responding is suppressed to that degree, however, stringent control procedures need to be used to demonstrate that this suppression is specific to behavior maintained by cocaine injections and not to the inability of the animal to engage in responding maintained by any reinforcer.

Bearing in mind these limitations, there has now accumulated a substantial body of evidence that cocaine exerts its effects on dopaminergic systems located in the mesolimbic pathways, at least in the rat. In an early study, Roberts et al. (1977) produced small discrete 6-OHDA lesions in both ascending noradrenergic and dopamine systems in the rat. Only lesions in the nucleus accumbens that depleted dopamine resulted in the suppression of cocaine self-administration. Control studies were also done that ruled out motor deficits and other nonspecific effects as explanations. Rather, it seems that these lesions had a specific effect on the reinforcing efficacy of cocaine (Roberts and Zito, 1987). Similar results were found with amphetamine self-administration (Lyness et al., 1979). The results of Roberts et al. (1977) were replicated in a study with more complete depletion of dopamine and more optimal testing conditions which also showed that an extinction-like burst of responding occurred prior to the cessation of responding (Roberts et al., 1980). Furthermore, Zito et al. (1985), by using kainic acid lesions of the nucleus accumbens which spare fibers of transport, demonstrated that the reduction in cocaine self-administration was due to the synaptic connections in that area. Koob et al. (1987b) attempted to avoid the problems of interpreting rate reductions in cocaine self-administration by using a progressive ratio schedule to evaluate the effects of 6-OHDA lesions in the nucleus accumbens on cocaine self-administration. After the lesion, breaking point maintained by cocaine decreased, suggesting a specific decrease in reinforcing effects.

An elegant demonstration that 6-OHDA lesions in the nucleus accumbens specifically decreased the reinforcing effects of cocaine has been provided by Dworkin and Smith (1988). They trained rats under a concurrent schedule with responding maintained by cocaine, food, and water. When training was completed, a dose-response function was determined for cocaine and it was shown that alterations in dose, as well as the substitution of saline, did not affect responding maintained by food and water. After 6-OHDA lesions in the nucleus accumbens, self-administration of cocaine on the ascending limb of the dose-effect curve was decreased but responding maintained by food and water was unaffected. Furthermore, the descending limb of the dose-response function, which presumably only reflects the rate-decreasing effects of cocaine, was unaltered. The investigators concluded that these results demonstrated that the nucleus accumbens specifically mediated the reinforcing effects of cocaine, as opposed to any of its other effects. This specificity was verified in an additional study showing that 6-OHDA lesions in the nucleus accumbens either did not appreciably alter or increased the effects of pretreatment with cocaine on responding maintained under a multiple FI-FR schedule of food reinforcement (Dworkin and Smith, 1987, 1988). In summary, the use of 6-OHDA lesions in the nucleus accumbens has indicated the importance of this structure in the pathway mediating cocaine's reinforcing effects.

Additional studies on the sites of action of cocaine's reinforcing effects have concentrated on delineating the entire pathway that is mediating cocaine's reinforcing effects by evaluating the effects of lesions in other structures that have projections to and from the nucleus accumbens. For instance, since the nucleus accumbens projects to the ventral pallidum and this connection has been shown to be important in the locomotor effects of psychomotor stimulants (Morgenson and Nielson, 1983; Swerdlow and Koob, 1984), Hubner and Koob (1987) showed that ibotenic acid lesions in this area also decreased cocaine self-administration and, more importantly, decreased breaking point in a progressive ratio schedule. Since dopamine cell bodies in the ventral tegmental area are a principal source of dopamine innervation to the nucleus accumbens, it is not surprising that Roberts and Koob (1982) showed that lesions in this area also disrupted cocaine self-administration and in some animals even totally eliminated self-administration, avoiding the argument concerning the interpretation of decreased rates of responding. However, it was also shown in that study that there was not a significant correlation between dopamine depletion in the nucleus

accumbens and the decrease in cocaine self-administration. Therefore, it is possible that dopamine innervation of other structures is also important for cocaine self-administration.

Evidence for the role of other dopaminergic brain sites comes from studies involving the intracranial self-administration of drugs. Bozarth (1983, 1987) believes that this approach has distinct advantages over lesion techniques in being able to determine the sites within the CNS where the reinforcing effects of drugs are initiated, although he cautions that extreme care must be taken to rule out nonspecific effects including leakage and diffusion (see Goeders, 1988, on methodology; also Goeders et al., 1985; Goeders and Smith, 1985, 1986). In contrast to lesion studies, most of the studies involving intracranial self-administration of cocaine indicate the importance of the prefrontal cortex rather than the nucleus accumbens in cocaine's reinforcing actions. This difference may reflect a difference in *initiation* of cocaine's action (mediated by the prefrontal cortex) and its *maintenance* (mediated by the nucleus accumbens). For instance, Goeders and Smith (1983), using an electrolytic microinfusion system, showed that cocaine maintained responding in a dose-dependent manner when it was injected into the prefrontal cortex but not when injected into the nucleus accumbens or ventral tegmental area. In contrast, amphetamine and lidocaine did not maintain responding when injected into that area (Goeders et al., 1986) although amphetamine does maintain responding when delivered into the nucleus accumbens (Hoebel et al., 1983).

The ability of cocaine to maintain responding when delivered into the prefrontal cortex was blocked when sulpiride was also administered into that area but not when atropine, propranolol, and SCH 23390 were given (Goeders et al., 1986), providing additional evidence that postsynaptic D-2 receptors are involved in cocaine's reinforcing effects. Lesions in this area produced by 6-OHDA eliminated intracranial cocaine self-administration but did not affect intracranial dopamine self-administration, indicating the importance of presynaptic terminals in that area (Goeders and Smith, 1986). On the other hand, Martin-Iverson et al. (1986) did not find that 6-OHDA lesions in the prefrontal cortex altered intravenous cocaine self-administration and made a case that the local anesthetic properties of the intracranially administered cocaine interfered with its reinforcing effects.

Although there is some disagreement in terms of the site of action within the mesolimbic/mesocortical pathways, it appears from both lesion and intracranial self-administration studies that the dopaminergic systems in these pathways are involved in mediating cocaine's reinforcing actions. Studies using dopamine antagonists lead to a similar conclusion about dopamine's principal role. However, there is debate about whether dopaminergic systems are uniquely related to the reinforcing effects of psychomotor stimulants and whether certain areas of the brain such as the nucleus accumbens mediate the reinforcing effects of both stimulants and opiates and Wise (1978) has even proposed a dopaminergic theory of reward.

The specificity of mediation has been evaluated pharmacologically by Ettenberg et al. (1982) who showed that flupenthixol, a dopamine receptor antagonist, increased cocaine self-administration but not heroin-maintained responding. Conversely, naltrexone increased heroin but not cocaine self-administration. Likewise, depletion of dopamine in the nucleus accumbens by 6-OHDA attenuated cocaine self-administration but did not appear to alter the reinforcing effects of heroin (Pettit et al., 1982). However, early pharmacological studies implicated dopaminergic systems in opiate self-administration (Glick and Cox, 1975; Smith and Davis, 1973) and lesion studies have shown that the nucleus accumbens and ventral tegmental area may be essential for opiate self-administration (e.g., Zito et al. 1985; Smith et al., 1985).

Intracranial opiate self-administration into both the nucleus accumbens and ventral tegmental area has also been reported (Olds, 1982; Bozarth and Wise, 1981; Goeders et al., 1984). Furthermore, as will be reviewed below, place preference and self-stimulation techniques suggest that the reinforcing effects of stimulants and opiates have overlapping mechanisms and sites of action (e.g., Phillips and LePiane, 1980; van der Kooy et al., 1982; Bozarth and Wise, 1981; Spyraki et al., 1983; Bain and Kornetsky, 1987; Wise and Bozarth, 1981). However, in a recent study using more sophisticated behavioral techniques, Dworkin et al. (1988b) failed to show that 6-OHDA lesions affected morphine self-administration and also had no effect on responding maintained by food and water. In an earlier study (Dworkin et al., 1988a), which also used a complex multiple schedule with responding maintained by morphine, water, and food, kainic acid lesions had been shown to decrease the reinforcing efficacy of morphine. However, the effect was most pronounced in rats that had only been exposed to a single dose of morphine before the lesion. When complete dose-response functions were determined before the lesion, which was also the case in the Dworkin et al. (1988b) study, morphine self-administration was not significantly altered.

In summary, there is a great deal of evidence obtained using a variety of strategies supporting the hypothesis that the mesolimbic or mesocortical dopaminergic pathway mediates the reinforcing effects of cocaine. This evidence also indicates that these pathways may mediate the reinforcing effects of other stimulants as well as opiates, but precise localization within each pathway still remains to be completely determined. While this evidence, particularly when viewed as a whole, is fairly convincing, there are also data that other neurochemical systems are involved and that a simple dopaminergic

hypothesis of cocaine's reinforcing actions involving a single pathway is not adequate. Dworkin and Smith (1987) have attempted to describe a more complex system mediating reinforcement for both stimulants and opiates, but clearly additional research will be necessary to establish its validity.

5. Other potential measures of reinforcing effects. Although techniques involving drug self-administration procedures have predominated, there are other methods that have been used to assess the reinforcing effects of drugs such as cocaine. These include place preference and self-stimulation procedures. It should be kept in mind, however, that the validity of these measures has not been adequately assessed. Nevertheless, they have been used extensively with cocaine. In addition, another procedure, conditioned taste aversion, has been used to measure the aversive effects of cocaine with extremely interesting results.

In place preference procedures, rats are placed into a chamber containing two distinctive compartments. After determining which compartment each animal prefers, they are exposed to a conditioning procedure in which the animals are placed into the nonpreferred compartment after an injection of drug, and into the preferred compartment after an injection of saline. After the animals have learned these associations, their relative preference for the two compartments is re-evaluated. To the extent that they spend a larger proportion of time in the compartment associated with the drug, that drug is presumed to have positive reinforcing effects (van der Kooy, 1987). With this procedure, cocaine has been shown by many investigators to produce a place preference in rats (Mackey and van der Kooy, 1985; Spyraki et al., 1982a; Morency and Beninger, 1986). Evidence that this effect is related to classical conditioning was provided by Bardo et al. (1986) since partial reinforcement (Mackintosh, 1974) due to repeated testing (i.e., exposing the animal to the chamber, or CS, in the absence of drug administration) attenuated the place preference. Bardo et al. (1986) also showed that conditioning could occur even after a single trial, which they believed indicated that cocaine was highly reinforcing.

Despite certain practical and theoretical advantages over other techniques, there is considerable debate about whether conditioned place preference procedures can be used to measure the reinforcing effects of drugs directly, or whether the results are due to other properties of the drug, such as its ability to produce physical dependence, tolerance, or conditioned locomotor effects (e.g., Mucha et al., 1982; Bardo et al., 1986). In a recent study, Nomikos and Spyraki (1988) described an elegant series of studies designed to demonstrate more clearly that place preferences induced by intravenous cocaine were associative in nature and reflected reinforcing effects.

Place preference techniques have also been used to determine the underlying mechanisms of cocaine's ability to function as a positive reinforcer. Like some self-administration studies (e.g., Woolverton and Balster, 1981), these studies have failed to demonstrate an attenuation of cocaine's reinforcing effects following treatment with dopamine antagonists such as pimozide, haloperidol, or α-flupenthixol (Spyraki et al., 1982a; Mackay and van de Kooy, 1985; Morency and Beninger, 1986), as would be expected based upon the majority of self-administration studies (e.g., de Wit and Wise, 1977; de la Garza and Johanson, 1982). Haloperidol did, however, block the locomotor effects of cocaine and attenuated the place preference conditioned using amphetamine (Spyraki et al., 1982a,b). In addition, 6-OHDA lesions in the nucleus accumbens did not affect the place preference induced by cocaine, although again, amphetamine's place preference was attenuated, at least in rats with almost complete depletions of dopamine (Spyraki et al., 1982a,b). This failure to attenuate cocaine's effects by these manipulations has led some investigators to criticize place preference techniques as inadequate measures of reinforcing effects (e.g., Dworkin and Smith, 1987). However, in a recent study, Spyraki et al. (1987) have shown that haloperidol can attenuate the place preference of cocaine if the intravenous route of administration, rather than intraperitoneal route, is used (see Nomikos and Spyraki, 1988, for a further discussion). Likewise, Morency and Beninger (1986) demonstrated that pimozide was able to reverse cocaine place preference when administered i.c.v. but not when given systemically. Furthermore, although procaine produces place preferences when administered systemically, this is not true if this drug is delivered i.c.v. (Spyraki et al., 1982a; Morency and Beninger, 1986). Therefore, it has been postulated that the i.p. cocaine and procaine induce place preferences due to their local anesthetic properties, which would not be expected to be influenced by dopaminergic antagonists, and in addition, these place preference are not due to the reinforcing effects of the drug (Spyraki et al., 1982a, 1987; Morency and Beninger, 1986; Nomikos and Spyraki, 1988).

As previously discussed, there is a great deal of disagreement concerning the specificity of the mediation of cocaine's reinforcing effects. Many have argued that cocaine's actions are unique and that mechanisms underlying the reinforcing actions of opiates are distinct, whereas other argue that the same dopaminergic pathway is important for both cocaine and opiates (Koob and Bloom, 1988). With the use of self-administration techniques, both positions have been supported (e.g., compare Ettenberg et al., 1982 and Zito et al., 1985). Studies using place preference techniques have indicated that dopamine systems are involved in the reinforcing actions of heroin (Bozarth and Wise, 1981; Spyraki et al., 1983). Bozarth and Wise (1981) believe that the failure to demonstrate increases in rate of heroin self-administration after the administration of dopamine antagonists

does not prove that dopamine is not involved in heroin's reinforcing effects because of the problems inherent in using rate of self-administration as a measure of reinforcing effects (see Wise, 1987, for a discussion of this issue). Thus, they argue for the use of approaches that do not rely on rate of responding such as place preference methods to assess underlying mechanisms. However, even with place preference procedures, some investigators have failed to show a role for dopamine in the effects of opiates (Mackey and van der Kooy, 1985).

Another procedure that has been suggested as a means of evaluating the mediation of the reinforcing effects of drugs is self-stimulation, i.e., responding maintained by electrical stimulation of certain brain structures. While these studies are similar to evaluations of the effects of cocaine on schedule-controlled responding maintained by food, shock presentation, or shock avoidance, as reviewed in a previous section, they may have a special significance because many investigators have postulated that alterations in self-stimulation by drugs may have implications for the mediation of their reinforcing effects (Kornetsky et al., 1979; Kornetsky and Esposito, 1979). In the 1950s, Olds and Milner (1954) demonstrated that animals would emit a response to receive electrical brain stimulation in certain areas of the brain. Electrical stimulation through electrodes placed in other areas resulted in avoidance responding. These results were interpreted as indicating that these structures were involved in mediating reward and punishment. It was subsequently shown that cocaine produced decreases in the current threshold required to sustain self-stimulation (Esposito et al., 1978; Kornetsky and Esposito, 1981; Wauquier and Niemegeers, 1974).

Similar results were found for opiates as well as for other drugs of abuse (Marcus and Kornetsky, 1974; Kornetsky et al., 1979; Kornetsky and Esposito, 1979). These investigators have hypothesized that there is a direct relationship between abuse potential and the ability of a drug to lower self-stimulation threshold and that self-stimulation methods can be used to understand the neural mechanisms of action of reinforcing drugs (Kornetsky et al., 1979; Kornetsky and Esposito, 1979), although this premise remains to be validated. Interestingly, neither tolerance nor sensitization has been shown to develop to the effects of cocaine on threshold and antidepressants, which have been suggested as a treatment for cocaine abuse, actually decrease threshold further (Frank et al., 1988a,b). In addition, because both stimulants and opiates lower threshold which can be reversed by naloxone, it has been argued that there is a common mechanism for the reinforcing effects of both types of drugs involving both dopaminergic and endogenous opiate systems (Bain and Kornetsky, 1987). Similar arguments for a common pathway but involving dopaminergic systems alone have been made based upon results from place preference studies as well (e.g., Bozarth and Wise, 1981). Although these studies are provocative, the specificity of self-stimulation techniques to measure reinforcing effects has not been completely established. For instance, it has been shown that tricyclic antidepressants which are not positive reinforcers in self-administration paradigms also modify self-stimulation responding (McCarter and Kokkinidis, 1988).

Conditioned taste aversions presumably measure the aversive properties of a substance. If certain consequences (e.g., lithium chloride-induced illness) occur after 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 (CTA) or gustatory avoidance conditioning (Garcia et al., 1955). Initially, it was believed that only agents that induce illness could produce a CTA. 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 properties of electric shock can be altered by environmental context (i.e., shock maintains responding leading to its presentation and avoidance), even drugs which are positive reinforcers can have aversive effects under certain conditions (e.g., Spealman, 1979b). However, results with cocaine have been inconsistent. While a CTA to cocaine has been demonstrated in many studies (e.g., Goudie, 1980), many investigators have only reported either minimal taste aversions (Booth et al., 1977; D'Mello et al., 1979; Goudie et al., 1978; Foltin et al., 1981; Foltin and Schuster, 1982; Franko and Wagner, 1983) or none at all (Cappell and LeBlanc, 1978). Foltin and colleagues (Foltin et al., 1981; Foltin and Schuster, 1982) attempted to determine what procedural variables might account for the inconsistent results and found some suggestion that cocaine's short duration of action was responsible. In summary, most investigators would agree that cocaine is a weak agent in inducing a CTA 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). These results may have implications for evaluations of the positive reinforcing effects of cocaine, since unlike other drugs, there may not be competing actions of cocaine that attenuate its ability to maintain responding.

E. Dependence-Producing Effects

Many drugs of abuse, such as heroin, produce physical dependence when administered repeatedly. However, it is generally believed that cocaine does not share this property (Jones, 1984). But the observations by Gawin and Kleber (1986) that cocaine abusers experience a predictable sequence of physiological and behavioral changes when they terminate cocaine use (see section VII B) has led to experimental studies designed to deter-

mine whether there are measurable behavioral changes after the withdrawal of cocaine. Wood and Lal (1987) trained rats to discriminate pentylenetetrazol (PTZ) from saline in a standard drug discrimination procedure. PTZ is believed to mimic the effects of anxiety and these investigators have postulated that the PTZ discrimination is an animal model of anxiety. After the discrimination training, animals were exposed to 7 days of 20 mg/kg/8-h of cocaine. When this chronic regimen was terminated, testing in the absence of PTZ indicated that the animals gradually began to distribute their responses on the PTZ-appropriate lever. These results may have indicated that cocaine withdrawal produces an anxiety-like state.

Other investigators have also used behavioral procedures which have indicated that drugs such as phencyclidine (Slifer et al., 1984) and Δ^9-tetrahydrocannibinol (Beardsley et al., 1986) produce behavioral dependence that is revealed as a disruption in performance when the drug is terminated (Schuster, 1969; Balster, 1985). For instance, Carroll and Lac (1987) were able to show that after 10 days of cocaine self-administration in rats, withdrawal of cocaine resulted in the disruption of responding maintained by a solution of glucose and saccharin and this disruption was reversed by the subsequent administration of cocaine. Likewise, Woolverton and Kleven (1988) showed that after a continuous infusion of i.v. cocaine in rhesus monkeys up to doses of 32 mg/kg/day over a several month period, responding maintained by food delivery was disrupted for a 3- to 4-day period when the cocaine infusion was terminated. They also provided evidence that the degree of withdrawal effects was dependent upon dose and duration of exposure. While it is clear that additional studies are required to elucidate the parameters of cocaine administration that produce behavioral dependence, whether physical signs and symptoms can also be measured, the long-term consequences of this effect, and whether withdrawal increases the probability of drug-seeking behavior, these early studies are provocative and may have important implications for behavioral and pharmacological treatment of cocaine abusers.

VI. Toxicity

One of the most significant consequences of cocaine abuse is the development of behavioral pathology in chronic users. In its most extreme form, a cocaine psychosis can be produced, characterized by paranoia, impaired reality testing, anxiety, a stereotyped compulsive repetitive pattern of behavior, and vivid visual, auditory and tactile hallucinations including delusions of insects crawling under the skin (Jaffe, 1985b; Post, 1975; Siegel, 1978). More subtle changes in behavior also result from cocaine abuse. These may include irritability, hypervigilance, extreme psychomotor activation, paranoid thinking, impaired interpersonal relations, and disturbances of eating and sleeping (Gawin and Ellinwood, 1988; Sherer et al., 1988). In the Bahamas, where use of free base cocaine enjoyed a period of extensive popularity, reports of a cocaine-induced psychosis increased dramatically (Manschreck et al., 1987). Severe depressive conditions, paranoia, and bizarre and violent psychotic disorders were common, lasting days or weeks. There was, in addition, a suggestion of residual symptomatic and cognitive impairments which have yet to be well defined. Although generally associated with abuse of stimulant drugs, an iatrogenic cocaine psychosis has been reported in a patient treated with a topical anesthetic containing 3 ml of 10% cocaine every 4 hours (Lesko et al., 1982). The psychosis abated within 60 hours of withdrawal of the cocaine and did not recur.

In view of these severe behavioral changes, the neurotoxicity of cocaine has been investigated in animals. Previous animal studies have shown that other psychomotor stimulants, such as methamphetamine, produce long-lasting alterations in levels of dopamine in the striatum and there is evidence that this is the consequence of reduction of dopamine uptake sites and neuronal degeneration (Seiden et al., 1975; Ricaurte et al., 1982, 1984). While these effects occur at doses considerably higher than those shown to produce typical stimulant behavioral effects, given the levels reported in humans where toxicity has been observed and considering that the effects are time-related, it is likely that these findings have relevance for observations of behavioral toxicity reported for methamphetamine in humans (Snyder, 1973). Because of the pharmacological similarities between methamphetamine and cocaine, it is not surprising that several investigators have conducted similar neurotoxicity studies with cocaine. Trulson and colleagues showed evidence of decreases in tyrosine hydroxylase activity in striatum as well as decreases in dopamine metabolism in a variety of brain regions 10 days after treatment with 10 mg/kg/day of cocaine in rats (Trulson et al., 1986; Trulson and Ulissey, 1987). However, Seiden and colleagues have been unable to replicate these effects and have found no evidence of long-lasting changes in either dopamine or serotonin neurochemistry (Seiden and Kleven, 1988; Kleven et al., 1988b). Additional studies, many of which are presently ongoing, are needed to resolve this discrepancy as well as to examine other possible neuronal changes, particularly in light of the increased reports of behavioral toxicity resulting from cocaine abuse. However, Seiden has proposed that differences between the neurotoxic effects of cocaine and methamphetamine may be due to their different mechanisms of action related to their relative ability to release dopamine as well as the pool from which release occurs (see Seiden and Kleven, 1988, for a discussion).

The apparently lethal and near-lethal effects of cocaine via any route of administration due to its actions on the cardiovascular system has received widespread attention. Published accounts of cocaine-related cardio-

vascular morbidity consist almost entirely of case reports (e.g., Mittleman and Wetli, 1984; Isner et al., 1986; Duke, 1986; Smith et al., 1987), but only minimal laboratory data-based discussion of the possible mechanism of this effect has been published (Wilkerson, 1988a,b,c; Wilkerson et al., in press). Myocardial infarctions temporally related to cocaine use have been reported (Cregler and Mark, 1985) even in young patients with normal coronary arteries (Smith et al., 1987). This finding has led a number of investigators to suggest that cocaine may induce coronary vasospasm (Isner et al., 1986; Zimmerman et al., 1987) or promote coronary thrombosis (Zimmerman et al., 1987; Gardezi, 1987). Wilkerson (1988c), in support of this suggestion, has pointed out that although circumstantial evidence of cocaine-induced coronary vasospasm exists, cocaine has been shown to cause vasospasm in other vessels.

The complex cardiovascular effects of cocaine are a function of both its local anesthetic effects and its inhibition of neuronal uptake of catecholamines. The local anesthetic effect on heart and blood vessels would be expected to result in antiarrhythmic and vasodilatory actions, while effects at adrenergic, dopaminergic, and serotonergic synapses within the central nervous system would result in excitation leading to seizure activity and increased peripheral sympathetic tone with accompanying tachycardia and vasoconstriction (Wilkerson, 1988c). There is evidence suggesting that cocaine's sympathomimetic actions predominate at lower doses while local anesthetic actions are more likely at the higher doses (Trendelenburg, 1968; Herman and Vick, 1987; Stewart et al., 1963; Lew and Angus, 1983; Jain et al., 1987). Thus, local anesthetic actions would predominate under conditions of rapid and complete absorption of a large dose, resulting in decreased arterial blood pressure, decreased pacemaker activity, and myocardial depression (Wilkerson et al., in press). In a recent study using a conscious dog model, Wilkerson (1988a) presented data showing that cocaine increases myocardial oxygen consumption while simultaneously interfering with the ability of the coronary circulation to adjust to this increased demand by decreasing its resistance to blood flow. In fact, there was a modest increase in coronary vascular resistance as a result of cocaine treatment. Although this increase was not statistically significant, the finding is consistent with the hypothesis suggested by other studies and case reports that cocaine-induced modification of coronary vascular function may be a possible mechanism for the cardiac toxicity associated with cocaine use.

A major proportion of the case reports of cocaine-related cardiovascular toxicity involve myocardial infarctions, the appearance of which do not appear to be related to dose or route of administration (Isner et al., 1986; Zimmerman et al., 1987; Smith et al., 1987). The possible causal relationship between myocardial ischemic and cocaine use is puzzling because of the loose temporal relationship between cocaine use and onset of symptons (30 min to 11 h after cocaine use, while cocaine has a half-life of only 50 to 90 min). The fact that myocardial infarctions occurred in patients with normal coronary arteries as shown by angiography certainly appears unusual, but there have been numerous reports of myocardial infarctions in patients with angiographically normal coronary arteries who have not used cocaine. Wilkerson (1988c) has pointed out that cocaine-induced vasospasm in large epicardial coronary arteries has not been demonstrated, and therefore the conclusion that cocaine causes focal epicardial coronary artery spasm is purely speculative. However, in several cases, symptoms of ischemia recurred after subsequent cocaine use (Zimmerman et al., 1987; Smith et al., 1987) suggesting that these episodes of myocardial ischemia may have been related to cocaine use. Cocaine-associated myocardial ischemic syndromes have also occurred in patients with coronary artery disease. Gradman (1988) has suggested that in these patients cocaine plays a role in precipitating a myocardial ischemic event by augmenting myocardial oxygen requirements beyond the ability of the coronary circulation to increase oxygen supply or inducing localized spasm. In support of a mechanism other than coronary artery spasm, a cocaine-related coronary thrombus in the absence of coronary artery spasm has been implicated in a cocaine-related acute myocardial infarction (Hadjimiltiades et al., 1988).

It has been suggested that cases of sudden unexpected death associated with myocardial infarctions may be due to ventricular arrhythmias. A number of case reports have been published describing specific arrhythmias temporally related to cocaine use (Nanji and Filipenko, 1984; Benchimol et al., 1978; Jonsson et al., 1983; Isner et al., 1986), including asystole, accelerated idioventricular rhythm and ventricular tachycardia which degenerated to ventricular fibrillation. Gradman (1988) has suggested that cardiac arrhythmias attributed to cocaine use may not be primary, but may be the result of substantial metabolic changes resulting from generalized seizures or acute ischemic syndromes. In support of arrhythmias being the cause of these deaths, Wilkerson et al. (in press) have pointed out that there are a number of cardiovascular effects of cocaine that may lead to the development of lethal arrhythmias: 1) increased sympathetic tone, 2) a local anesthetic effect, 3) development of myocardial ischemia, and 4) development of myocarditis. Consistent with these possibilities, one laboratory study has reported cocaine-induced ventricular fibrillation after exercise in dogs with myocardial ischemia (Billman and Hoskins, 1988).

Although any of the changes produced by cocaine could be detrimental to normal functioning of the cardiovascular system, except for Billman and Hoskins (1988), laboratory studies have not demonstrated a causal relationship between cocaine use and any of the cardiovas-

cular disorders implicated in the dozens of case reports recently published. This discrepancy may be due in part to clinicians asking patients with cardiac problems whether they have used cocaine and reporting positive responses in the absence of clear indications of a causal relationship. In addition, it is likely that drug taking in the natural ecology occurs under markedly different situations from those present in laboratory settings. Suggestive of this possibility, Fischman and Foltin (in press) have presented laboratory data from a number of studies indicating that increased cardiovascular responsivity is a function of an interaction of ongoing behavior with the direct effects of the drug (Capriotti et al., 1988; Foltin et al., 1989; Foltin and Fischman, 1989). Subjects performed a simple serial acquisition learning task, earning points which could be exchanged for money. Intranasal cocaine and cocaine in combination with alcohol during task performance resulted in larger cardiovascular effects (heart rate or blood pressure) than might have been predicted from each condition alone. Although the data did not demonstrate cardiovascular abnormalities, they suggest that in susceptible users the interaction of the drug they have taken with the activities in which they are engaged may partially account for the sporadic but dangerous toxicity occasionally reported from single doses of cocaine. In addition, of course, cocaine purchased "on the street" may contain other substances which cause arrhythmias or can potentiate the effects of cocaine.

Cocaine use has also been implicated in the onset of cerebrovascular accidents (Schwartz and Cohen, 1984; Brust and Richter, 1977; Lichtenfeld et al., 1984), which are assumed to be due to hypertension with possible subclinical cerebral vascular pathology. A large increase in systemic blood pressure has also been implicated in a case of acute rupture of the ascending aorta during cocaine intoxication (Barth et al., 1986). A growing number of reports of subarachnoid hemorrhage after rupture of aneurysms of arteriovenous malformations have also been reported (e.g., Cregler and Mark, 1986; Altes-Capella et al., 1987; Tuchman et al., 1987; Wojak and Flamm, 1987). Mangiardi et al. (1988) recently speculated that disruption of autoregulation of cerebral blood flow might occur after sudden transient cocaine-induced blood pressure increases, accounting for occurrence of intracerebral hemorrhage. These elevations in blood pressure are not seen by the time the patient is taken to the emergency room because of cocaine's short duration of action. Levine et al. (1987) recently summarized 13 reported cases of cocaine-associated cerebrovascular complications, both ischemic and hemorrhagic, pointing out that although the exact mechanism of cocaine-related stroke remains uncertain, enhanced sympathetic activity combined with blood pressure elevation could play a role, as could increased synaptic levels of serotonin, a potent vasoconstrictor for large and medium size arteries. In addition, preliminary data now exist suggesting that repeated cocaine use may decrease cerebral blood flow, especially in the frontal and temporal cortex (Volkow et al., 1987).

Cocaine has been shown to produce hyperpyrexia (Ritchie and Greene, 1985), which can contribute to the development of seizures. Laboratory data with nonhumans has indicated that cocaine may "kindle" neurons, reducing the seizure threshold on future drug-taking occasions (Post et al., 1976; see section V A). Seizures can also be secondary to central nervous system-induced cardiac events such as ventricular tachycardia and fibrillation (Cregler and Mark, 1986).

Chronic cocaine use may cause significant alterations in a variety of other physiological functions and also may be toxic to other specific organs or tissues. There are some data suggesting that the venoconstrictive and venoocclusive effects of cocaine may result in damage to the gastrointestinal tract (Nalbandian et al., 1985; Fishel et al., 1985) and renal and pulmonary systems (Tashkin et al., 1987). In addition, cocaine-mediated hepatotoxicity has been reported in both nonhumans and humans (Perino et al., 1987; Kloss et al., 1984). The suggested mechanism of action of this hepatotoxicity involves the secondary metabolic pathway which produces norcocaine nitroxide and other metabolites which are hypothesized to bind to hepatic proteins causing cell death. Cocaine users with pseudocholinesterase deficiencies would be at greater risk for this problem since the most common metabolic route for cocaine would not be available, and more of the cocaine would have to be metabolized via the oxidative route. In addition, ethanol pretreatment potentiates cocaine-induced liver disease as well as cocaine-induced lethality (Kreek, 1988).

There are, of course, medical complications of cocaine use related to the route by which it is administered. Thus, perforation of the nasal septum, chronic rhinitis, and loss of sense of smell can occur in users who habitually inhale the drug. Parenteral use is associated with diseases introduced by use of dirty needles contaminated with the blood of previous users as well as extra substances in the drug. The three most common severe diseases resulting from intravenous drug abuse are bacterial or viral endocarditis, hepatitis, and acquired immunodeficiency disease (Kreek, 1988). Thrombophlebitis and pulmonary toxicity manifested as spontaneous pneumomediastinum, black sputum, and abnormal large and small airways function are all more common in smokers of "crack" or "free base" (Cregler and Mark, 1986; Tashkin et al., 1987; Weiss et al., 1987; Wiener and Putnam, 1987). It has been suggested that the probable cause of the pneumomediastinum is the respiratory maneuvers used by cocaine smokers to augment drug absorption rather than the drug itself (Palant et al., 1988) and minimal clinical intervention other than cessation of smoking is required.

Cocaine crosses the placenta via diffusion and rapidly penetrates mucous membranes due to its high lipid solubility, low molecular weight and low ionization at physiological pH (American Society for Pharmacology and Experimental Therapeutics and Committee on Problems of Drug Dependence, 1987). Placental vasoconstriction, decreasing blood flow to the fetus (Sherman and Gautieri, 1972), and an increase in uterine contractility (Lederman et al., 1978) have been reported in pregnant women using cocaine. Data have been collected suggesting that cocaine use by pregnant women influences the outcome of pregnancy as well as neonatal behavior as measured by the Brazelton Neonatal Behavioral Assessment Scale (Chasnoff et al., 1985). Cocaine use during pregnancy is associated with increases in preterm labor and delivery (MacGregor et al., 1987), fetal loss resulting from both spontaneous abortions (Chasnoff et al., 1985; Ryan et al., 1987), and fetal death (Bingol et al., 1987; Ryan et al., 1987), as well as infant abnormalities such as decreased birth weight and head circumference, genitourinary malformations, and neurobehavioral abnormalities measured by instruments such as the Brazelton Neonatal Behavioral Assessment Scale and Apgar scores (Chasnoff et al., 1985, 1987a; Ryan et al., 1987; Chouteau et al., 1988). A recent report of ocular abnormalities in infants of cocaine-using mothers stated that these abnormalities of iris vasculature, present at birth, disappeared by 3 months (Inkelis et al., 1988). The maternal problems at delivery and the neonatal abnormalities were significantly associated with cocaine use when compared with pregnant women receiving maintenance doses of methadone (Chasnoff et al., 1987a). It is, however, true that the pregnant cocaine abuser is generally abusing more than one substance. MacGregor et al. (1987), for example, reported that only 34% of their sample used cocaine alone. Nutritional deficits in cocaine users might also play a role in diminished fetal size and other abnormalities since it is known that cocaine can act as a suppressor of food intake and a large portion of the pregnant woman's financial resources are being devoted to the purchase of cocaine.

In addition to crossing the placenta during pregnancy, cocaine also can be found in breast milk. Several reports have been published of infants with signs of cocaine intoxication such as dilated pupils, hypertension, tachycardia, and convulsions subsequent to breast-feeding (Chasnoff et al., 1987b; Chaney et al., 1988). Cocaine and its metabolites persist in breast milk for 48 h after last use (Chasnoff, 1987) and neonates metabolize cocaine at a much slower rate than do adults.

Cocaine toxicity may also result from an interaction with other drugs (Kreek, 1988). Cocaine abusers, particularly those who free base or inject it intravenously in substantial amounts, also frequently take heroin to counteract the "overstimulation" accompanying their high dose stimulant use. This kind of self-medication can also involve alcohol or other sedative-hypnotics, but an increasing number of cocaine abusers have become heroin abusers as well, showing tolerance and physical dependence in addition to heroin-seeking behavior each day. In addition to the sequential use of cocaine and heroin, they have commonly been used in combination intravenously ("speedballs"), and this practice may also be increasing since, with the increasing purity of heroin, its interactive effects with cocaine are enhanced (Kreek, 1988). These drugs in combination can either potentiate or protect against some of the adverse effects of each of the drugs taken separately. Thus, for example, if cocaine has been administered, a larger dose of an opiate antagonist is required to block opiate actions than in the absence of cocaine (Blumberg and Ikeda, 1978), and cocaine may potentiate heroin's respiratory depressant effect when used in high doses (Hunt et al., 1984). This latter finding may be one of the causes of the sudden death frequently reported to be related to cocaine use.

In summary, toxicity associated with cocaine use has been related to virtually every physiological system, from cardiovascular to reproductive. In addition, obvious toxicities can result from the route by which it is administered. Much of the data is anecdotal or supported by data from a few case studies and generally without independent verification of cocaine use. Nevertheless, as reports continue to be published and the most clearly relevant toxicities studied in the laboratory (e.g., cardiovascular), a better understanding of the way in which cocaine is exerting its toxic effects is emerging. However, it is clear that laboratory research must taken into account the conditions under which cocaine is taken (e.g., Foltin and Fischman, 1989; Capriotti et al., 1988).

VII. Treatment

A. Psychological and Behavioral Approaches

A variety of psychological and behavioral approaches have been suggested for the treatment of cocaine abuse. Early approaches tended to rely on models found useful in treating abusers of other substances. Thus, cocaine recovery support groups modeled after Alcoholics Anonmyous (Erlich and McGeehan, 1985), a combination of group and individual therapy (Smith, 1986), and supportive psychotherapy mixed with aerobic exercise (Siegel, 1985), have all been used, but little outcome data have been presented. Siegel (1985) reported that 50% of his sample of 32 heavy cocaine smokers who received a combination of supportive psychotherapy, training in self-control techniques, exercise, and hospitalization during detoxification, dropped out. Eighty percent of the remaining patients, however, were cocaine-free at 9-month follow-up.

Treatment approaches which incorporate principles derived from behavioral research have also been developed. The first published behavioral cocaine treatment study was carried out by Anker and Crowley (1981),

using contingency contracting. In this study, the patient and therapist signed a contract specifying that if the patient did not remain drug-free, as indicated by a cocaine-positive or missed urine specimen, the therapist would punish the behavior with an agreed-upon consequence. The consequence was generally a potential adverse effect of cocaine abuse already feared by the patient (i.e., one that would likely happen anyway if the patient did not discontinue drug use). For instance, it was likely that a cocaine abuser who was a physician might lose his/her medical license with continued drug use. Thus, the contract in this case might specify that if this patient continued to take drug, the therapist would notify the licensing board (i.e., loss of license was "re-scheduled" to occur at the next cocaine use). In addition to the contract, patients were also treated with a standard type of psychotherapy. Forty-eight percent of the sample of those seeking treatment for cocaine abuse agreed to sign a contingency contract, and more than 80% of them remained abstinent for the duration of their contract, which averaged 3 months. Half, however, suffered a relapse following completion of the contract (Crowley, 1984). Contract length in these initial patients ranged from 1 to 18 months. Relapse appeared to be uncommon after 6 months on a contract, and patients subsequent to this study were therefore encouraged to sign contracts longer than 6 months in order to maximize the probability of abstinence (Crowley, 1984). The 52% who refused to sign contingency contracts were treated with the same type of supportive therapy as the contingency group; more than 90% of this group dropped out and/or resumed cocaine use within 2 to 4 weeks. It is clear that contingency contracting was efficacious in this situation although the self-selected nature of the experimental group limits generalizability. However, this initial pilot study does provide the framework for future treatment studies using this approach, particularly ones that manipulate the severity of the consequences and attempt to randomly assign patients to the different groups (see Kleber and Gawin, 1986, for a discussion). The important point to be gained from these data is that cocaine-taking is a behavior which can, for certain users and under appropriate conditions, be modified by manipulation of the consequences maintaining it.

Behavioral techniques have also been successfully utilized in the prevention of relapse to cocaine use by adapting procedures originally developed by Marlatt and Gordon (1985). Washton (1987) has described these procedures as including techniques such as breaking contacts with friends who use drugs, changing telephone numbers, getting rid of cocaine-using paraphernalia, and in general, avoiding situations that are associated with cocaine use and signal its availability. In addition, urinalysis to verify compliance with the treatment program has been incorporated into the overall design of most programs. However, since cocaine metabolites are only reliably present for 2 days, random testing one to three times weekly is essential. Many programs, in addition to cocaine abstinence, require abstinence from all drugs, often because these have been used in conjunction with cocaine and act as powerful cues for cocaine-taking.

Classical conditioning has been postulated to play a role in relapse to cocaine abuse, and treatment methods are now being developed which take this process into account (Childress et al., 1988a,b). This work is based on research with opioid abusers which has demonstrated that naloxone-precipitated opiate withdrawal (the UCS) can be classically conditioned to environmental stimuli, and that a broad range of environmental stimuli (e.g., a syringe, a photograph of drug, etc.), initially associated with opiate use outside of the laboratory or clinic, can elicit drug-related responses (e.g., reports of craving, skin temperature change, etc.) under experimental conditions (O'Brien et al., 1976, 1977). Such conditioned responses can increase the likelihood of relapse to drug-taking, even after a long period of abstinence.

Treatment for opiate abusers has included extinction procedures to eliminate the conditioned responses that might be important in drug use relapse (O'Brien et al., 1980). Childress et al. (1987), working with cocaine abusers, have shown that certain types of stimuli that are associated with cocaine administration or withdrawal reliably elicit both conditioned physiological changes (e.g., decreased skin temperature) and verbal responses of "high," "craving," or "withdrawal." The extinction of these conditioned responses appears to be slow, with arousal to the initial cocaine cue still evident after a substantial number of sessions. Since a series of cues must be used during extinction, the procedure is extraordinarily time-consuming, with no evidence at this time that such an intervention with cocaine-related cues will generalize to situations outside of the laboratory. O'Brien et al. (1988) have reported that the addition of an extinction component to their standard cocaine treatment program has resulted in a reduction in reports of "craving" in response to drug-related stimuli in the extinction group and not in the standard treatment group. Whether this technique can reduce either drug use or relapse rate, however, has not yet been shown. Although promising, the extinction procedure also requires the use of individualized stimuli specific to each patient (e.g., a paycheck stub) as well as general drug-related stimuli (e.g., a syringe). Because of the time required and the labor-intensive nature of these procedures, it is unlikely that they alone will be sufficient treatment, but it is possible that these procedures can be successfully incorporated within a general treatment paradigm, including drug counseling or psychotherapy, as O'Brien and his colleagues are attempting. Careful delineation of cocaine-related cues may ultimately be more usefully employed in a relapse prevention paradigm which, by providing users with procedures for dealing with a range of drug-

taking cues under a variety of circumstances, would prove to be more practical.

Most of the methods described above have been designed to be used in an outpatient setting. However, the conditions under which there is a need for inpatient treatment of cocaine abusers remain unresolved. Kleber and Gawin (1986) have reported little need for hospitalization, while Gold and his colleagues (1986), Siegel (1984), and Washton (1987) have all stressed the importance of hospitalization, at least for initial treatment. It was initially suggested (Kleber and Gawin, 1984a,b) that the only clearly acceptable factors indicating need for hospitalization are severe depression or psychotic symptoms lasting more than 1 to 3 days as well as repeated outpatient treatment failures. More recently, heavy free-base or i.v. use has been added to this list (Kleber, 1983). Washton (1987) has summarized reasons for hospitalization including chronic free-base or i.v. use, concurrent dependence on other drugs, psychiatric or medical problems of a severe nature, lack of family or social supports, etc. Although it is less difficult to control drug-taking on an inpatient unit, behavioral research has clearly pointed to the importance of conditioning factors in drug-taking, as described above (Childress et al., 1988a,b). Outpatient treatment has the advantage of allowing the patient to confront the stimuli under which drug-taking occurred and thereby allow the process of extinction to take place. Hospitalization defers this process, but does not eliminate the need for it to take place. Users must eventually learn to cope with these stimuli to avoid relapse (Marlatt and Gordon, 1985). Since such a process is slow and requires a long-term commitment, it is important to begin this process as early as possible.

B. Pharmacological Approaches

Until recently, pharmacological interventions have not been used in the treatment of cocaine abuse. Use of pharmacological interventions has focused either on treating a disorder for which cocaine users might be self-medicating (e.g., attention deficit disorder; Khantzian and Khantzian, 1984), or in looking for agents that might block cocaine-related changes such as euphoria or withdrawal (e.g., Gawin and Kleber, 1984). Several reports evaluating psychiatric symptomatology in cocaine users have suggested that these patients frequently present for treatment with a range of other psychiatric disorders. Studies of DSM-III Axis 1 symptomatology in cocaine abusers (Weiss and Mirin, 1986; Gawin and Kleber, 1985, 1986) have reported comparable results: 30% of the population had depressive disorders, and 20% showed bipolar disorders including cyclothymia. In addition, in approximately 5% of the patients, attention deficit disorder residual type (ADD) was diagnosed. Thus, it is possible that a large proportion of cocaine users had pre-existing psychopathology which they were attempting to alleviate with cocaine, i.e., self-medication. For instance, six of seven abusers of cocaine who also had diagnoses of ADD responded to appropriate stimulant medications, methylphenidate and pemoline, and were still abstinent at 6 months (Weiss et al., 1985; Khantzian et al., 1984). In those patients for whom ADD was not a diagnosis, after an initial decrease in cocaine use, continued maintenance doses of methylphenidate resulted in tolerance which required increased doses. At these higher doses, the effects produced by methylphenidate acted as a stimulus cue for cocaine use which then increased and even exceeded pre-existing levels (Gawin et al., 1985). It has also been reported that cocaine can act as a cue for reports of increased "craving" or "wanting" cocaine (Jaffe et al., 1989), suggesting that once a cocaine-taking occasion has begun, users may have difficulty stopping. Such effects are similar to those reported after methylphenidate administration.

In an open trial of cocaine abuse treatment with lithium, four of five cyclothymic patients who had not responded to psychotherapy treatment alone responded to lithium treatment with cessation of cocaine use and diminished craving. None of the five noncyclothymic cocaine abusers in that study (Gawin and Kleber, 1984) responded similarly to lithium. Thus, although lithium has been postulated to block the amphetamine-induced euphoria (Van Kammen and Murphy, 1975), it would appear that the therapeutic effect of lithium in cocaine users was diagnosis-specific. Lithium treatment has also been used successfully in the treatment of acute cocaine-induced psychosis (Scott and Mullaly, 1981). The data for patients in who ADD is diagnosed and cyclothymic patients suggest that subpopulations of cocaine users may be responsive to specific pharmacotherapies. However, the numbers of subjects thus far described are small, the studies were not well-controlled, and it was not always possible to determine whether the psychopathology pre-dated the use of cocaine.

Antidepressant therapy has also been used in the treatment of cocaine abusers, and the results suggest that antidepressants may be generally useful therapeutic tools (Rosecans, 1983; Gawin and Kleber, 1984). It has been hypothesized (Gawin and Kleber, 1984) that long-term treatment with tricyclic antidepressants produces effects opposite to those found after long-term administration of cocaine, so that administration of these drugs should reverse the signs and symptoms of cocaine withdrawal. Clinical reports of decreased craving after desipramine (Gawin and Kleber, 1984) and reversal of hypersomnolence related to cocaine abstinence (Baxter, 1983) support this hypothesis. There is a paucity of laboratory studies in humans evaluating the interactions of this class of drugs with cocaine.

A laboratory study of the effects of trazodone, a nontricyclic triazolopyridine derivative which does not block norepinephrine reuptake, showed that single doses, administered in combination with cocaine, diminished the cardiovascular effects of cocaine but did not alter cocaine

metabolism or change subjects' rating of cocaine's effects (Rowbothan et al., 1984). However, no data were collected on cocaine-taking behavior. Desipramine maintenance under laboratory conditions, in contrast, had no effect or potentiated cocaine's blood pressure-increasing effects, did not alter cocaine self-administration, but did significantly alter subjects' ratings of cocaine's effects including how much subjects "wanted" the drug (Fischman and Foltin, 1988; see section V). Gawin and Kleber (1984) have used desipramine hydrochloride in open clinical trials in severe, psychotherapy-resistent, outpatient cocaine abusers and have reported significant decreases in cocaine "craving." Cocaine abstinence was observed in 90% of the desipramine-treated subjects as compared with 50% of the patients given other pharmacological agents or who were only exposed to the psychotherapy portion of the treatment (Gawin and Ellinwood, 1988). A recently completed double-blind trial of desipramine maintenance in cocaine abusers has shown comparable effects (Gawin et al., 1989). Tennant and Tarver (1984), on the other hand, reported no difference in the effects of desipramine versus placebo in a double-blind treatment trial of cocaine abusers. They, however, used low doses of desipramine (75 to 100 mg/day) and the trial only lasted an average of three weeks. Therefore, it is not comparable to those carried out by Gawin and his colleagues (Gawin and Kleber, 1984; Gawin et al., 1989).

Rosecans (1983) reported that another tricyclic antidepressant, imipramine, was also successful in producing increased cocaine abstinence in an open trial with cocaine abusers. Gawin (1986b) ruled out the possibility that the antidepressant therapy might simply be treating an underlying major depression by successfully treating with desipramine a group of 10 cocaine abusers who were screened to eliminate any patients with a diagnosis of major depression. Gawin et al. (1989) have recently suggested that the desipramine treatment might simply be providing "a window of opportunity" (i.e., a relatively short period of 3 to 8 weeks when the antidepressant reverses the neurochemical changes hypothesized to be caused by chronic cocaine use and therefore helps the patient to become abstinent) during which a carefully designed behavioral treatment intervention with a relapse prevention component might well be effective. That is, the drug, by helping the patient achieve initial abstinence, makes successful outpatient therapy without an initial inpatient period more possible. Desipramine was not effective in a short-term (less than 2 weeks), low dose (less than 100 mg) intervention in the treatment of cocaine abusers (Tennant and Rawson, 1983) nor has it been reported to be effective in the treatment of cocaine abuse in methadone maintenance patients when their cocaine use was compared to that of a group that was not maintained on desipramine (Kosten et al., 1987). The lack of a desipramine effect when it was used for only a few days suggests that it requires a period of time for the desired neurophysiological changes to occur. Others (Gawin and Kleber, 1984; Gawin et al., 1989) suggest that approximately 2 weeks of desipramine maintenance (blood levels of approximately 150 ng/ml) are required before cocaine use is significantly decreased. This marks the beginning of the treatment "window of opportunity" described by Kleber (1988) and is consistent with desipramine's clinical course in treating depression, although Gawin (1986b) has reported that the desipramine is not acting by treating an underlying major depression.

Other pharmacological agents have been used in an attempt to increase dopaminergic neurotransmission in cocaine abusers since it has been hypothesized (e.g., Gawin and Kleber, 1986) that repeated cocaine use might result in altered dopaminergic receptor sensitivity, suggesting that drugs which facilitate dopaminergic neurotransmission could modify these effects (Extein and Gold, 1988). Thus, dopaminergic agonists, such as bromocriptine or amantadine, have been reported to alleviate the symptoms of cocaine abstinence in chronic users (Tennant and Sagherian, 1987; Dackis et al., 1987; Giannini et al., 1987). In addition, Giannini et al. (1987) combined bromocriptine and desipramine therapy and reported a significant increase in improvement of cocaine withdrawal symptoms, with continued improvement after the bromocriptine was discontinued after 30 days. Unfortunately, none of these studies report data on cocaine abstinence or retention in a cocaine treatment program, although one double-blind trial comparing bromocriptine and amantadine reported a 70% dropout rate resulting from bromocriptine's side effects (Tennant and Sagherian, 1987). Although changes in self-reported symptons may provide interesting information for the clinician, the behavior under treatment is cocaine-taking behavior (or, at least, attendance at a treatment program). Without data on these variables, efficacy of the intervention cannot be measured. Other drugs such as carbamazepine, an anticonvulsive (Kemp et al., 1988), and maprotilene, a noradrenergic antidepressant (Brotman et al., 1988), have been reported to decrease cocaine use in open clinical trials with small numbers of patients. Although suggestive, use of these drugs cannot be accepted without adequate double-blind trials.

It has also been suggested that the depression and hypersomnolence seen immediately after a cocaine binge (i.e., the "crash," see below) is related to dopamine and norepinephrine depletion and can be alleviated by using neurotransmitter precursors such as tyrosine or tryptophan (Gold et al., 1983; Trachtenberg and Blum, 1988). Adequate double-blind studies, however, have not been carried out. Further, the crash phase, self-limited and relatively brief, has been described as a period during which cocaine-taking is of low probability. Shortening or alleviating it might be counterproductive for the longer-term goal of decreased cocaine use.

While no clear evidence for physical dependence on

cocaine currently exists (see section V E 5), it has been suggested that recognizing the symptoms associated with cessation of cocaine use might well be important in the treatment of cocaine abusers (Gawin and Kleber, 1986). A number of authors (e.g., Siegel, 1982) have observed that depressed mood, fatigue and prolonged sleep disturbances, lasting for days or weeks, frequently accompany discontinuation of cocaine use. Such observations have been unsystematic, based on retrospective clinical judgments. Gawin and Kleber (1986), however, carried out a naturalistic study of 30 long-term cocaine users and developed a three-phase model of abstinence symptomatology related to cocaine abuse. They categorized these as the "crash," "withdrawal," and "extinction" phases, based on their observations of the subjects as well as on historical accounts related to them by their subjects. Of importance is the fact that the authors of this study believe that these phases have important implications for treatment.

During the relatively short crash phase (9 hours to 4 days), the user is generally uninterested in obtaining or using cocaine, showing symptoms similar to those of major depression. Thus, erroneous diagnoses can be made if the therapist is unaware of this phase in abstinence. The withdrawal phase, however, which lasts 1 to 10 weeks, is the period of maximal relapse potential to cocaine use. The final phase, extinction, is of unlimited duration, but patients require continued monitoring because conditioned cues, which must be extinguished, can still trigger craving. Brower and Paredes (1987) have argued that the generalizability of this work may well be narrow since the population for this study were outpatients and the data generally anecdotal. Further, they strongly suggest that the crash and withdrawal phases are not distinct from each other.

Despite the naturalistic nature of the data collection in the Gawin and Kleber (1986) study, it remains one of the few carefully documented descriptions of the symptoms temporally associated with cessation of cocaine use. Of importance is the analysis which points to a chronology of symptoms, some of which require a treatment intervention. The utility of differentiating behavioral categories such as withdrawal and extinction, which imply different treatment needs, will best be evaluated after clinicians have had the opportunity to assess behavioral differences and relate them to treatment. By differentiating a phase of low probability of relapse from a high probability of relapse period, those authors have pointed to the need for intense treatment intervention at certain periods. Nevertheless, the validity of this model remains to be demonstrated in future treatment intervention studies.

In summary, few studies have been reported evaluating the effects of treatment on either cocaine-taking behavior and/or retention in treatment. Most studies have reported changes in "craving," depressed mood or other subjective effects related to an hypothesized withdrawal syndrome. Since there are no data indicating that such subjective measures, taken in the treatment clinic, are predictive of cocaine use under naturalistic conditions, the value of such measures in the evaluation of treatment efficacy are suggestive, at best. Clearly, studies utilizing analysis of urine specimens for evidence of abstinence from cocaine, retention in treatment, and measures of social functioning such as employment and arrest record, all under double-blind conditions, are necessary before comparisons of treatment approaches can be made. Although such studies are clearly labor-intensive and take years to complete, they must be carried out before decisions about treatment of cocaine abuse can be made. Our current level of knowledge would suggest that, at least for outpatients, some combination of behavioral and pharmacologic interventions will prove most useful.

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