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# VARIABLES WHICH INFLUENCE THE REINFORCING PROPERTIES OF COCAINE IN THE RHESUS MONKEY

by

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of the requirements for the degree of
Doctor of Philosophy
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ABSTRACT

VARIABLES WHICH INFLUENCE THE REINFORCING PROPERTIES OF COCAINE IN THE RHESUS MONKEY

by

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The abuse of the psychomotor stimulant drugs has become worldwide and has reached alarming proportions in the last decade. The increase in the frequency of the abuse of these agents among young adults and teenagers has raised serious concern among the medical and political community. As of yet, no successful method of treating drug dependence of this type has been developed. Once the variables which influence the rewarding or reinforcing effect of these compounds are delineated, rational treatment methods can be initiated. This paper describes the methods and results of studies which were designed to determine what some of these variables are. These experiments also were designed to explore the mechanism mediating the reinforcing effects of these compounds in the central nervous system.

The subjects for these studies were Rhesus monkeys in which chronic indwelling jugular catheters had been implanted. The subjects were restrained in individual experimental cubicles. A lever and stimulus light were located in the cubicle; depression of the lever during the illumination of this light produced an intravenous injection of a given dosage of a psychomotor stimulant, e.g., cocaine, phenmetrazine, methylphenidate,

etc. Each subject self-administered the same relative amount of drug daily under conditions of limited access to the drug. The effects of the following manipulations on this baseline level of drug intake were studied: food deprivation, food satiation, alterations in the magnitude of reinforcement, i.e., dosage per injection, changes in the behavioral output required to obtain an injection (the number of lever-presses which must occur before an injection would result), and treatment with other drugs.

Neither three days of food deprivation nor five days of food satiation produced significant changes in total daily drug intake.

The magnitude of reinforcement, i.e., unit dosage, and the frequency of drug self-administration were inversely related over a wide range of unit dosages. The frequency of responding for these drugs and the number of responses required to obtain an injection (fixed ratio size) were directly related. However, the total daily drug intake in mg/kg remained constant in spite of changes in both the magnitude or reinforcement and the schedule of reinforcement. This constancy of total intake suggests the possibility of a central regulatory system functioning to limit the amount of a drug which is self-administered or that the actions which the self-administered drug exert on behavior limit the total amount of drug taken.

Acute treatment with drugs which are thought to mimic or facilitate central noradrenergic function (d-amphetamine, phenmetrazine, imipramine, and pargyline) decreases the self-administration of psychomotor stimulants. On the other hand,

treatment with drugs which are thought to antagonize central noradrenergic function (chlorpromazine, trifluoperazine, reserpine, and alpha-methylparatyrosine) increases psychomotor stimulant self-administration. These results were interpreted as a potentiation and antagonism respectively of the reinforcing effects of the psychomotor stimulants, since increases and decreases respectively in unit dosage produced the same results. Treatment with nonspecific central depressants (morphine and pentobarbital) reduced self-administration behavior. Furthermore, treatment with agents which do not enter the brain in appreciable quantities (phentolamine, phenoxybenzamine, and methylatropine) had no effect on self-administration behavior. Treatment with atropine and physostigmine produced an increase and decrease respectively in this behavior. These effects may reflect an antagonism and potentiation respectively of a central cholinergic behavioral inhibitory system.

The fact that the propensity to self-administer stimulants can be manipulated with drug pretreatments offers promise for the development of effective therapeutic procedures for treating human subjects dependent on psychomotor stimulants.

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# I. INTRODUCTION

## A. GENERAL BACKGROUND INFORMATION

### 1. Pharmacology and abuse of psychomotor stimulants.

The term "psychomotor stimulant" has been applied to a group of drugs which have a number of common properties. Cocaine, D-amphetamine, phenmetrazine, pipradrol and methylphenidate have been included in this category. Although the term has been widely used, its definition is difficult to obtain. In general, all of these compounds increase locomotor activity, produce anorexia, promote a feeling of well-being or euphoria, and delay fatigue. It is probably these latter effects which are responsible for the world wide abuse of these compounds which, in the case of cocaine, has occurred for centuries. The distinction between these compounds and the other central nervous system stimulants, i.e., analeptics, e.g., strychnine, picrotoxin and pentylenetetrazol, is that these behavioral effects are produced by dosages which do not produce convulsions.

The psychomotor stimulants potentiate or mimic the action of norepinephrine on the effectors of the autonomic nervous system. Some of the compounds appear to be direct acting sympathomimetics; however, others potentiate the action of norepinephrine via other mechanisms. Therefore, even though the compounds are very similar, I will discuss individually their basic pharmacology and abuse which, in this dissertation, will be defined as the consumption of drug apart from medicinal need or in excessive frequency or quantity.

Cocaine is an alkaloid obtained from the leaves of the coca plant. Its most important clinical use is to block nerve conduction when applied locally. It has been used as a local anesthetic for many years and more specifically for surface anesthesia when applied topically to the mucous membranes of the nose and eye. However, the cycloplegia, mydriasis, and ulceration produced by corneal application have now precluded its use in ophthalmology.

Cocaine, when administered systemically, produces hyperthermia by decreasing heat loss via vasoconstriction and by increasing heat production via increased muscle activity due to its central stimulating action. Another systemic effect is tachycardia, which is thought to be due to an increased central sympathetic stimulation.

The action of cocaine on the central nervous system is initially stimulatory and then depressive, proceeding from top to bottom of the neural axis. Initially there is increased locomotor activity, restlessness, and excitement, but as the dose of cocaine is increased, lower motor centers are affected and spinal cord reflexes stimulated, initially resulting in tremors, then clonic and tonic convulsions. With increasing dosage, central stimulation is followed by depression at first in the higher centers. Finally, the medullary respiratory center is depressed and death results from respiratory failure.

Cocaine's action on the autonomic nervous system has been studied extensively in recent years. Cocaine has been shown to potentiate the actions of norepinephrine and sympathetic nerve stimulation in sympathetically innervated tissues.(26,196,187,118,213)

This was first demonstrated by Frohlich and Loewi in 1910.[71]

There has been much discussion as to the exact mechanism of the potentiation, but it appears to be due to a prevention of norepinephrine reuptake from the synaptic cleft into the adrenergic neuron from which it was previously released.[197,131,96] The result is that norepinephrine, whether released by neural activity or administered locally or systemically, persists in the vicinity of the receptors of the effector organ in larger concentration for longer periods of time.

The mechanism of cocaine's central action is not known. There is relatively little known regarding the importance of the reuptake mechanism for conservation of norepinephrine in the brain as compared to the autonomic nervous system. However, uptake and concentration of norepinephrine by brain minces[129], brain slices[7], nerve ending rich fractions[50], and by the brain in vivo[72] have been reported.

Some evidence has been gathered indicating that cocaine can interfere with the uptake process centrally. Cocaine does prevent the accumulation of exogenous norepinephrine in brain slices[55,92]. Samorajski has shown, using autoradiographic techniques, that cocaine reduces labeled norepinephrine uptake in the mouse hypothalamus.[164] However, Glowinski and Axelrod demonstrated that cocaine did not prevent the accumulation of labeled norepinephrine in the intact rat brain.[76] Other investigators have shown that acute and chronic cocaine administration have very little effect on brain norepinephrine levels in the rat.[6,88]

Although extensive pharmacological data has been obtained about cocaine, very little is known about its behavioral and subjective effects apart from data collected from studies of cocaine abuse.

The coca plant (Erythroxylon Coca), which is the source of cocaine, is indigenous to the South American countries of Peru, Bolivia, Columbia and Ecuador. Other species of Erythroxylon rich in cocaine grow in India, Australia, Africa and Malaysia. The Incas had been growing the coca plant and had been using cocaine for centuries by the time Columbus landed in the Western Hemisphere.(14) The Indians rolled the leaf into small balls and chewed them. This at first produced a tingling sensation but soon the sense of taste was gone, due to the local anesthetic property of cocaine. A feeling of happiness soon develops and any feeling of fatigue is reduced and one feels he has the capacity to accomplish strenuous physical tasks.(84)

Coca played a vital role in the culture and economy of the Inca nation. Among the highest rewards which an Inca could receive was the right to chew the sacred coca leaf.

Following the conquest of the Incas by the Spaniards in the 16th Century, the use of coca, previously limited to a few, became universal among the Indians. Quickly the Spaniards realized the subjugating effect of the leaf on the Indians and gave the leaf to them freely in an effort to control them more tightly. The Indians worked harder and longer and ate less, all of which was beneficial to the Spanish.(14)

Soon the word of the coca leaf spread to Europe and for

two centuries students of Medicine argued for and against the virtues of the coca leaf. Cocaine was isolated from the leaf in 1859 and soon there were advocates for the universal use of cocaine not only as a treatment for almost any illness, including morphine addiction, but also as a means of increasing the mental and physical capabilities.(130) One of the most famous advocates of cocaine was Sigmund Freud. Freud wrote:

> "The psychic effect of cocaine consists of exhileration and lasting euphoria which does not differ in any way from the normal euphoria of a healthy person. . . I have tested the effects of cocaine which wards off hunger, sleep, and fatigue and steels one to intellectual effort some dozen times on myself. . . Opinion is unanimous that the euphoria induced by coca is not followed by any feeling of lassitude or other state of depression. . . It seems probable that coca if used protractedly but in moderation is not detrimental to the body."(132)

Freud later reversed his opinion of cocaine when one of his closest friends became a cocaine addict. This man had been a morphine addict whom Freud had treated with cocaine, and who subsequently substituted a cocaine habit for that of morphine. The man died from cocaine toxicity.(132)

The Parke, Davis Company became an advocate of cocaine use in America, where cocaine was received with interest and widespread use. In 1885, a company monograph stated that:

> "Cocaine is a drug which, through its stimulant properties, can supply the place of food, make the coward brave, the silent eloquent, free the victims of alcohol and opium habit from their bondage, as an anesthetic render the suffering insensitive to pain and make attainable to the surgeon heights of what may be termed 'aesthetic surgery' never reached before."(132)

One could purchase a cocaine case containing the drug in over a

dozen forms, as well as the instruments needed for its administration, from Parke Davis.

Although the use of cocaine as a local anesthetic in surgery was at the time justified and widespread, the use of cocaine for other medicinal purposes declined rapidly. The world gradually became aware of the dangers associated with cocaine use, so that today the medicinal use of cocaine is limited to its local anesthetic property.

The abuse of cocaine is now only a small fraction of what it once was. The method of administration was most commonly by sniffing the white flaky powder referred to as "snow". This commonly resulted in perforations of the nasal septum due to the intense vasoconstriction produced. As the illegitimate supply of cocaine diminished and the price increased, the more efficient method of intravenous administration was used.

Many people administered cocaine with morphine or heroin because it was believed that the toxic effects of cocaine were reduced by the narcotics; however, this is not true. The combination was referred to as a "speedball". In the United States, pure cocaine addiction is rare; however, the number of cocaine addicts in England is increasing, but most of these individuals are using cocaine with heroin either for the aforementioned reason or to support a narcotic addiction.(216)

The subjective effects of cocaine include an elevation of mood which may become euphoric excitement. The euphoria is accompanied by generalized sympathetic stimulation, a decrease in hunger, and an overestimation of one's physical and mental

capabilities.[111] The administration of large amounts of cocaine may produce anxiety and suspicion and, if the dose is high enough, a toxic syndrome characterized by paranoia, delusions of persecution, and visual, auditory and tactile hallucinations.

The duration of action of cocaine is brief, due to its rapid metabolism, and therefore if one wants to maintain the euphoria, he must take multiple injections in a relatively short time span.

There is no well-defined abstinence syndrome associated with cocaine addiction, although addicts complain of depression, fatigue and lassitude after cocaine is withheld following chronic administration. Tolerance does not develop to many of the effects of cocaine. The effects of chronic administration of cocaine have been studied in rabbits, rats, cats, dogs, guinea pigs and monkeys. In all species, it was demonstrated that there is no tolerance to the excitatory effects of cocaine, and on the contrary there is a pronounced increase in excitation with repeated daily administration.[57,58,190]

Although the amphetamines have a much shorter history than cocaine, much more research has been conducted with these agents. Amphetamine was first synthesized in 1927 by George Alles, who turned his patent over to Smith, Kline and French (SKF). SKF discovered that when amphetamines were used in the vaporous state, intense vasoconstriction was produced in the nasal mucosa, so consequently the Benzedrine inhaler was introduced in 1932. At about the same time, Alles observed the respiratory stimulant,

bronchodilatory and analeptic actions of amphetamines which were identical to those produced by sympathomimetics.[1,2] It was later shown that amphetamine is a indirect acting sympathomimetic agent peripherally. Therefore, amphetamines will produce the same qualitative response in a sympathetically innervated tissue as does electrical stimulation of the sympathetic nerves supplying that tissue.

The central stimulant effects of amphetamines were used first in 1935 in treating narcolepsy[158], but subsequently amphetamines have been used to treat obesity, fatigue, and poisoning by central nervous system depressants. Although the CNS stimulatory action of amphetamines has been known for many years, the mechanism by which this action occurs is not known. Many hypotheses have been offered to explain these effects. Amphetamines may stimulate neuronal activity directly by acting on postsynaptic receptors of various central monoamine transmitters.[172,180] The ability of amphetamines to produce central stimulation, even after norepinephrine depletion by reserpine, may be related to such a direct action of amphetamine.

Amphetamine could act centrally like it does peripherally, i.e., causing the release of norepinephrine from adrenergic nerve terminals. Glowinski et. al. have shown that amphetamine causes a marked decrease of norepinephrine in the particulate fraction of brain homogenates, suggesting that norepinephrine may have been released selectively from synaptic structures.[77] This conclusion is further supported by histochemical studies which have shown the disappearance of norepinephrine fluorescence from the terminals of central neurons after they were

treated with amphetamine.[31] When endogenous stores of rat brain norepinephrine are labeled with radioactive norepinephrine and amphetamine is administered to the animals, the patterns of radioactive metabolites found is consistent with the theory that amphetamine releases norepinephrine. More of the norepinephrine was metabolized by the extraneuronal enzyme catechol o-methyl transferase than the intraneuronal monoamine oxidase.[76] The decrease in the deaminated metabolite, however, may have been due to amphetamine's inhibiting effect on monoamine oxidase which was shown by Pratesi.[157]

Another possible mechanism of amphetamine's central action has been postulated. In peripheral sympathetically innervated tissue, the accumulation of exogenous norepinephrine is retarded by amphetamines.[25] In the central nervous system, a similar impairment occurs in brain slices[31], in vivo in the whole brain[76] and in various degrees in different parts of the brain.[31,78] Therefore, the central stimulating action of amphetamines could result from their affects on norepinephrine metabolism, which are thought to include increased release, decreased reuptake and decreased deamination. Perhaps a direct action of amphetamines on receptors is also important. Regardless of the exact mechanism of the stimulation, it is probably the effects of this stimulation, which include arousal, anorexia, wakefulness, euphoria, lessening of fatigue, increased energy and self-confidence, and an increased sense of well-being, which are responsible for the abuse of amphetamine.[41,116,209] These effects are very similar to the central subjective actions of cocaine.

Newspaper publicity concerning the euphoric effects of the Benzedrine (d-l-amphetamine) inhaler led to the initial abuse of these compounds. The first abuse of amphetamines was thought to occur in 1936 at the University of Minnesota, where psychology students found that by taking amphetamines they could stay awake for "cramming" before examinations.[84] The first reported cases of amphetamine addiction were reported in 1940 by Friedenberg[70] and Hohne[98]. Even though SKF introduced D-amphetamine in 1945 to treat obesity, and during the Second World War amphetamines were provided to troops to increase alertness and to delay fatigue, only forty-two cases of amphetamine addiction had been reported by 1958.[10] This is not to say that there were not any other cases, because later reports established that thousands of cases of amphetamine addiction had occurred beginning with the end of the Second World War throughout the world. Japan, France, England, Sweden and the United States were the countries most affected.[41,42,60,111,219] There is also no evidence that amphetamine abuse is decreasing. The World Health Organization defines drug dependence of the amphetamine class as follows:

> "A state arising from repeated administration of amphetamine, or an agent with amphetamine like effects, on a periodic or continuous basis. There are four general characteristics of this type of dependence and these include: (1) a desire or need to continue taking the drug; (2) consumption of increasing amounts to obtain greater excitatory and euphoric effects or to combat more effectively depression and fatigue, accompanied in some measure by tolerance development; (3) a psychic dependence on the effects of the drug related to a subjective and individual appreciation of the drugs effects; and (4) general absence of physical dependence so that there is no characteristic abstinency syndrome when the drug is discontinued.[220]

There has been some disagreement about the last point among investigators and addicts. Many claim that lassitude, fatigue, depression, extreme hunger and increase in REM sleep seen when amphetamines are discontinued, is a well-defined abstinency syndrome[111,143,48] of amphetamine dependence. It should be considered an abstinence syndrome even if it is free from the great discomfort and dangers which occur with opiate and barbiturate withdrawal.

In England and the United States, the majority of people who abuse amphetamines take them orally in conjunction with barbiturates. However, a large number of amphetamine abusers, who many people refer to as "speed freaks," tend to use the amphetamines alone, and usually in the form of methamphetamine intravenously.[111,10,42] The barbiturates are usually used to counteract the jitters, restlessness and anxiety produced by the amphetamines, and perhaps also to potentiate the euphoric action of amphetamines, since either agent can produce euphoria. There have been cases reported in which individuals were dependent on both amphetamines and barbiturates.

Cocaine addiction and amphetamine addiction are similar in many ways.[10] The drugs produce the same subjective effects. Kramer has reported that amphetamine addicts cannot differentiate between the euphoria produced by the amphetamines and that produced by cocaine.[111] Tolerance develops to some of the central effects of both, i.e., one must increase the dose in order to produce the same effects.[111] The anorexic effects of the amphetamine decreases with repeated administration[116]; and there is tolerance to the euphoric effects, since chronic users must

frequently increase the dosage in order to obtain the desired results. Schuster has shown that tolerance also develops to some of the behavioral effects of amphetamines in rats, while in the same subjects there was no evidence of tolerance development to the increased locomotor activity effect.[169,223] The continued effectiveness of d- and dl-amphetamine in the treatment of narcolepsy indicates that tolerance does not develop to the awakening action of these drugs[146]; the insomnia of the amphetamine addict also attests to this absence of tolerance.[111] The withdrawal symptoms of fatigue, depression, extreme hunger and increased REM sleep, are identical with both drugs. Also, the psychosis produced by an overdosage of these agents is similar. Paranoid schizophrenia occurs with both drugs and can occur after acute or chronic use. In most cases, the psychosis disappears within a couple of weeks after cessation of drug administration.[111,41] It is indeed tempting to associate the similar effects of these compounds on central and peripheral norepinephrine metabolism, i.e., potentiate of the actions of norepinephrine with the common characteristics of their abuse.

During the last few years, amphetamine addicts have begun using other psychomotor stimulants when the illicit supply of these compounds has been reduced. These agents include phenmetrazine, diethylpropion, and methylphenidate.[10,12,43,143,163,28,63] There have been no cases of pipradrol abuse reported as of now. The abuse of these compounds has been increasing significantly, especially in countries such as Sweden which have been exercising tighter restrictions on the amphetamines. The addiction produced by these drugs is very similar to that seen with cocaine

and amphetamines; therefore, it appears that addiction to psychomotor stimulants can be regarded as an entity to itself, as is narcotic addiction, barbiturate addiction, and alcoholism.

The pharmacology of pipradrol, methylphenidate, phenmetrazine and diethylpropion is very similar in many regards to that of cocaine and the amphetamines. Le Douarec and Schmitt have demonstrated the anorexic action of phenmetrazine in the rat and dog.(117) Phenmetrazine also increases spontaneous locomotor activity and blood pressure.(74) Grouping of subjects increases the toxicity of phenmetrazine(74), which is also true for the amphetamines. Ever since the original studies by Gunn and Gard(87) and those by Chance(35), many authors have tried to establish the reason for the increase in toxicity of amphetamine when animals are grouped. This effect has been attributed to anxiety(35), to hyperthermia(207), and to cerebral catecholamine levels(113,130), which are said to be different in grouped animals. This grouped toxicity phenomenon has also been reported with cocaine.(113)

The first descriptive summary of the effect of methylphenidate was by Meier et al. They showed that parenteral or oral administration increased coordinated motor activity in mice, rats, rabbits and dogs.(125) In monkeys, the pattern of the increased activity is different from that in other species. Cole and Glees reported that the drug reduced locomotor activity; however, there was an increase in small, restless, picking movements.(37) Methylphenidate is also more toxic in grouped situations and a correlation was shown between increased lethality, increased motor activity and hyperthemia.(83)

Cole and Glees proposed that methylphenidate acts through hypothalamic sympathetic activity, either by removal of an inhibitory influence on sympathetic areas or by direct stimulation of these areas.[38] The work of Meier et. al. also suggests central sympathetic activity.[125] The work of Meier et. al. and Gruber et. al.[125,86] demonstrated that the potency and effectiveness of methylphenidate in man and in animals as a psychomotor stimulant seem to lie between amphetamine and caffeine.

Animal research has demonstrated that methylphenidate, at dosages which are substimulating, reduces food intake.[107] Karczman and Howard suggest that this response is due to disorientation rather than a specific anorexic effect. The work of Karli supports this conclusion.[108] This author showed that methylphenidate and amphetamine interrupt drinking, agressive and sexual behavior in rats.

Methylphenidate produces a slight increase in blood pressure. This was initially shown by Meier et. al.[125]; Ursillo and Jacobson[199], and Maxwell et. al.[121,122] have demonstrated that methylphenidate potentiates the cardiovascular effects of norepinephrine and will antagonize a phentolamine induced block of norepinephrine activity. Maxwell et. al.[123] have also shown that methylphenidate interferes with the uptake and binding of norepinephrine. However, it has not as yet been demonstrated that a direct cause-effect relationship exists between this interference with reuptake and the potentiation of norepinephrine. The same author has shown that endogenous norepinephrine is a prerequisite for methylphenidate's action on the nictitating

membrane of the cat.

Pipradrol also increases motor activity in a wide variety of species and also increases reactions to environmental stimuli.[22] Garberg and Sanberg[74] showed that pipradrol is 1/6 as potent as d-amphetamine in increasing motor activity in rats to three times control activity. The mechanism for the central stimulatory property of pipradrol and methylphenidate appears to be via stimulation of the reticular formation.[161] Pipradrol, like methylphenidate, decreases the amount of pentylenetetrazol required to produce clonic convulsions in mice.[36] Greeblatt and Osterberg have shown that pipradrol toxicity is increased in a grouped environment. They observed a correlation between hyperthermia, lethality and locomotor activity.[83] The work of Tripod et. al. suggests that pipradrol has some central adrenergic activity, since the central stimulant activity is antagonized by phentolamine.[198] In dogs and cats, pipradrol increases blood pressure slightly.[22] Pipradrol, like methylphenidate, decreases food intake in cats at dosages which are substimulating.[107]

Animal experimentation utilizing techniques evolved in experimental psychology have demonstrated that the actions of all of these psychomotor stimulants on behavior are very similar. Psychomotor stimulants increased conditioned behavior maintained by aversive control. Teitelbaum and Derks[193] demonstrated that amphetamine increased shock avoidance responding when the response was licking a water drinking device. They suggested that the reason for this result was that amphetamine had increased the aversiveness of the shock. Many other studies have shown this

increase in avoidance responding with amphetamine[95,211,33,202], pipradrol[145,146,184], cocaine[145,146], and methylphenidate.[186]

Hearst and Walen conducted a study in which d-amphetamine increased discriminated shock avoidance responding. They also noticed that the topography of the animals behavior was effected by the drug, e.g., freezing behavior upon presentation of the warning stimulus was reduced, thereby increasing the likelihood that the subject would come into contact with the response lever. These authors and Pearl argue that this decrease in freezing behavior, due to the psychomotor stimulants increasing motor activity, is the mechanism involved in the increase in avoidance responding. If these compounds acted by increasing the aversiveness of shock, then one would expect to see improved avoidance performance with increased shock intensity; however, studies have failed to show this relationship.[193]

Dl-amphetamine and d-amphetamine have been shown to decrease responding in the presence of a stimulus paired with shock, i.e., conditioned emotional response. Responding in the absence of the shock-paired stimulus was increased. If the dose of the drug is increased, responding during presentation of the stimulus is also increased.[193,19]

The effects of psychomotor stimulants on conditioned behavior maintained by positive reinforcement depend not only on the dose of the drug, but also on the type of schedule employed, parameters of the schedule, and control rate of responding. Amphetamine increases and decreases response rate on a fixed ratio (FR) schedule for food and water reinforcement. At low

FR values, increases were found[20,56,212,185]; whereas at high FR values response rates were decreased.[143] Similar results have also occurred with methylphenidate[13] and pipradrol.[20] Larger doses of amphetamines decrease response rates in fixed ratio paradigms in which smaller doses produce an increase in response rate.[20,128] Low dosages of amphetamine increase responding on both a fixed interval and variable interval schedule of reinforcement; whereas high doses of amphetamine decrease responding.[20,193,109] Amphetamines also increase responding on a differential reinforcement of low response rate (DRL) schedule of reinforcement.[124,169]

Mechner and Latranyi have shown similar effects with methamphetamine and methylphenidate on a fixed interval schedule of reinforcement[124], and Gray showed similar results with pipradrol on a variable interval (VI) schedule of reinforcement in rats using food as a reinforcer.[82] High doses of pipradrol depressed responding and low doses increased responding on a given VI schedule.

Amphetamines also tend to increase conditioned behavior maintained by positive reinforcement when the reinforcers are not food and water. Amphetamine increases responding in rats when the reinforcement is activation of a heat lamp.[210] Amphetamine also increases the rate at which monkeys will turn on a light in a dark cage[69], and amphetamines increase the rate of responding in rats when the reward is intracranial stimulation in a previously designated "reward" area.[141,180]

Therefore, the effects of psychomotor stimulants on conditioned behavior maintained by positive or negative reinforcement

depend upon many experimental variables. These include the dosage of the drug employed (high dosages decrease and low dosages increase response rates); the type of reinforcement schedule being utilized (a given dosage depresses fixed ratio responding before fixed interval responding when both schedules are generating equal control response rates)[109]; the control response rate (low rates are increased; high rates decreased by a given dosage); and the nature of the reinforcer. Anorexic effects of these compounds would also influence their effects on food reinforced behavior.

Although there are some quantitative and qualitative differences in the pharmacology and abuse of these psychomotor stimulants, I believe that due to their striking similarities, which I have alluded to, we can treat them as a single compound. Experimental results in the body of this dissertation will further substantiate this conclusion.

2. History and behavioral basis of animal drug self-administration studies. In 1929, Tatum, Seevers and Collins[191] demonstrated that the biological factors involved in drug dependence could be studied in animals. Although Spragg[176] in 1940 showed that chimpanzees which were physically dependent on morphine exhibited "morphine-seeking" behavior and Masserman and Yum[120] reported in 1946 that cats drank an increased amount of alcohol in a conflict situation, it has only been recently accepted that the behavioral aspects of drug dependence could be studied in animals. One can interpret the behavioral aspects of drug dependence in man or animals by utilizing the principles

of operant conditioning, which were described by Skinner in 1938.[171] The fundamental concept involved is that the frequency of emitting a given response is determined by the consequences of that response. If the frequency of the behavior is increased, it is said to be reinforced and the consequence is called a reinforcer. Reinforcers may be positive, i.e., the presentation of an object, e.g., water, food, or negative, i.e., the prevention of an aversive situation, e.g., shock.

The first animal experiments which demonstrated that the behavioral aspects of drug dependence could be studied utilizing operant conditioning techniques and theories were conducted in 1955. Headler, Coppock and Nichols[94] described an apparatus and technique for studying drug self-administration in rats and they were the first to demonstrate clearly that drug-administration could act as a reinforcing consequence for animals. Rats were trained to laterally turn their heads which in turn broke a photo-electric beam, thus starting an infusion pump. The pump infused a morphine solution through a hypodermic needle which was inserted through the body wall into the peritoneal cavity. The frequency of these head movements was increased above control levels, so, therefore, morphine administration, i.e., the consequence of the response, was reinforcing. These have been the only investigators to utilize the intraperitoneal route of administration in self-administration studies. Most self-administration studies since then have utilized either oral or intravenous routes of administration. Jarvik has assessed the reinforcing property of tobacco smoke in monkeys

using two tubes, one providing heated air and the other tobacco smoke, following puffing by the subject.[102] Some investigators have utilized an intracerebral route of administration. Old and Olds showed that iproniazid would be self-administered by rats via pipettes chronically implanted in the lateral hypothalamus[140]; however, further studies demonstrated that this result was due to the volume injected and PH of the solution.[138] Myers has designed a system for chronic intracerebral drug self-infusion for primate use.[133] In oral self-administration studies, animals are simultaneously presented with two or more solutions, one of which, at least, contains an active drug. The others serve as controls for taste and palatability, e.g., water, quinine, sucrose. The initiation of oral self-administration behavior often requires either prior drug administration to produce physical dependence[136,215], the imposition of a stressful situation[106,2,120], or the acquisition by the licking response of a conditioned reinforcing property.

It has been demonstrated, though, that rats will drink morphine solutions without pretreatment or environmental stress.[93] In these preference procedures, one measures the tendency to ingest the drug solution versus the control solutions. There are several problems inherent with this procedure. These include not only the use of proper controls for positional habit, water deprivation, taste and palatability, but also difficulty in the initiating drug seeking behavior due to the delay between response and reinforcement. This latter problem occurs because the drug must first be absorbed from the gastrointestinal tract

before the unconditioned reinforcing effect can occur.

Due to these problems, most of the recent studies conducted with drug self-administration have utilized the intravenous route of administration. A significant development for studies of drug dependence was the arrangement for the subject to control the operation of an infusion pump which was connected to an indwelling venous catheter. The first study of intravenous self-administration in rats was conducted by Weeks.[203] Other systems have subsequently been described by Davis[51] and Pickens[150]. Yanagita, Deneau, and Seevers, and Schuster and Thompson have described chronic intravenous methods of studying drug self-administration in rhesus monkeys.[221,167] These investigators utilized a chronic polyethylene catheter, motor powered syringe driver, and a stainless steel harness and arm designed for subject restraint and catheter protection, to study morphine self-administration in restrained rhesus monkeys. Pickens et. al. have developed a similar partial restraint and catheter protection system involving flexible conduit and a leather vest.[151] Methods for drug self-administration in unrestrained animals have also been reported.[194]

The drugs which have been shown to serve as reinforcers, i.e., maintain self-administration behavior in animals, include only those compounds which are abused by man. Several studies have shown that morphine acts as a reinforcer in rats[203,209,205,39] and monkeys.[221,167,195,218] Deneau has reported the self-administration of methadone by the rhesus monkey[53], and Collins and Weeks have studied the reinforcing properties of intravenously

administered codeine, methadone and dihydromorphinone in rats.[39] Amobarbital and Hexobarbital have been shown to be self-administered by rats under conditions of intermittent unavoidable shocks[48,49], and Deneau has shown that pentobarbital and phenobarbital are self-administered by naive Rhesus monkeys.[53]

Rats have been shown to self-administer alcohol solutions orally[126,134], and monkeys will self-administer alcohol solutions intravenously.[221] Many studies have demonstrated that the psychomotor stimulants, which are abused by man, are self-administered by both the rat and rhesus monkey. Nicotine is self-administered intravenously and inhaled as tobacco smoke by the Rhesus monkey.[52,102] Cocaine has been shown to be a reinforcer intravenously in rats[149,153,154] and monkeys[217,218,222], and methamphetamine is self-administered by rats[147,148,149], and d-amphetamine by monkeys[53] and rats[149,152,153]; SPA (1-2 diphenyl 1-dimethyl amino ethane hydrochloride), which has been abused in Japan, is also self-administered by the monkey.[62,217,218] Therefore, rats and monkeys self-administer the same compounds which are abused by man. These include the opioids, barbiturates, ethyl alcohol, and the psychomotor stimulants. Under similar conditions, monkeys will not self-administer nalorphine, chlorpromazine or mescaline.[54]

## B. STATEMENT OF THE PROBLEM

Since Rhesus monkeys self-administer intravenously the psychomotor stimulants which man abuses, one can use these subjects to evaluate some of the pharmacological and environmental

variables which may interact with the reinforcing efficacy of these compounds in man. Once it becomes possible to alter this reinforcing property by environmental alteration or pharmacological intervention, possible approaches for use in the treatment of those people who abuse the psychomotor stimulants can be initiated. This knowledge also will provide information concerning the possible mechanism of the reinforcing effect of these compounds. Therefore, the problem which was studied and is described in this dissertation was as follows: What are some of the variables which can alter the reinforcing property of the psychomotor stimulants in Rhesus monkeys.

## C. PRIOR STUDIES PERTINENT TO THE PROBLEM

Schuster and Thompson have classified the variables which influence the self-administration of drugs as environmental, pharmacological and organismic.[168] However, most of the experiments in which these variables were studied involved subjects which were self-administering either alcohol, morphine, or barbiturates. However, one of the environmental variables which has been studied, using subjects self-administering psychomotor stimulants, is the schedule of drug reinforcement. Skinner[171], and Ferster and Skinner[65], have shown that the pattern and persistence in emitting a given response depends largely on the schedule or reinforcement. Therefore, this variable could largely influence drug self-administration behavior. Most self-administration studies have utilized a continuous reinforcement (CRF) schedule of

reinforcement. With such a schedule, each correct response emitted by the subject results in drug administration.

Intermittent schedules of reinforcement have been utilized in studies in which drug administration served as the reinforcer for emitting a given response. However, only fixed ratio (FR) schedules of reinforcement have been employed in studies in which psychomotor stimulants were the reinforcement. With such a schedule, the subject must emit a specific constant number of correct responses before drug administration will occur. Pickens[149], Pickens and Thompson[153,154], Pickens and Harris[152], and Pickens et. al.[147], have studied the effect of varying fixed ratio values on psychomotor stimulant self-administration in rats. These investigators varied ratio values from FR-1 (CRF) to FR80 over a wide range of dosages of cocaine, methamphetamine and d-amphetamine.

Two important pharmacological variables have been studied in subjects self-administering psychomotor stimulants. Studies have been conducted by Pickens and Thompson[154], and Pickens et. al.[147], in which the effect of treating rats which were self-administering either cocaine or methamphetamine with the same compound being self-administered, was determined. These investigators also studied the effects of treatment with other drugs on psychomotor stimulant self-administration.

The effect of varying the magnitude of reinforcement, i.e., the dosage per administration on psychomotor stimulation self-administration behavior, has also been investigated. The effectiveness of the reinforcer in maintaining a given behavior is directly related to the magnitude or amount of reinforcement

obtained following emission of the appropriate response. An inverse relationship between dosage per administration and number of responses was demonstrated by Deneau and Inoki[52] in Rhesus monkeys which were self-administering nicotine intravenously. A similar inverse relationship between response rate and magnitude of reinforcement exists in rats which self-administer either cocaine, d-amphetamine or methamphetamine.[148,152,153,154] These three variables, i.e., magnitude or reinforcement, schedule of reinforcement, drug interaction, as well as food satiation and food deprivation, were studied in Rhesus monkeys who were self-administering psychomotor stimulants. This dissertation presents the methods, results and interpretation of this research.

## II. PSYCHOMOTOR STIMULANT INTAKE AS A FUNCTION OF DOSAGE PER INJECTION (COCAINE, METHYLPHENIDATE, PHENMETRAZINE, PIPRADROL AND SPA).

### A. INTRODUCTION

One of the most influential variables which functions in initiating and maintaining a given behavior is the magnitude of reinforcement which is presented following completion of the appropriate response. The exact nature of this relationship appears to depend somewhat upon the nature of the reinforcer. In general, increases in the amount of food and water reinforcement result in an increase in the level of performance.(110) However, with other reinforcers, e.g., heat or sucrose solutions, curvilinear relationships have been found between amount of reinforcement and performance.(208,89) Weeks and Collins demonstrated that with rats physically dependent on morphine, the frequency of morphine self-administration was inversely related to infusion dosage.(205) However, as the infusion dosage of morphine was increased, the mean daily intake of morphine self-administered increased significantly. Therefore, there is a linear relationship between infusion dosage and the total daily intake. Woods and Schuster demonstrated, using Rhesus monkeys which were self-administering morphine intravenously, that response rate on a variable interval schedule of reinforcement varies in an inverted "U" shaped manner as a function of the magnitude of reinforcement in the range of 10 to 1000 mcg/kg/infusion.(218) The decrease in response rates seen with increasing infusion dosage, i.e., the descending limb of the curve,

was interpreted as being due to the dose-related depressant properties of morphine. In this study, total daily intake was directly related to infusion dosage which corroborated the study of Weeks and Collins.

The relationship between response rate and magnitude of reinforcement has been investigated in rats self-administering either cocaine, d-amphetamine or methamphetamine intravenously. Pickens et. al. demonstrated that the frequency of responding decreases with increases in unit dosage of methamphetamine over the range of 0.5-2.0 mg/kg.(148) However, these results differ from those obtained with morphine by Weeks and Collins, and Schuster and Woods, in that total drug intake remained relatively constant over this range of unit dosage.

Pickens and Harris have studied the self-administration of d-amphetamine in rats.(152) The magnitude of reinforcement, i.e., unit or infusion dosage, was varied from 0.25 to 1.0 mg/kg. Increases in unit dosage were associated with decreases in the frequency of self-administration, and decreases in the unit dosage were associated with increases in the frequency of self-administration. A similar inverse relationship between response rate and magnitude of reinforcement was reported by Hodos and Valenstein using intracranial stimulation as reinforcement.(97)

Pickens and Thompson reported similar results using cocaine as the reinforcer.(154) The exact relationship was such that regardless of the unit dosage, total drug intake over time was relatively constant. These investigators also demonstrated that an identical relationship exists when food is the reinforcer. Equally important was the result that, regardless of the magnitude

of reinforcement, the total number of reinforcements, i.e., food pellets consumed each day, was relatively the same.

Furthermore, Deneau and Inoki, using Rhesus monkeys which self-administered nicotine intravenously, demonstrated that an inverse relationship existed between response rate and the magnitude of reinforcement.(52) However, there was a direct relationship between magnitude of reinforcement and total drug intake which was not demonstrated with cocaine and d-amphetamine self-administration. Therefore, there is definitely an inverse relationship between magnitude of reinforcement and response rate within the range of unit dosages which can maintain psychomotor stimulant self-administration behavior. Depending upon the range of unit dosages, i.e., magnitude of reinforcement studied, one may also see a direct relationship at low unit dosages, i.e., the work of Woods and Schuster, between these two variables. There appears to be a different relationship between total drug intake and magnitude of reinforcement when opiates were the reinforcer, i.e., total intake increases as a function of unit dosage, than when psychomotor stimulants were the reinforcer, i.e., total intake remains relatively constant.

The first group of experiments to be discussed were designed to determine if similar relationships exist between unit dosage and response rates and between unit dosage and total drug intake in Rhesus monkeys self-administering psychomotor stimulants intravenously.

B. METHODS

1. Subjects. The subjects for this study were ten adult

Rhesus monkeys which had no prior drug history and which weighed between 3.6 and 5.8 kilograms. After the subjects had adapted to their new environmental situation for seven days, they were anesthetized with pentobarbital sodium (30 mg/kg intravenously) and were prepared with a chronic indwelling jugular catheter. A small incision was made ventral to the right internal jugular vein in the neck region. The vein was isolated and ligated and was then entered by making an incision with iris scissors. A siliconized rubber, e.g., Vivosil, catheter (O.D. = .065 inches, I.D. = 0.32 inches) was inserted into the vein and the tip was threaded downward until it approximated the area of the right atrium. The catheter was secured in the vein by means of a suture tied around the vein below the point of catheter entry. The catheter was also held in place by two sutures which were attached to the catheter with Silastic adhesive at the point of exit from the view. These sutures were tied to overlying muscle. The catheter was then passed, via a stylet, subcutaneously over the shoulder and down the back, and exited the back through an incision made between the shoulder blades. Following the surgical procedure, 600,000 units of benzathine penicillin-G, 300,000 units of procaine penicillin-G, and 300,000 units of potassium penicillin-G, i.e., All Purpose Bicillin, was administered intramuscularly to each subject.

If at any time during the study the catheter was rendered useless due to clotting, damage, or removal by the subject, the catheter was removed surgically and an attempt was made to insert another catheter into the same vein. If this was not possible, a catheter was placed in the left internal jugular vein.

2. Apparatus. The subjects were housed in individual open-faced experimental cubicles. This latter property permitted observation and maintenance of the subject, but also allowed the subject to observe other subjects, as well as laboratory personnel conducting other experiments and carrying out their routine work assignments. There likewise was no auditory isolation. The lower back wall consisted of a stainless steel panel; the ceiling, sides and remainder of the back were made of non-transparent white plastic. The floor was one inch galvanized steel mesh. A covered food tray was located in one back corner. The stainless steel panel contained apertures for two levers; however, only one lever was used throughout the study. Whenever 100 grams of force was applied to the lever, a microswitch was closed, which in turn activated an automatic injector which was mounted on a stainless steel shelf attached to the outside of the back wall of the cage. A red neon lamp (4 watts) was centered on the stainless steel panel and located directly beneath this was a water spout which delivered water when pressure was applied to the end.

The subjects were restrained in the cubicles by a stainless steel harness and arm, initially described by Yanagito, Deneau and Seevers[222] and later illustrated by Goldberg.[81] The arm was attached to the back wall of the cage and to the harness. This arm and harness arrangement allowed the subject to move relatively freely about the cubicle. The catheter which exited the subject's back was connected to an 18 gauge juncture located on the back of the harness. A second piece of Vivosil tubing of identical dimensions as the catheter was attached to

this juncture and passed through the restraining arm out through the back of the cubicle to the injector unit. Figure 1 shows a subject, restrained by a stainless steel harness and arm, sitting in an experimental cubicle.

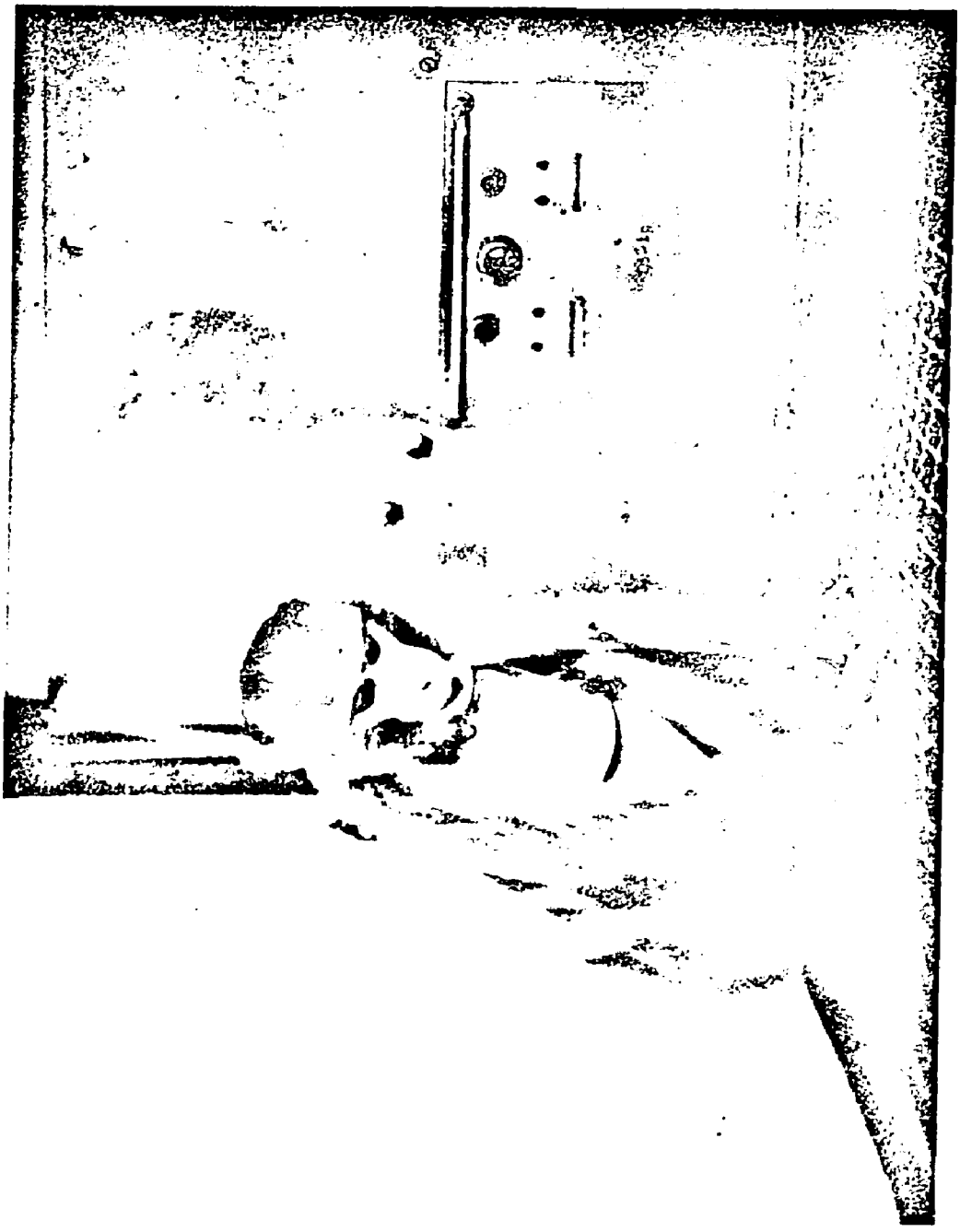
When the red light was illuminated, depression of the lever resulted in the intravenous administration of a given volume of a drug solution or of physiological saline. All lever responses were recorded, whether or not they were emitted while the light was illuminated, using an Esterline Angus Event Recorder. Programming and recording equipment were located in an adjacent room.

All subjects had unlimited access to water and were fed 10-15 Purina Monkey Chows twice daily, at 8:00 a.m. and 4:00 p.m. All cubicles were cleaned every four hours by means of an automatic cage washing system.

3. General procedure. Following catheterization, the subjects were returned to the experimental cubicles. The stimulus light was turned on and remained on all day for seven days. Every lever-press made during this period resulted in the administration of 0.2 cc/kg of body weight of sterile physiologic saline. During an injection cycle which lasted approximately forty-five seconds, the stimulus light was turned off and lever presses, although recorded, had no consequence. In order to prevent the formation of blood clots in the catheter, an automatic timer was programmed to deliver a saline injection every four hours. Each subject's lever-pressing frequency for saline during this period was determined and this value served as a control for

Figure 1. Subject restrained by a stainless steel harness and arm, sitting in an experimental cubicle.

Figure 1



future experiments in these subjects.

A 1.0 mg/cc solution of cocaine hydrochloride in sterile physiologic saline was substituted for the saline at the end of this seven day period. The stimulus light remained on twenty-four hours a day and each lever-press resulted in the intravenous administration of 0.2 mg/kg of cocaine hydrochloride. As with saline, programmed administrations occurred every four hours. If a subject did not initiate responding within three days, a plexiglass extension (2.0 x 2.0 inches) was attached to the lever to increase the chance of the subject, either due to curiosity or accident, depressing the lever. All subjects initiated lever pressing behavior within five days after substitution of cocaine for saline. Once a subject initiated this behavior, the access period to cocaine was reduced from twenty-four hours to four hours daily. This was done to reduce the neurotoxic effects of cocaine administration, which usually appeared within five to seven days if subjects were allowed unlimited access to cocaine. Also, under unlimited access conditions, daily cocaine intake varied tremendously and for the purposes of the present study it was necessary to maintain stable daily intake. Previous studies by Pickens and Thompson[154], Pickens and Harris[152], Pickens et. al.[148], Deneau and Inoki[52], have demonstrated that rats and monkeys self-administering psychomotor stimulants under unlimited access conditions alternate between periods of regularly spaced responding and periods of no responding, i.e., abstinence. The periods of responding usually lasted from twenty-four to forty-eight hours, and would terminate abruptly. Periods of abstinence, during which the subjects ate and slept, would last for a similar

length of time and then the cycle would be initiated again. This cyclical pattern is very similar to that reported by Kramer et. al.[111] to occur in people who abuse psychomotor stimulants intravenously. Woods and Schuster[218] demonstrated that if one limits the access period in monkeys who were self-administering SPA (1,2 diphenyl-1-dimethyl aminoethane hydrochloride), which is a psychomotor stimulant, that daily intake becomes very stable. Thus, baseline levels of drug intake can be established and this gives one the opportunity to study the effects of different variables on this baseline intake.

The four-hour drug access period, which was from 11:00 a.m. to 3:00 p.m., was indicated by the illumination of the stimulus light. During the other twenty-hour period the light was never illuminated, and lever presses had no consequence but were recorded. Programmed administrations occurred every four hours.

After each subject established stable self-administration patterns for cocaine at a unit dosage of 0.2 mg/kg/injection, the cocaine solution was then replaced with a solution of either SPA hydrochloride, methylphenidate hydrochloride, phenmetrazine hydrochloride, pipradrol hydrochloride or cocaine hydrochloride of a different concentration. The volume of the injection remained constant throughout the study, and all drugs were dissolved in physiologic saline and dosages calculated on the basis of the salt. Only the concentration of the drug solutions changed during the study. New solutions were prepared every third day, and old solutions discarded to prevent decomposition and maintain potency.

Subjects were maintained at each unit dosage level for seven consecutive days. Between the testing of each unit dosage, the subjects were returned to the baseline unit dosage, i.e., the unit dosage of that particular compound to which they were first exposed, i.e., cocaine hydrochloride 0.2 mg/kg, for five sessions to insure that their sensitivity had not changed. Following stabilization of the animal's lever-pressing response frequency for the baseline unit dosage of a given compound, the unit dosage was unsystematically varied over a wide range, which for cocaine was 0.025-1.2 mg/kg; SPA, 0.05-1.0 mg/kg; phenmetrazine, 0.025-0.8 mg/kg; methylphenidate, 0.025-0.4 mg/kg; and pipradrol, 0.025-0.4 mg/kg.

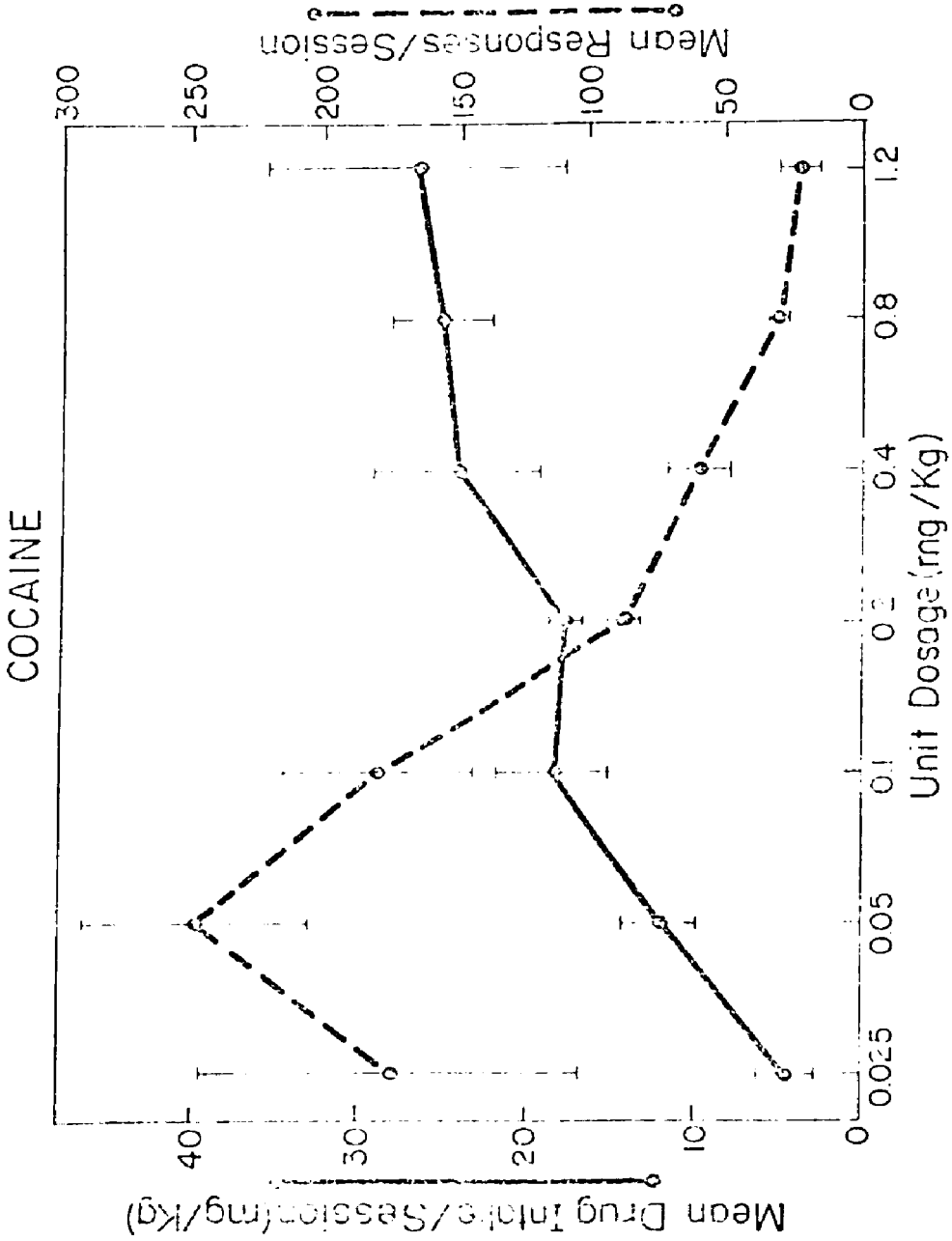
The effects of varying the unit dosage, i.e., magnitude of reinforcement, of cocaine was studied in five subjects, SPA in four subjects, pipradrol in four subjects, phenmetrazine in four subjects and methylphenidate in three subjects. The same subjects were utilized in studying phenmetrazine, methylphenidate, and pipradrol. Every subject was exposed to each unit dosage of the compound being tested and studies with one compound were completed before a different compound was studied in a given subject. Three of the subjects used in studying SPA were also used in studying cocaine, i.e., M1095, M2069, M2068.

C. RESULTS

Figure 2 illustrates mean number of responses per session and mean drug intake per session as functions of the unit dosage of cocaine hydrochloride. Each point represents the mean of data obtained from five subjects on days three through seven at each

Figure 2. Mean number of responses per session (broken line) and mean drug intake per session (solid line) as functions of unit dosage of cocaine hydrochloride. Each point represents the mean of data obtained from five subjects on days three through seven of exposure to each unit dosage level. Vertical lines represent the range.

Figure 2


COCAINE
Mean Drug Intake/Session(mg/kg)
Mean Responses/Session
Unit Dosage(mg/Kg)
0
10
20
30
40
50
100
150
200
250
300
0.025
0.05
0.1
0.2
0.4
0.8
1.2

unit dosage level. The vertical lines represent the range. As the unit dosage was increased from 0.05 mg/kg to 1.2 mg/kg, the mean number of responses emitted, i.e., injections received, decreased from 250 to 5. Mean drug intake per session increased from 4.2 to 18.0 as the unit dosage was increased from 0.025 to 0.1 mg/kg; however, further increases in unit dosage produced only small increments in drug intake. Mean drug intake increased only from 18.1 to 24.8 mg/kg. As the unit dosage was increased from 0.1 to 1.2 mg/kg, the range of drug intake per session overlapped, i.e., this function is essentially flat.

At a unit dosage of 0.025 mg/kg, variability in responding was significant; I feel that this occurred because this unit dosage approached the threshold reinforcing dose of cocaine. In some animals this unit dosage was reinforcing; whereas in others it was not, and hence variability in responding was significant. As the unit dosage was increased this variability decreased.

When the unit dosage was 0.05 mg/kg, limitations of the equipment prevented the subjects from self-administering as much cocaine as was self-administered at higher unit dosages. Each injection cycle lasted 45-60 seconds, depending on the weight of the animal; therefore, approximately only 300 injections could be self-administered during the four hour session.

The amount of cocaine self-administered by these subjects appears to be independent of unit dosage, i.e., magnitude of reinforcement, over a range which maintained self-administration behavior. Even though unit dosage was increased by a factor of twelve, i.e., from 0.1 to 1.2 mg/kg, mean daily drug intake increased by only a factor of two. However, there is a distinct

inverse relationship between unit dosage and the response rate.

Figures 3 and 4 illustrate the same data obtained from individual subjects. The grouped data is very representative of that obtained from individual subjects.

Figure 5 illustrates a selected session record at each unit dosage of cocaine studied in subject M2023. Each vertical line represents a single response, i.e., one self-administration. At unit dosages of 0.025 and 0.05 mg/kg, the infusion pump was operating almost constantly throughout the session. As the unit dosage was increased from 0.1 to 2.0 mg/kg, the number of lever presses decreased. Furthermore, the subjects seemed to respond at a fairly constant rate throughout the session. A characteristic pause between responding, i.e., self-administration, occurred at each unit dosage level. This pause increased in length and became more regular as the unit dosage was increased.

The results obtained with SPA self-administration were very similar to those obtained with cocaine self-administration. Figure 6 shows the mean number of responses per session (broken line) and mean drug intake per session (solid line) as functions of the unit dosage of SPA hydrochloride. Each point represents the mean of data obtained from three subjects (M2068, M2069, and M1095) on days three through seven of exposure to each unit dosage level. Vertical lines represent the range. As the unit dosage of SPA is increased from 0.05 to 1.0 mg/kg, the mean number of responses per session decreased from 189 to 21. Therefore, as occurred with cocaine self-administration, there is an inverse relationship between response rate and unit dosage. Variability in responding decreased as unit dosage was increased.

Figure 3. Mean number of responses per session (broken line) and mean drug intake per session (solid line) as functions of unit dosage of cocaine hydrochloride. Each point represents the mean of data obtained from the last five days of exposure to each unit dosage level. Vertical lines represent the range.

Figure 3

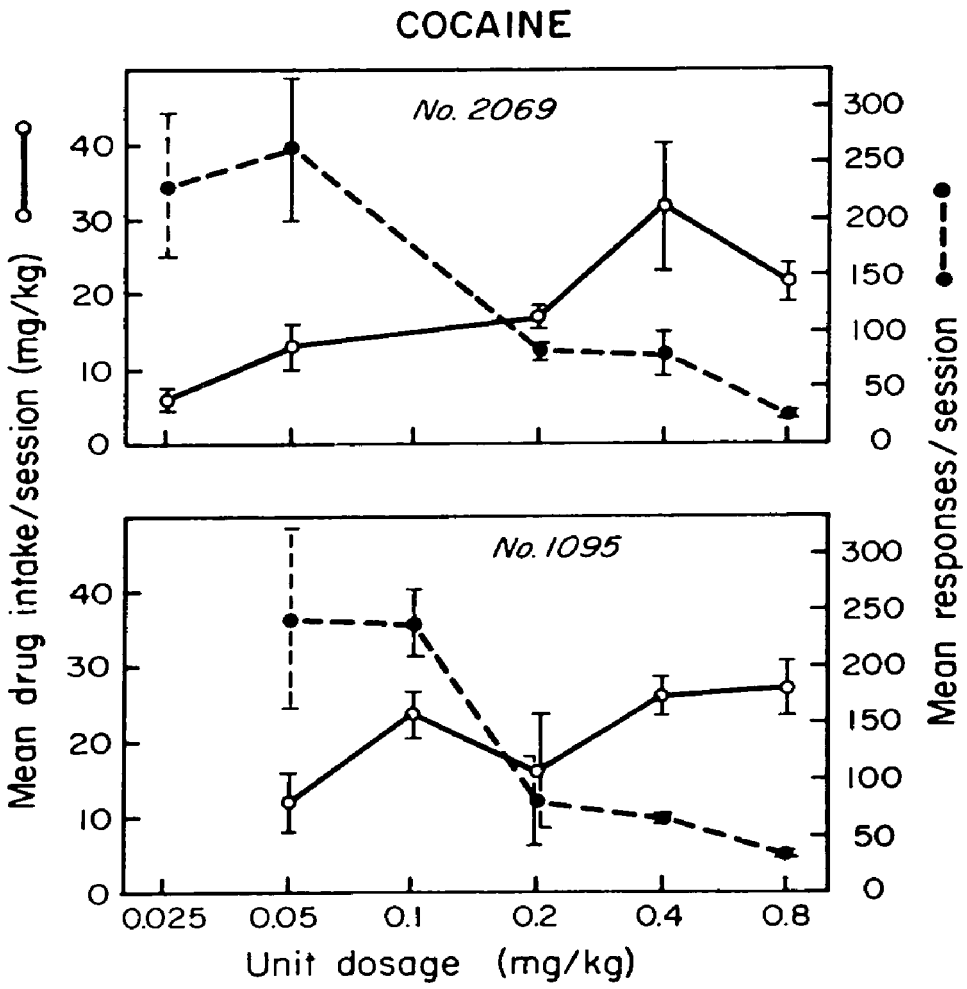

COCAINE
No. 2069
No. 1095
Mean drug intake/session (mg/kg)
Mean responses/session
0
10
20
30
40
50
100
150
200
250
300
0.025
0.05
0.1
0.2
0.4
0.8
Unit dosage (mg/kg)

Figure 4. Mean number of responses per session (broken line) and mean drug intake per session (solid line) as functions of the unit dosage of cocaine hydrochloride. Each point represents the mean of data obtained from the last five days of exposure to each unit dosage level. Vertical lines indicate the range.

Figure 4

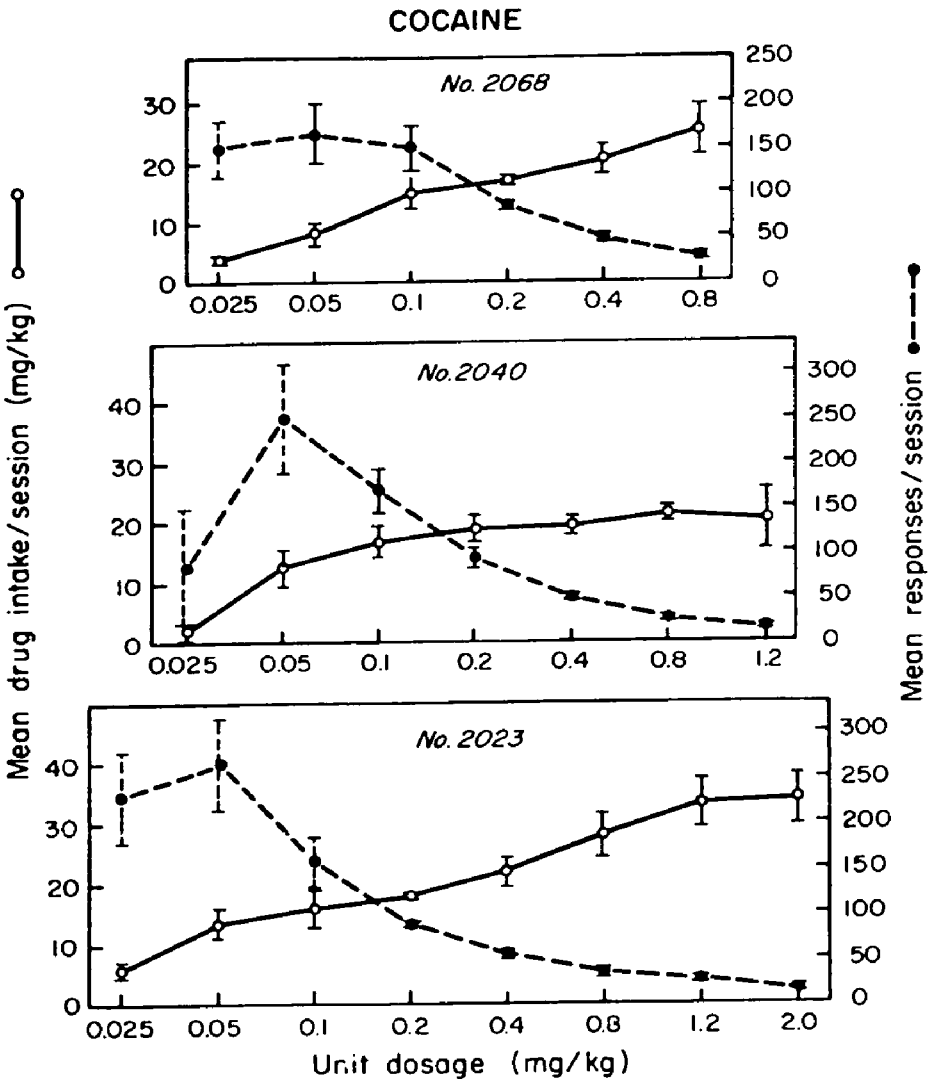

COCAINE
No. 2068
No. 2040
No. 2023
Mean drug intake/session (mg/kg)
Mean responses/session
Unit dosage (mg/kg)
0.025
0.05
0.1
0.2
0.4
0.8
1.2
2.0

Figure 5. Selected session records at each unit dosage value of cocaine studied in subject M2023. Each vertical line represents one response or one self-administration.

Figure 5

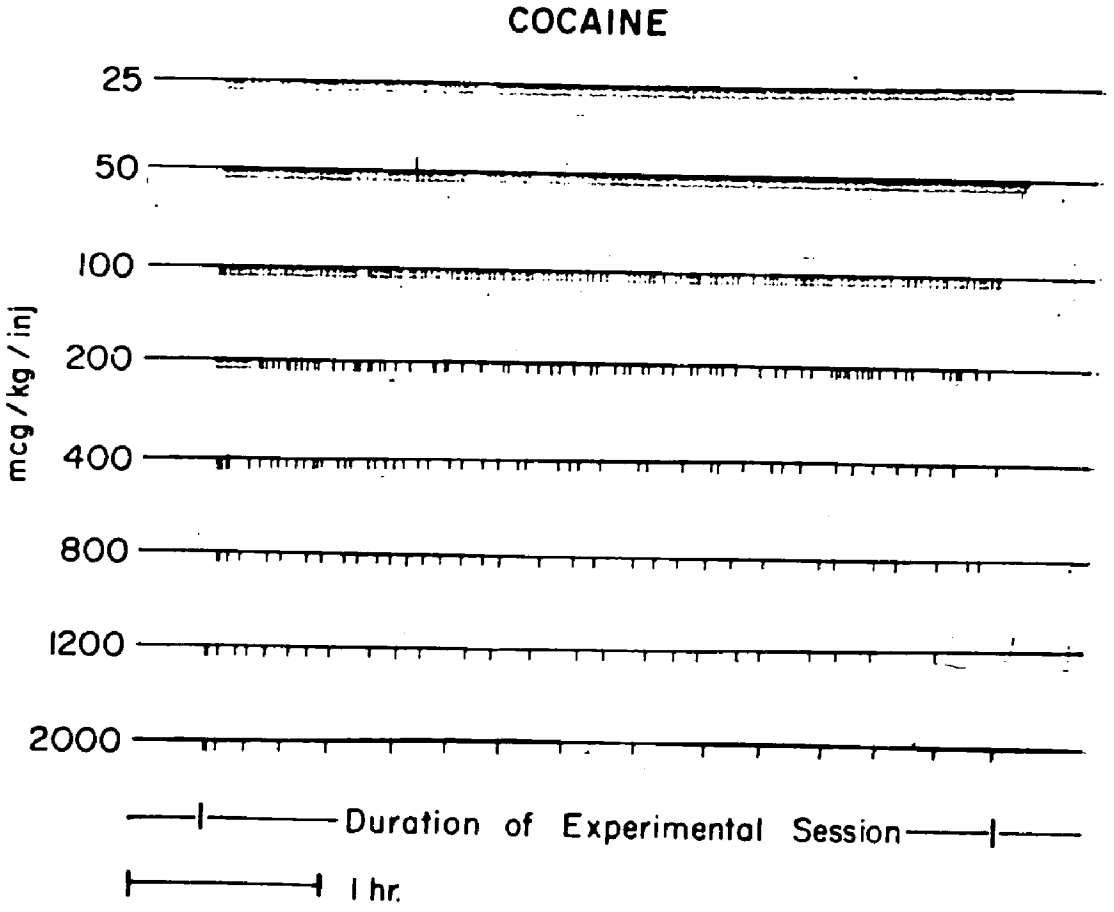
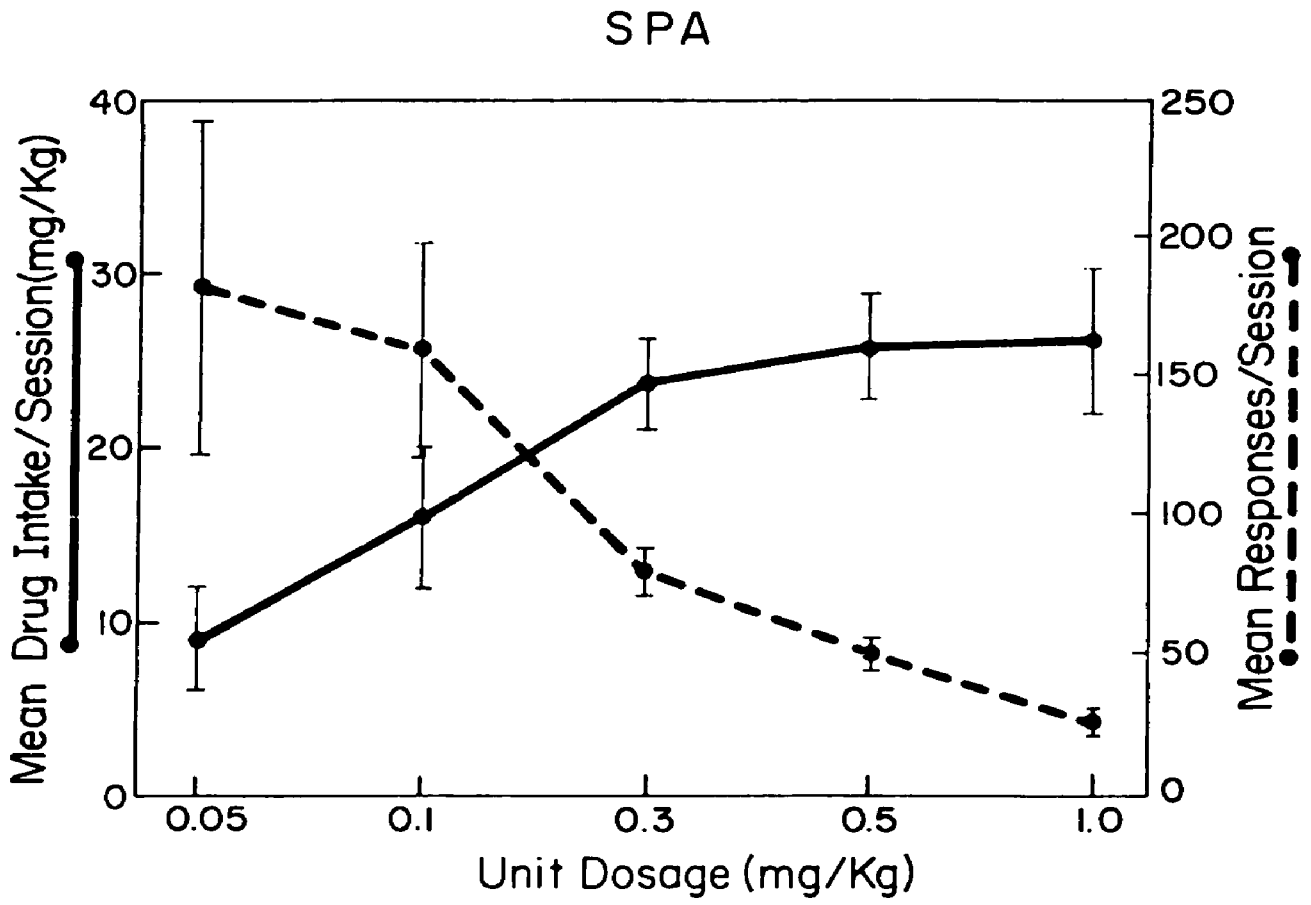

COCAINE
25
50
100
200
400
800
1200
2000
mcg / kg / inj
Duration of Experimental Session
1 hr.

Figure 6. Mean number of responses per session (broken line) and mean drug intake per session (solid line) as function of unit dosage of SPA hydrochloride. Each point represents the mean of data obtained from three subjects on days three through seven of exposure to each unit dosage level. Vertical lines represent the range.

Figure 6


SPA
Mean Drug Intake/Session(mg/Kg)
Mean Responses/Session
Unit Dosage (mg/Kg)
0
10
20
30
40
0
50
100
150
200
250
0.05
0.1
0.3
0.5
1.0

Mean drug intake per session increased from 9.2 to 22.3 mg/kg as the unit dosage of SPA was increased from 0.05 to 0.3 mg/kg. However, further increases in unit dosage produced only a very slight increase in mean SPA intake per session. Mean SPA intake was independent of the magnitude of reinforcement, i.e., unit dosage at these levels, i.e., 0.3 to 1.0 mg/kg.

Figure 7 shows the same data as Figure 6, except that in the former case the data is presented for individual subjects. Data obtained from M AC77 was not included in calculations used in preparing Figure 6, because this subject was only run for two hours daily rather than the customary four hours. The grouped data is very representative of the data obtained from individual subjects.

Figure 8 illustrates selected session records at each unit dosage level of SPA studied in M1095. Each vertical line represents one response or one self-administration. As the unit dosage was increased from 0.05 to 1.0 mg/kg, the number of responses emitted decreased. A characteristic pause is evident after each self-administration and the length of this pause increases with increases in unit dosage. As occurred with cocaine, responding occurred at a rather uniform rate throughout the session. The highest rate of responding occurred at the beginning of the session; this also was seen in subjects self-administering cocaine.

Similar results were obtained with pipradrol self-administration. Figure 9 illustrates the mean number of responses per session (broken line) and mean drug intake per session (solid line) as functions of the unit dosage of pipradrol hydrochloride. Each point represents the mean of data obtained from four subjects on

Figure 7. Mean number of responses per session (broken line) and mean drug intake per session (solid line) as functions of unit dosage of SPA hydrochloride. Each point represents the mean of data obtained from the last five days of exposure to each unit dosage level. Vertical lines represent the range.

Figure 7

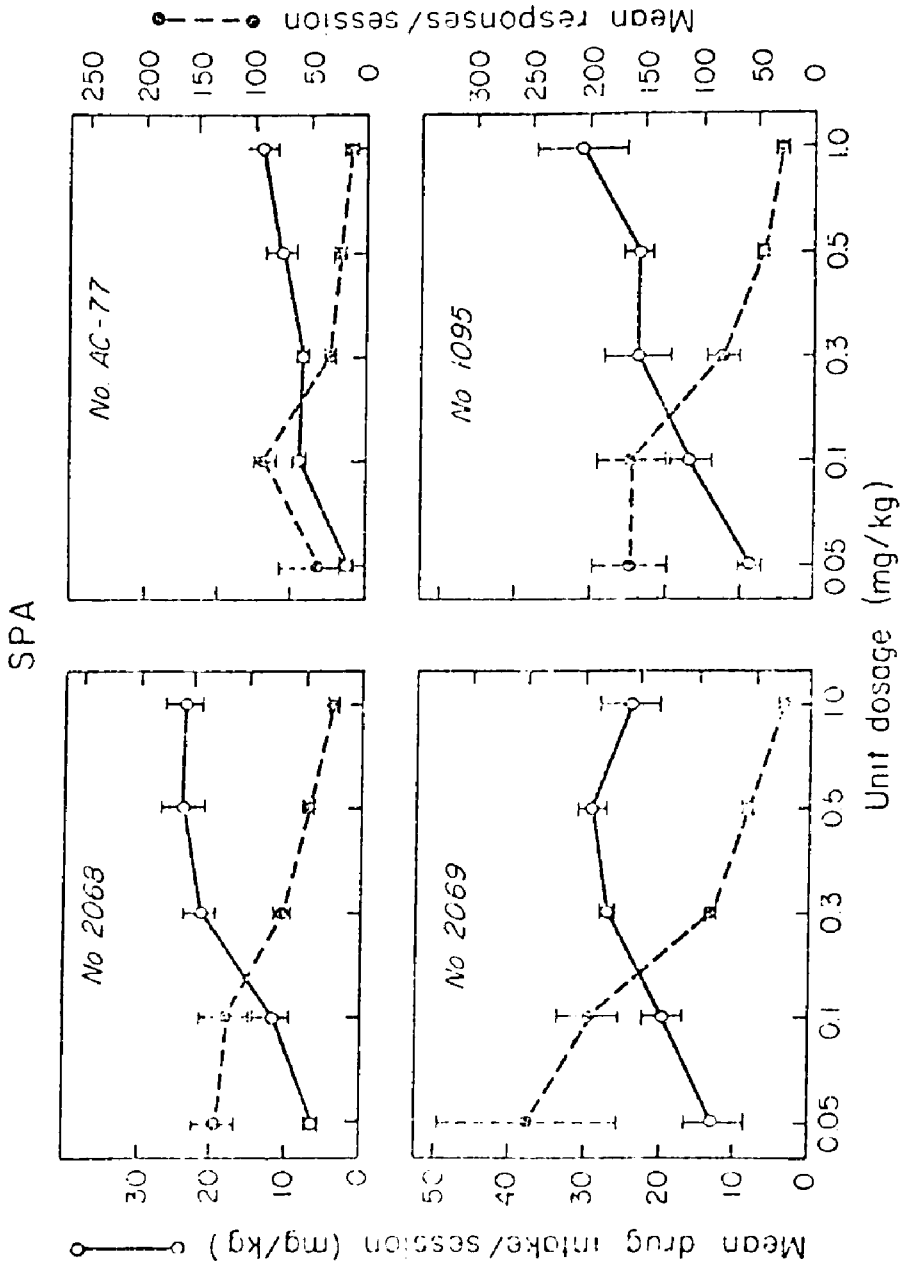

SPA
No AC-77
No 1095
No 2068
No 2069
Mean drug intake/session (mg/kg)
Mean responses/session
Unit dosage (mg/kg)
0.05
0.1
0.3
0.5
1.0

Figure 8. Selected session records at each unit dosage level of SPA studied in subject M1095. Each vertical line represents one response or one self-administration.

**Figure 8**

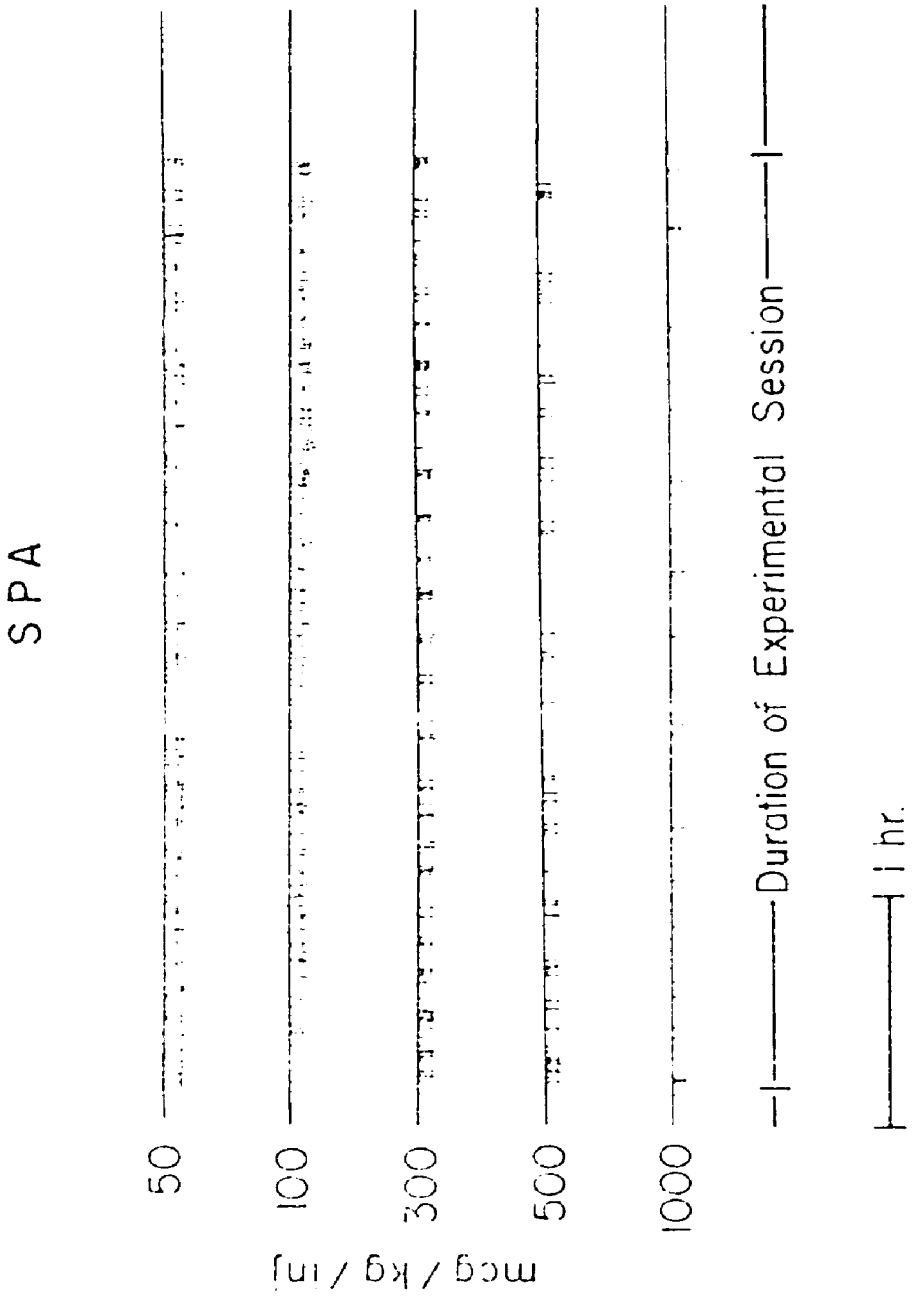
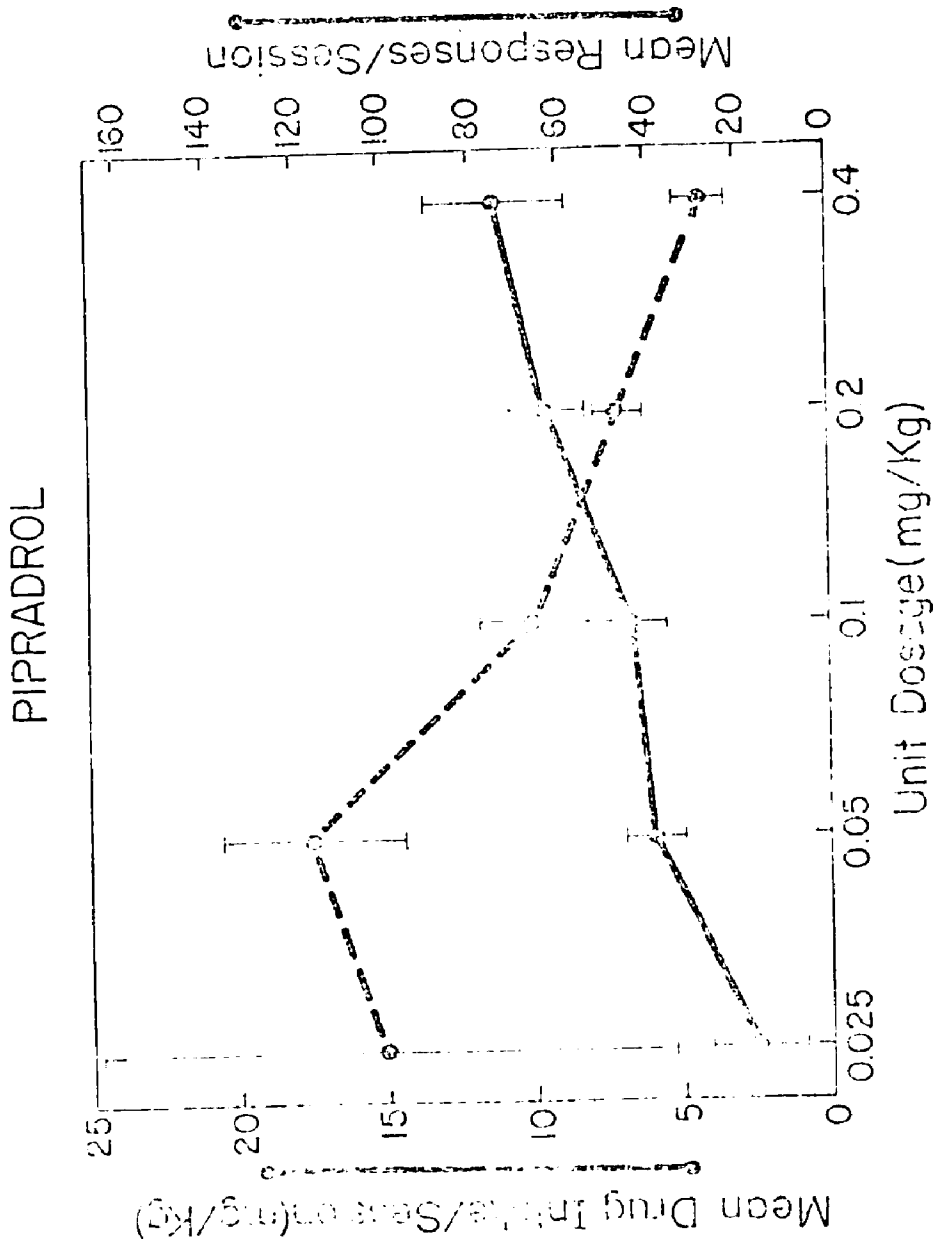

SPA
mcg / kg / inj
50
100
300
500
1000
Duration of Experimental Session
1 hr.

Figure 9. Mean number of responses per session (broken line) and mean drug intake per session (solid line) as functions of unit dosage of pipradrol hydrochloride. Each point represents the mean of data obtained from four subjects on days three through seven of exposure to each unit dosage level. Vertical lines represent the range.

Figure 9


PIPRADROL
Mean Responses/Session
160
140
120
100
80
60
40
20
0
Mean Drug Intake/Session (mg/Kg)
25
20
15
10
5
0
0.4
0.2
0.1
0.05
0.025
Unit Dosage (mg/Kg)

days three through seven of exposure to each unit dosage level. Vertical lines represent the range. Pipradrol was self-administered at unit dosage levels of 0.025-0.4 mg/kg. As the unit dosage was increased from 0.05 to 0.4 mg/kg, the mean number of responses per session decreased from 118 to 27. The large variability seen when the unit dosage was 0.025 is probably attributable to intersubject variability in the threshold reinforcing dose of pipradrol. Response rate variability decreased as the unit dosage increased. Mean drug intake per session increased from 5.8 to 11.2 mg/kg, as unit dosage was increased from 0.05 to 0.4 mg/kg. Therefore, there was only a two-fold increase in drug intake produced by an eight-fold increase in unit dosage. As occurred with SPA and cocaine, response rate was inversely proportional to unit dosage and total drug intake was almost independent of unit dosage at unit dosage levels shown to be reinforcing.

Figure 10 shows the same data plotted for individual subjects; group data was representative of individual data.

Figure 11 illustrates selected session records at each unit dosage level of pipradrol studied in subject M2176. Each vertical line represents one response or one self-administration. As the unit dosage of pipradrol was increased, response rate decreased and length of pausing after each reinforcement, i.e., self-administration, increased. Response rate at each unit dosage was fairly constant throughout the duration of the session; however, at the onset of the session, the rate was higher than at any other time during the session.

Figure 10. Mean number of responses per session (broken line) and mean drug intake per session (solid line) as functions of unit dosage of pipradrol hydrochloride. Each point represents the mean of data obtained from the last five days of exposure to each unit dosage level. Vertical lines represent the range.

**Figure 10**

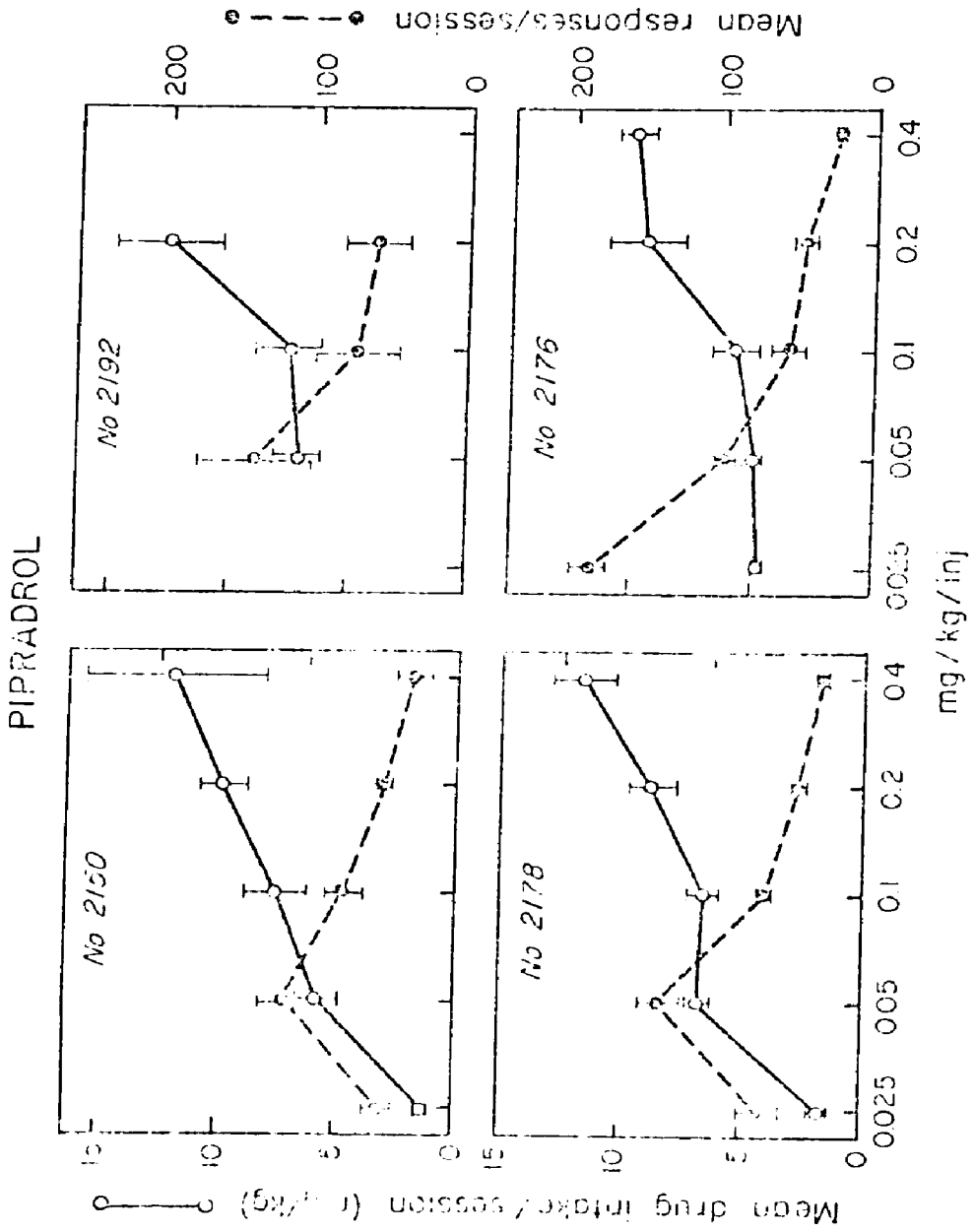
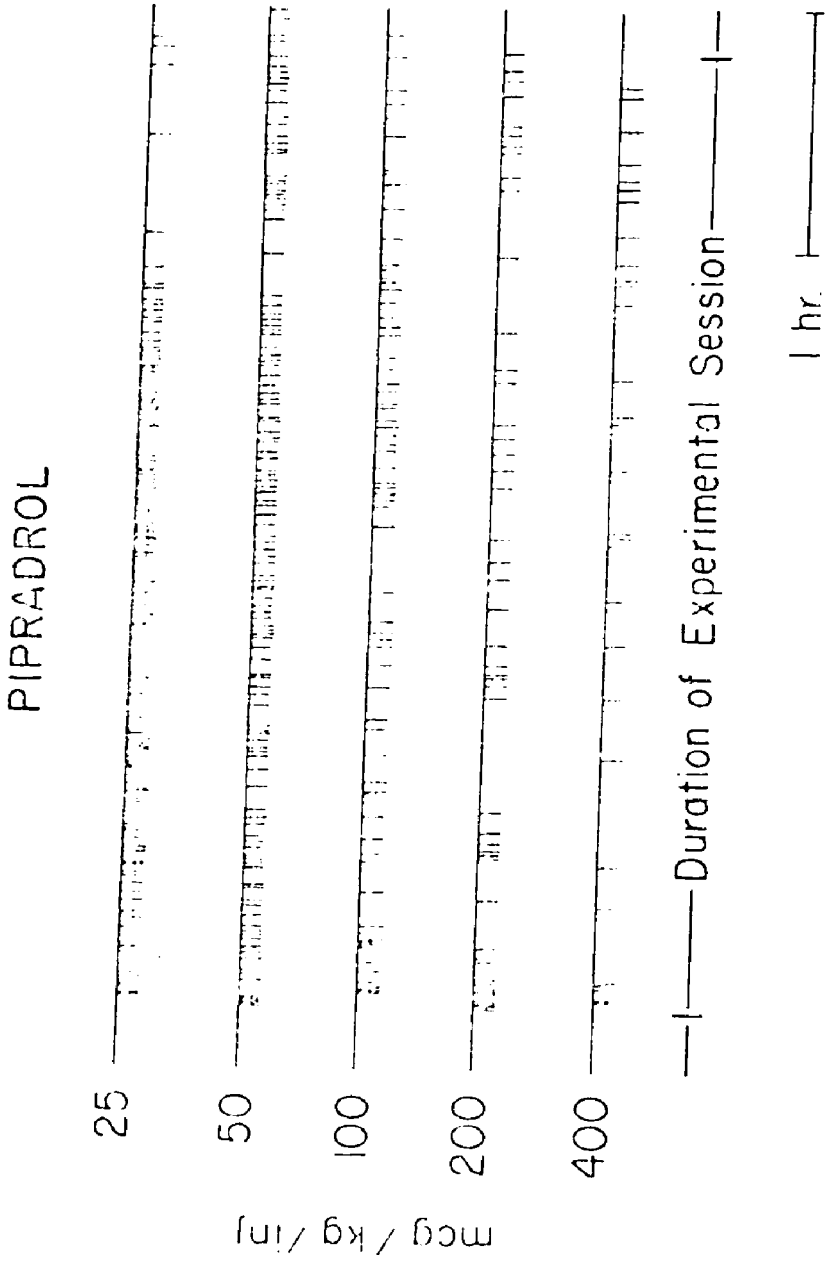

PIPRADROL
No 2192
No 2176
No 2150
No 2178
Mean responses/session
Mean drug intake/session
mg/kg/inj
0
100
200
0.0025
0.005
0.01
0.02
0.04
0.2
0.4
5
10
15

Figure 11. Selected session records at each unit dosage level of pipradrol studied in M2176. Each vertical line represents one response or one self-administration.

Figure 11


PIPRADROL
25
50
100
200
400
mcg / kg / inj
Duration of Experimental Session
1 hr.

Response rate and unit dosage were also inversely related in animals self-administering methylphenidate. Figure 12 illustrates the mean number of responses per session (broken line) and mean drug intake per session (solid line) as functions of the unit dosage of methylphenidate hydrochloride. Each point represents the mean of data obtained from three subjects on days three through seven of exposure to each unit dosage level. Vertical lines represent the range. As unit dosage increased from 0.025 to 0.4 mg/kg, mean responses per session decreased from 159 to 24. Variability in responding was greatest at the lowest unit dosage and decreased as unit dosage was increased. Mean drug intake per session increased from 4.1 to 8.7 mg/kg over this range of unit dosage. Drug intake then only doubled while unit dosage increased by a factor of sixteen.

Figure 13 shows the same data obtained from individual subjects. The grouped data is very representative of the individual data.

Figure 14 illustrates session records obtained from M2176 at each unit dosage level of methylphenidate studied. Increases in unit dosage produced a decrease in responding. Response rate at a given unit dosage, except for an initial higher rate at the start of the session, was fairly constant throughout the session. The pause in responding seen after each injection increased in length as the unit dosage was increased.

The results obtained with phenmetrazine self-administration are very comparable to those obtained with cocaine, SPA, methylphenidate and pipradrol. Figure 15 shows the mean number of responses per session (broken line) and mean drug intake per

Figure 12. Mean number of responses per session (broken line) and mean drug intake per session (solid line) as functions of unit dosage of methylphenidate hydrochloride. Each point represents the mean of data obtained from three subjects on days three through seven of exposure to each unit dosage level. Vertical lines represent the range.

Figure 12

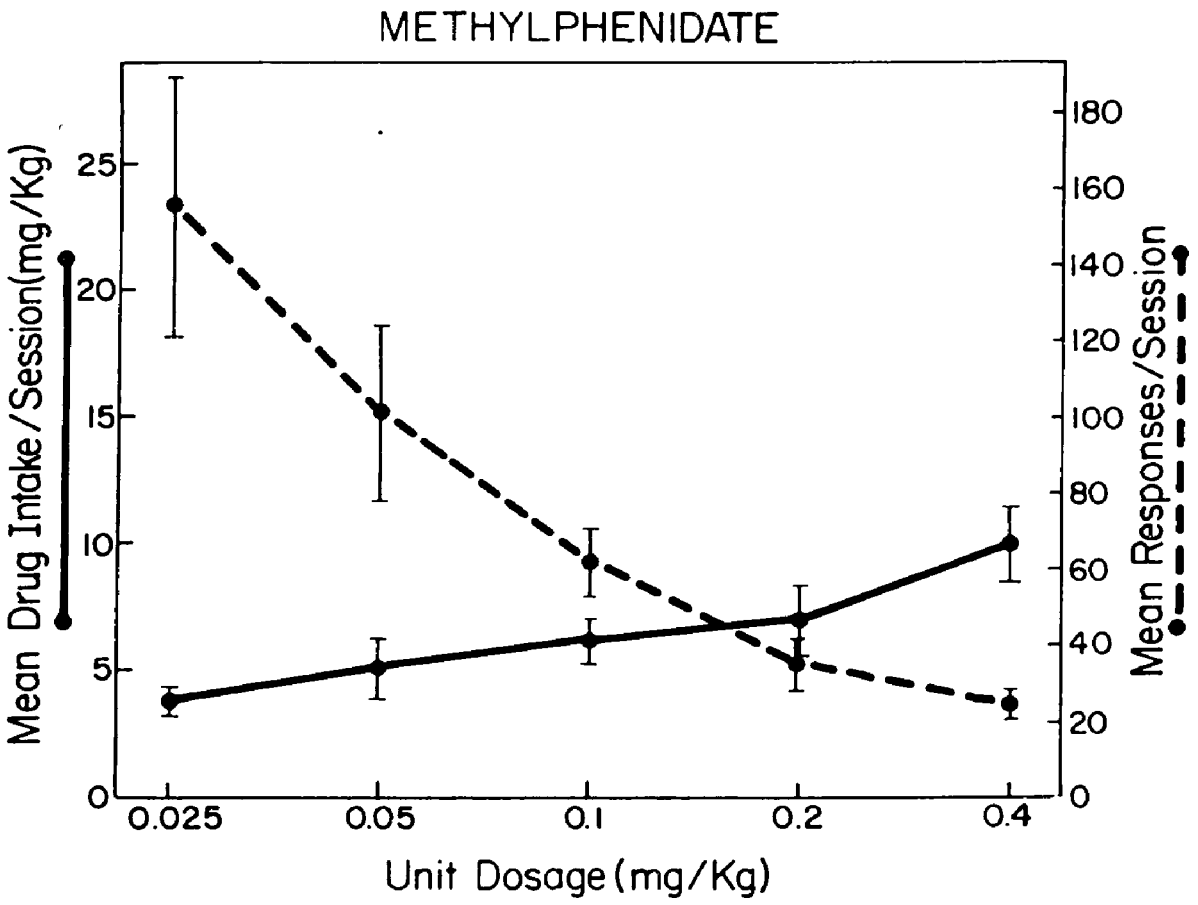

METHYLPHENIDATE
Mean Drug Intake/Session(mg/Kg)
Mean Responses/Session
Unit Dosage (mg/Kg)
0
5
10
15
20
25
0
20
40
60
80
100
120
140
160
180
0.025
0.05
0.1
0.2
0.4

Figure 13. Mean number of responses per session (broken line) and mean drug intake per session (solid line) as functions of the unit dosage of methylphenidate hydrochloride. Each point represents the mean of data obtained from the last five days of exposure to each unit dosage level. Vertical lines indicate the range.

Figure 13

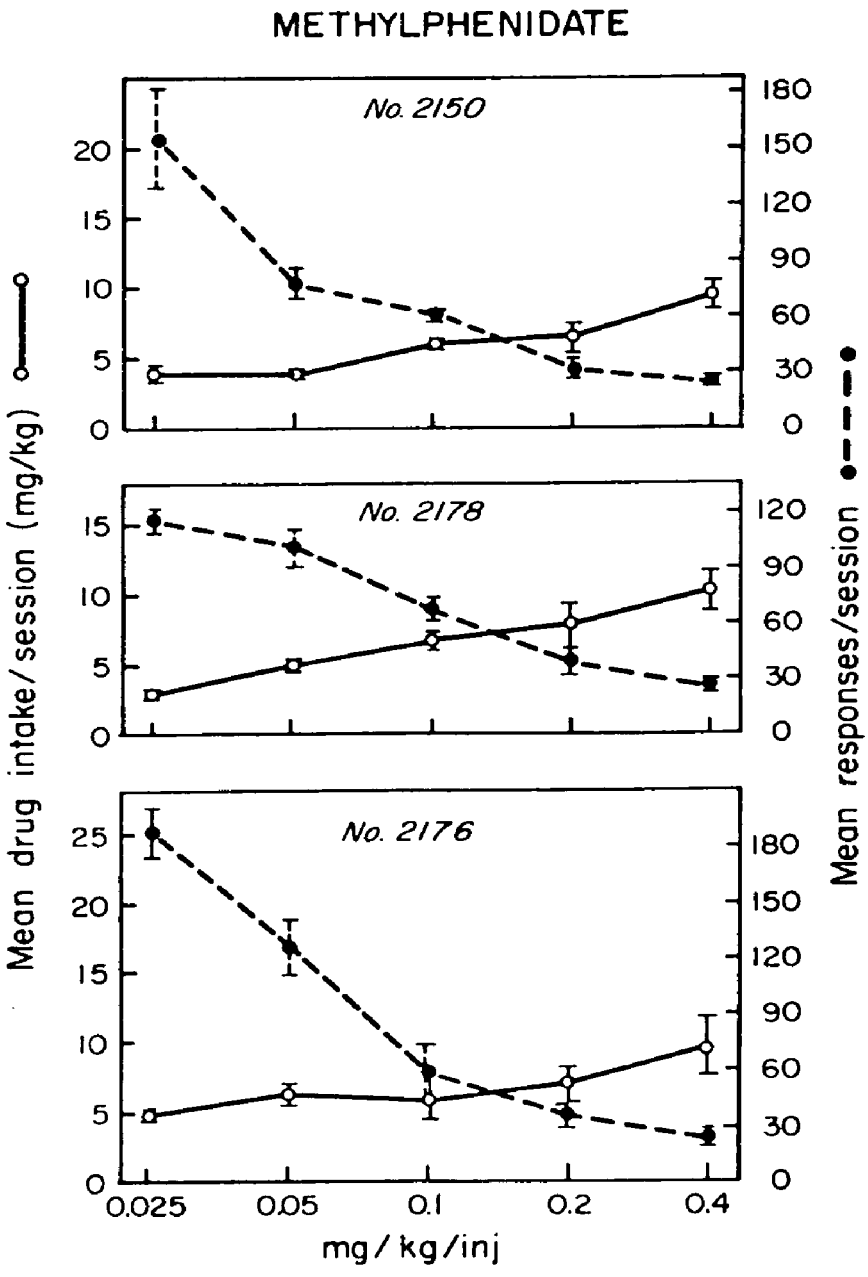

METHYLPHENIDATE
No. 2150
No. 2178
No. 2176
Mean drug intake/session (mg/kg)
Mean responses/session
mg/kg/inj
0.025
0.05
0.1
0.2
0.4

Figure 14. Selected session records at each unit dosage value of methylphenidate studied in M2176. Each vertical line represents one response or one self-administration.

Figure 14

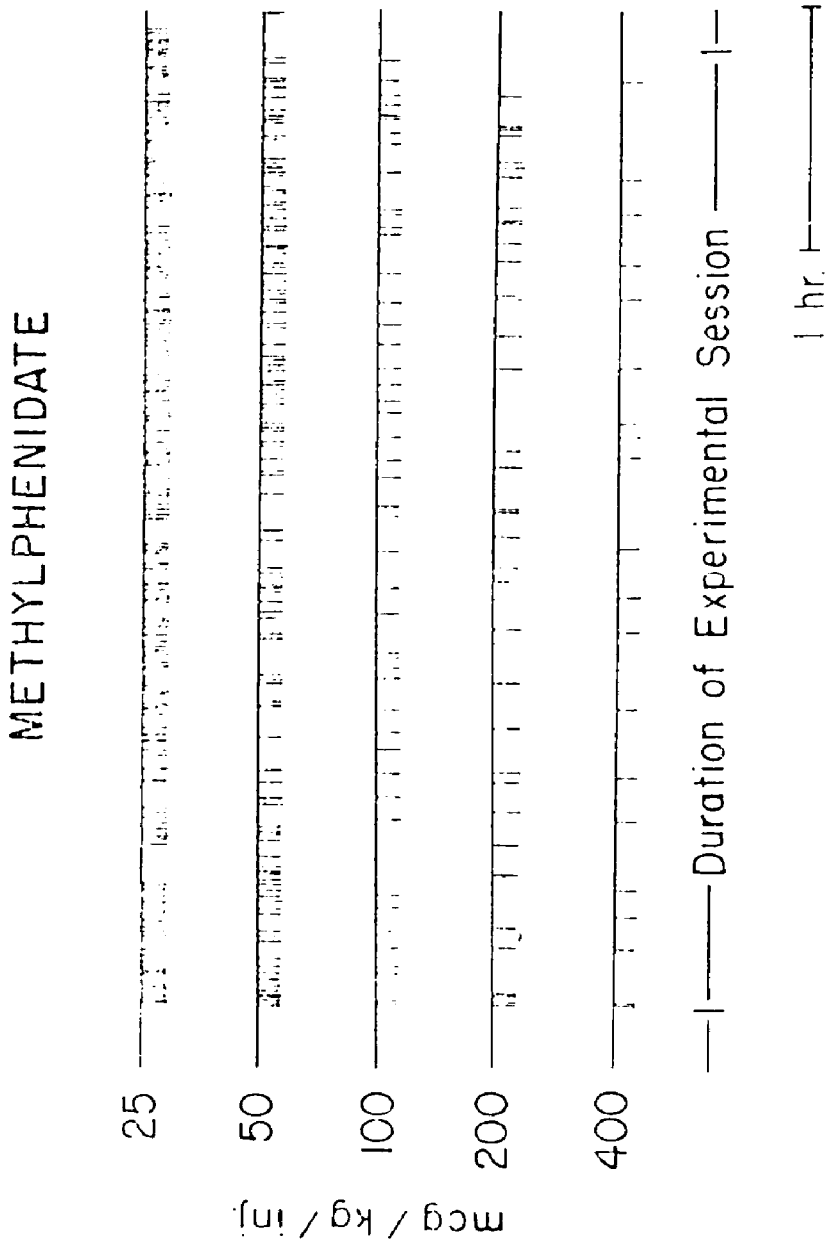
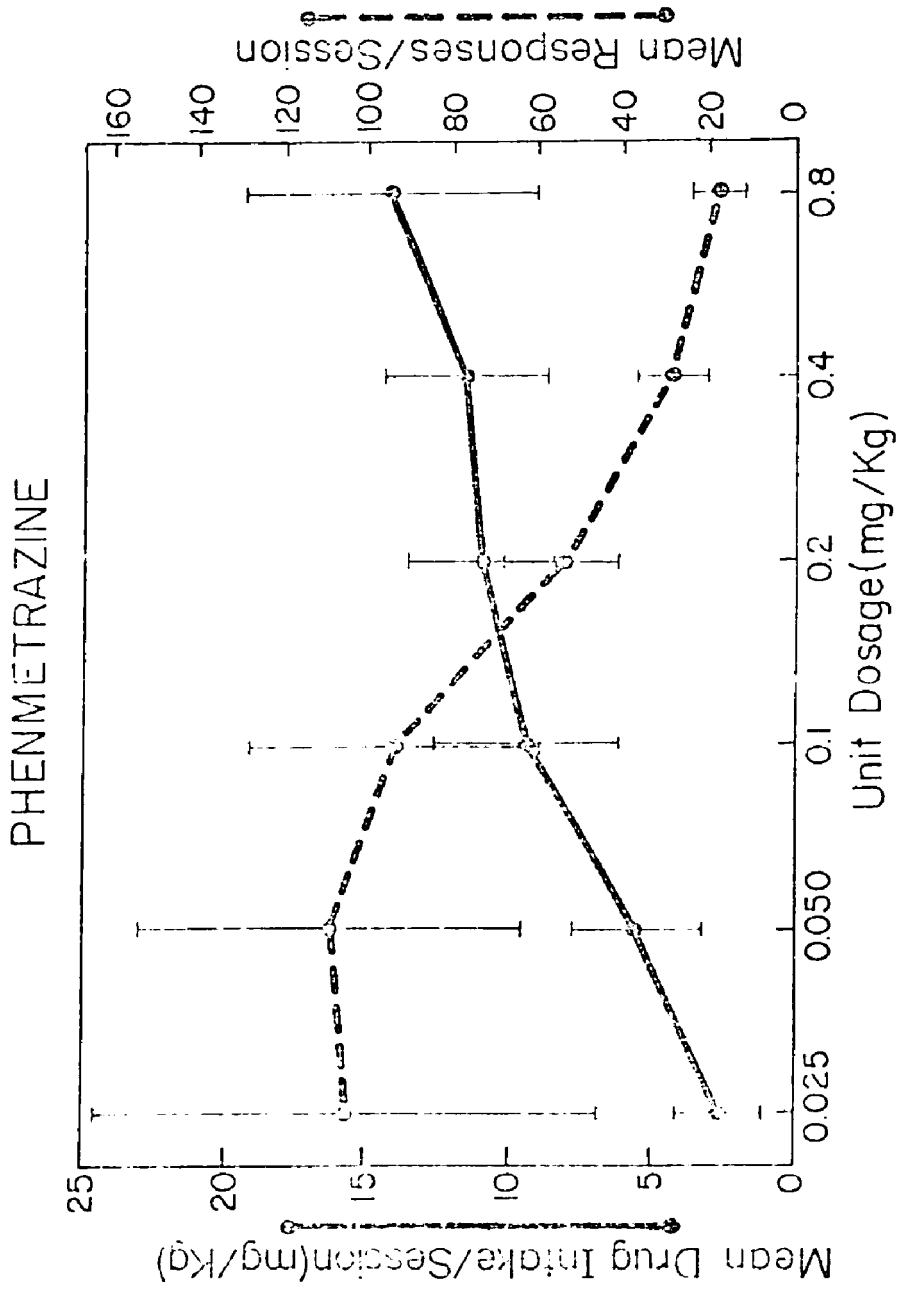

METHYLPHENIDATE
mcg / kg / inj.
25
50
100
200
400
Duration of Experimental Session
1 hr.

Figure 15. Mean number of responses per session (broken line) and mean drug intake per session (solid line) as functions of unit dosage of phenmetrazine hydrochloride. Each point represents the mean of data obtained from four subjects on days three through seven of exposure to each unit dosage level. Vertical lines represent the range.

Figure 15


PHENMETRAZINE
Mean Drug Intake/Session(mg/Kg)
Mean Responses/Session
Unit Dosage(mg/Kg)
0.025
0.050
0.1
0.2
0.4
0.8
0
5
10
15
20
25
0
20
40
60
80
100
120
140
160

session (solid line) as functions of the unit dosage of phenmetrazine hydrochloride. Each point represents the mean of data obtained from four subjects on days three through seven of exposure to each unit dosage value. Vertical lines represent the range. As the unit dosage is increased from 0.05 to 0.8 mg/kg, the mean number of responses per session decreased from 108 to 18. Mean drug intake per session over the same range of unit dosage only increased from 5.2 to 14.6 mg/kg. Therefore, although unit dosage had been increased by a factor of sixteen, there was only a three-fold increase in drug intake. As occurred with the other compounds, variability in responding was greatest at the lowest unit dosage. This variability decreased as unit dosage was increased.

The data from each subject is graphed separately in figure 16. Individual data very closely resembles the grouped data. As unit dosage is increased, lever-pressing behavior decreases and drug intake, after an initial increase, remains relatively constant in each subject.

Figure 17 illustrates selected session records at each unit dosage value of phenmetrazine studied in subject M2176. As unit dosage increased, the length of pausing after reinforcement, though regular, increased and the response rate decreased. Response rates were constant at a given unit dosage throughout the session following an initial burst of responding at the beginning of the session.

Figure 18 is a summary graph illustrating the relationship between unit dosage and the mean number of responses per session for all five of the psychomotor stimulants studied,i.e., cocaine,

Figure 16. Mean number of responses per session (broken line) and mean drug intake per session (solid line) as functions of unit dosage of phenmetrazine hydrochloride. Each point represents the mean of data obtained from the last five days of exposure to each unit dosage level. Vertical lines represent the range.

**Figure 16**

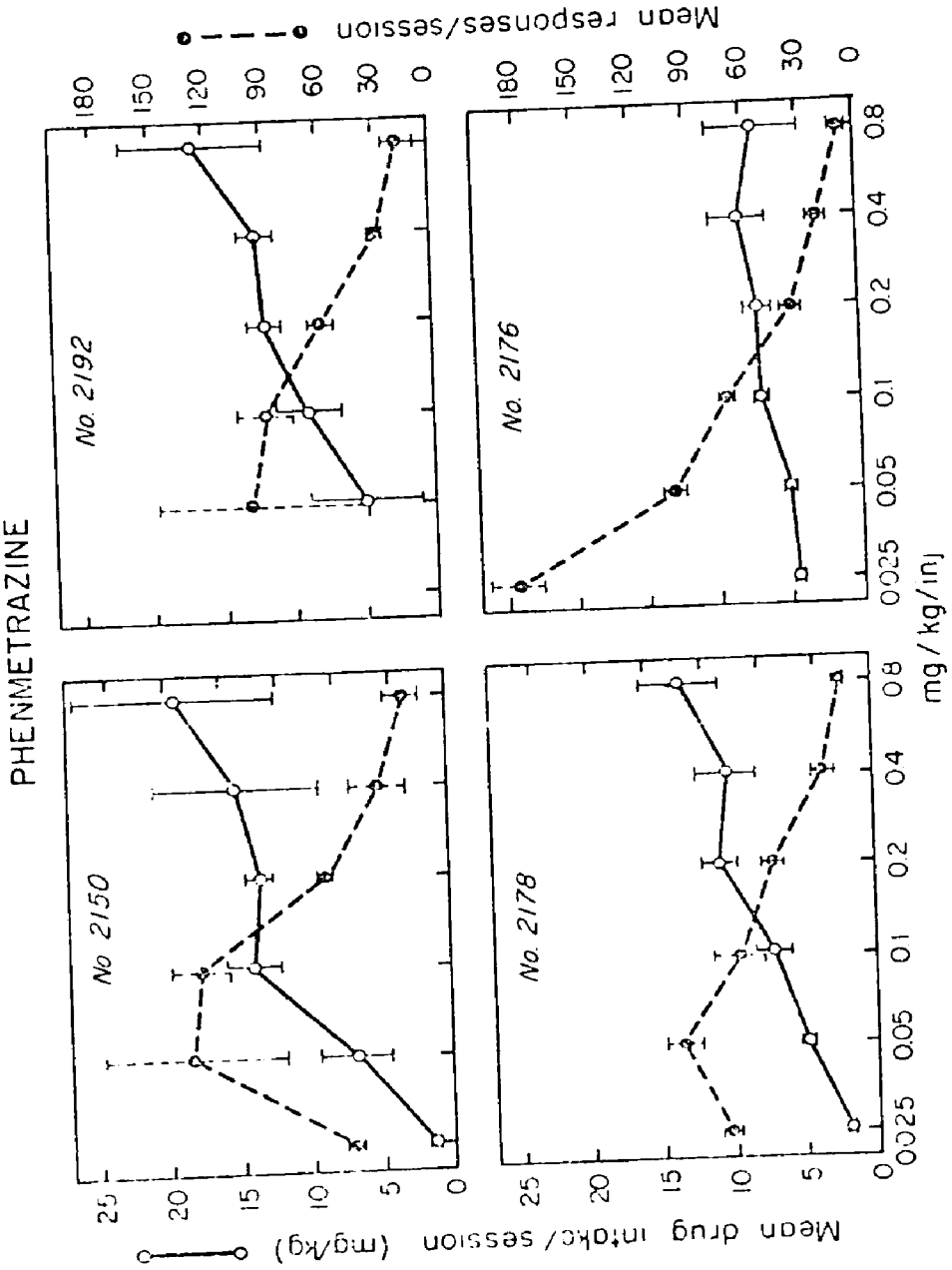

PHENMETRAZINE
Mean responses/session
Mean drug intake/ session (mg/kg)
mg / kg/ inj
No. 2192
No. 2176
No. 2150
No. 2178
180
150
120
90
60
30
0
25
20
15
10
5
0
0025
0.05
0.1
0.2
0.4
0.8

Figure 17. Selected session records at each unit dosage level of phenmetrazine studied in subject M2176.

Figure 17

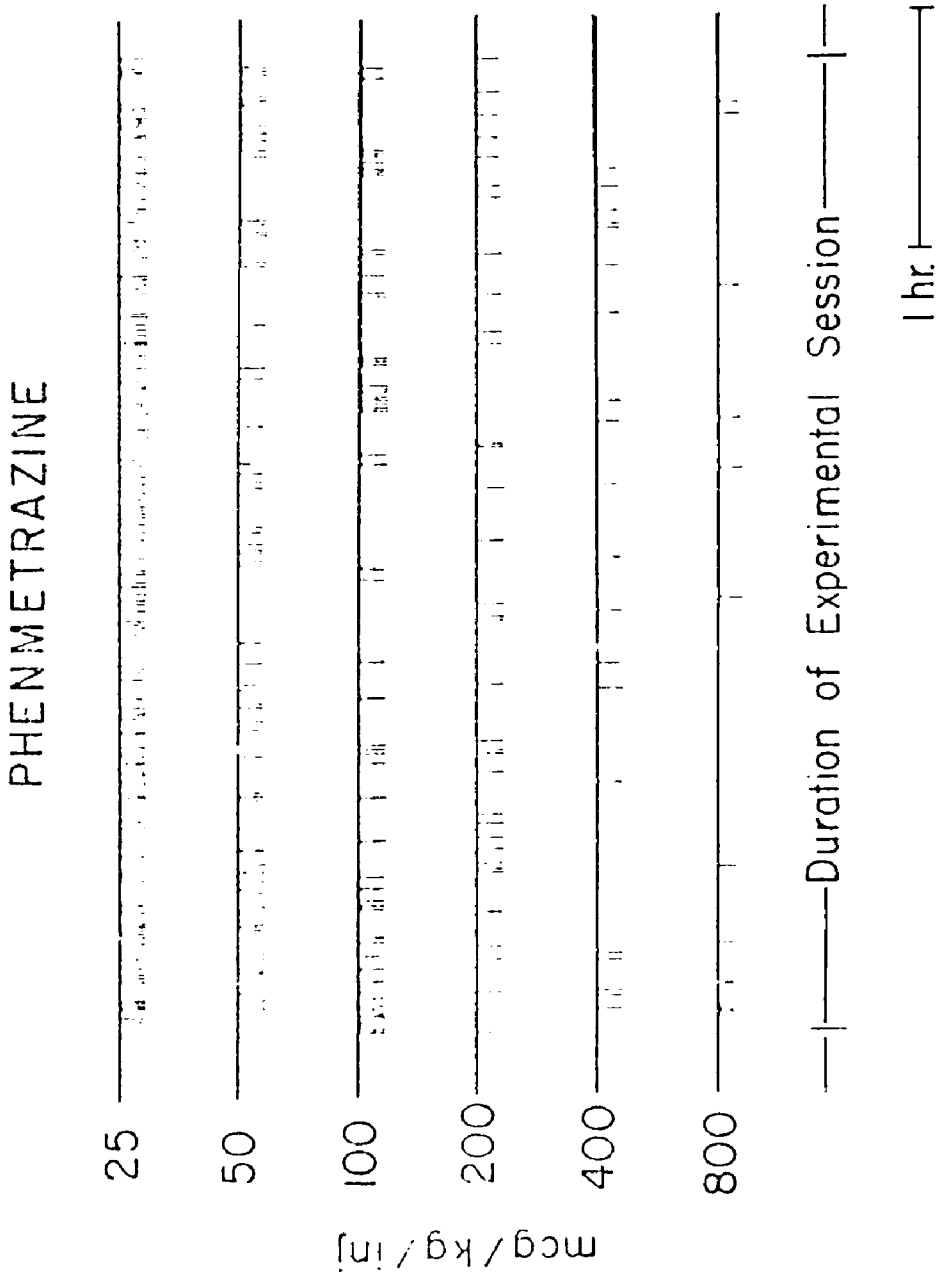
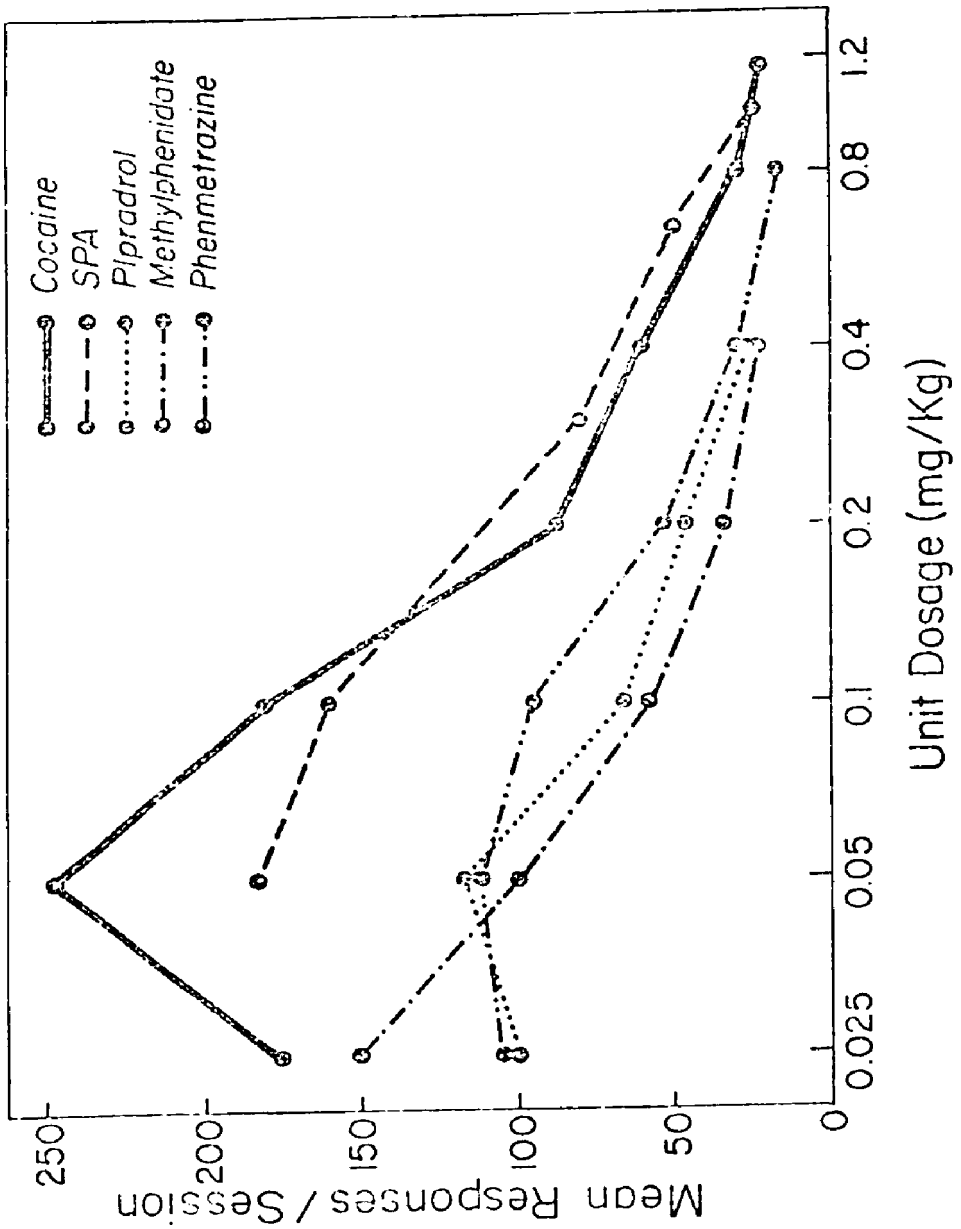

PHENMETRAZINE
25
50
100
200
400
800
mcg/kg/inj
Duration of Experimental Session
1 hr.

Figure 18. Mean number of responses per session as a function of unit dosage of cocaine hydrochloride, SPA hydrochloride, pipradrol hydrochloride, methylphenidate hydrochloride and phenmetrazine hydrochloride.

Figure 18


Cocaine
SPA
Pipradrol
Methylphenidate
Phenmetrazine
Mean Responses / Session
250
200
150
100
50
0
0.025
0.05
0.1
0.2
0.4
0.8
1.2
Unit Dosage (mg/Kg)

SPA, pipradrol, methylphenidate and phenmetrazine. The number of responses per session decreased with increases in unit dosage with all of these compounds. At every unit dosage, the number of responses per session was higher with cocaine or SPA self-administration than with methylphenidate, pipradrol, or phenmetrazine self-administration.

Figure 19 is a summary graph which illustrates the relationship between mean drug intake per session and unit dosage which occurred with cocaine, SPA, pipradrol, methylphenidate and phenmetrazine self-administration. As the unit dosage of these compounds was increased from 0.025 to 0.1 mg/kg, the amount of drug self-administered per session increased. However, further increases in unit dosage produced little change in daily drug intake. At these unit dosages, drug intake was independent of unit dosage. At any given unit dosage, more cocaine or SPA was self-administered per session than phenmetrazine, pipradrol or methylphenidate.

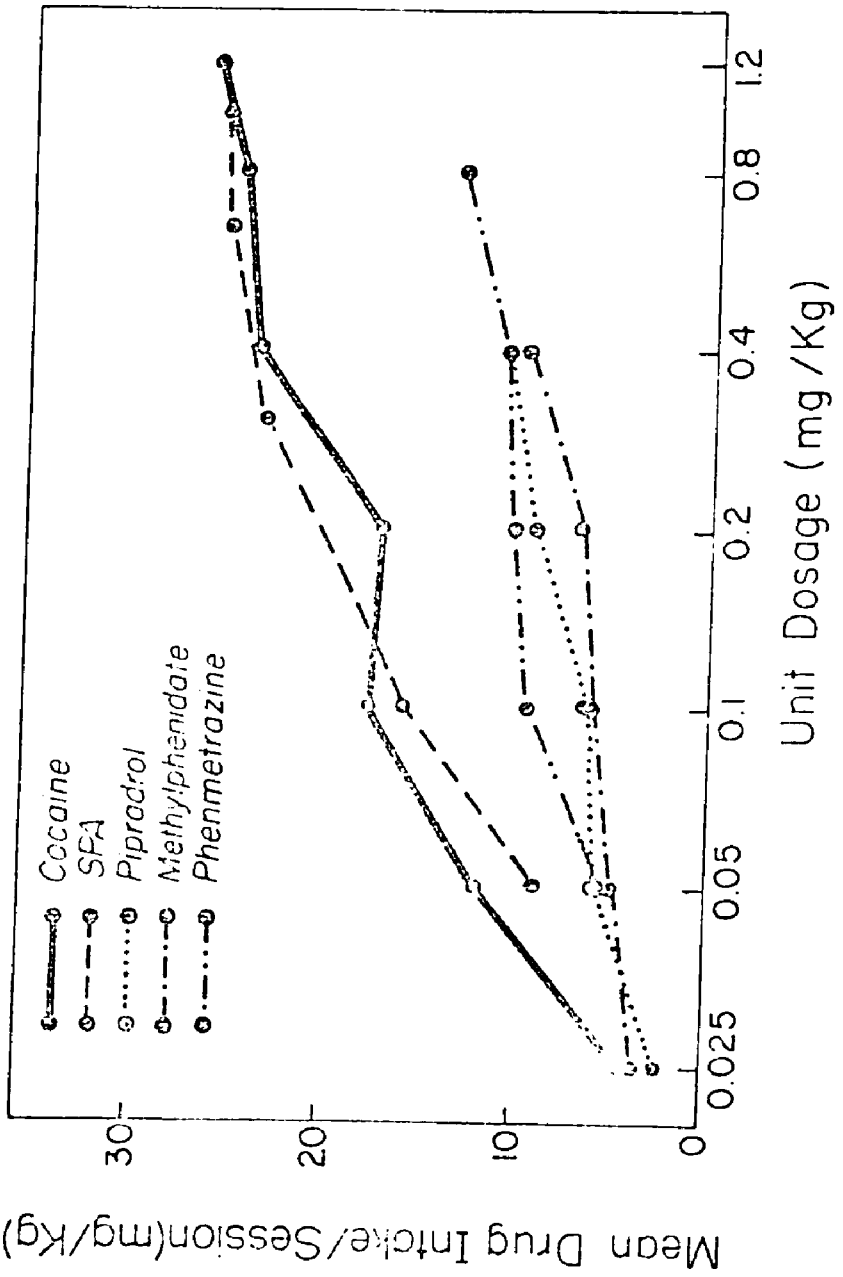
## D. DISCUSSION

The results of this study demonstrate that the magnitude of reinforcement, i.e., unit dosage, is a primary determinant of the frequency of lever-pressing behavior in Rhesus monkeys self-administering cocaine, SPA, methylphenidate, pipradrol and phenmetrazine. Pickens and Thompson[154], Pickens et. al.[148], and Pickens and Harris[152], have shown that a similar inverse relationship between magnitude of reinforcement and response rate exists in rats self-administering cocaine, methamphetamine, and d-amphetamine.

However, across a wide range of unit dosages, magnitude of reinforcement was not an important determinant of daily drug intake.

Figure 19. Mean drug intake per session as a function of unit dosage of cocaine hydrochloride, SPA hydrochloride, methylphenidate hydrochloride, pipradrol hydrochloride and phenmetrazine hydrochloride.

Figure 19


Mean Drug Intake/Session(mg/Kg)
0
10
20
30
0.025
0.05
0.1
0.2
0.4
0.8
1.2
Unit Dosage (mg/Kg)
Cocaine
SPA
Pipradrol
Methylphenidate
Phenmetrazine

Daily drug intake was independent of unit dosage. It has been shown by Woods and Schuster[218] that the mean daily intake of SPA or cocaine is very stable at a given unit dosage, i.e., variability never exceeded ±10%. Their data suggested that some mechanism was involved in regulating or limiting drug intake; the results of this present study also tend to implicate such a system.

Pickens and Thompson[154] have demonstrated in rats self-administering cocaine that total daily drug intake was independent of the magnitude of reinforcement. These authors demonstrated that the same relationship exists in rats working for food pellets. The number of pellets obtained was constant; whereas the number of responses decreased or increased with increases or decreases in the magnitude of reinforcment, i.e., number of pellets received per response.

It appears that subjects self-administering psychomotor stimulants adjust their response rate accordingly when changes are made in unit dosage, so that the end result is the self-administration of a given amount of a psychomotor stimulant daily. One could argue that a central regulatory mechanism exists similar to those which control the self-administration of other reinforcers, e.g., food and water.

Another possible explanation of this result may be that after a given amount of a psychomotor stimulant is administered, all on-going behavior or reinforcement-seeking behavior is suppressed. It has been frequently demonstrated that large doses of psychomotor stimulants decrease responding in a variety of behavioral tasks in which reinforcers other than drugs were used. Pickens and

Thompson[154] demonstrated that an IV infusion of cocaine completely disrupted lever-pressing behavior in rats working on a FR-10 schedule of food reinforcement. The duration of this disruption was directly related to the amount of cocaine infused. The pattern of responding for psychomotor stimulants by the monkeys lends credence to this explanation. The initial burst of responding at the onset of the session may result in the administration of a sufficient quantity of drug to interfere with additional drug seeking behavior. As soon as some of the drug is metabolized, one would expect the animal to again initiate lever-pressing behavior, which he does. This cycle would then be repeated throughout the duration of the session. As the unit dosage was increased, the length of the pause after each injection increased. This may occur because more time is required for the drug present in each injection to be metabolized.

Another possible explanation for these results would be that these compounds may produce aversive effects when a sufficient amount has been self-administered. Further injections would result only in increased aversive effects, so the subject refrains from self-administering these compounds until a sufficient amount of the drug is metabolized, thereby reducing the aversiveness. The subjects now self-administer more of the compound until this aversive level is again reached. This cycle would then be repeated throughout the session.

The dose level at which this aversive effect or behavioral disrupting effect occurs varies with the psychomotor stimulant in question. Perhaps smaller amounts of phenmetrazine, pipradrol, or methylphenidate are required to produce aversive effects,

or behavioral disruption, than of cocaine or SPA. Maybe this is the reason why more cocaine or SPA is self-administered on a mg/kg basis than phenmetrazine, methylphenidate, or pipradrol.

Plutchik et. al.[156] have shown that a similar relationship may exist between current intensity and self-stimulation rates in rats. Depending upon the location of implanted electrodes, there is an increase in self-stimulation rates with increases in current intensity; however, with further increases in intensity, self-stimulation behavior decreases. Perhaps, with increasing intensity of stimulation, "punishment" areas of the brain in close proximity to these "reward" areas become stimulated, thereby decreasing the reinforcing effect of brain stimulation. This may be analogous to the hypothesis that aversive effects are produced by psychomotor stimulants when a sufficient quantity is administered, and it is these aversive effects which limit the amount of psychomotor stimulants which are self-administered.

This study, then, has demonstrated three important facts. One, monkeys will self-administer cocaine, SPA, pipradrol, methylphenidate, and phenmetrazine. Two, the magnitude of reinforcement, i.e., unit dosage, and the rate of responding in self-administering these compounds, is inversely related. Three, total daily drug intake is independent of unit dosage over a wide range of unit dosages. This indicates that the subjects can compensate, via some mechanism, for changes in unit dosage so that daily drug intake remains stable, even after large changes in unit dosage.

## III. COCAINE INTAKE AS A FUNCTION OF THE SCHEDULE OF REINFORCEMENT.

### A. INTRODUCTION

The results of the previous study demonstrated that one of the reinforcement factors which influenced the rate of responding for psychomotor stimulants was the magnitude of reinforcement. A second important variable which may influence this rate of responding is the schedule of reinforcement. A schedule of reinforcement may be defined without reference to its effect on behavior. Therefore, a response may be reinforced on the basis of the time which has elapsed since the preceding reinforcement, i.e., interval schedule, or on the basis of the number of responses which have been emitted since the preceding reinforcement, i.e., ratio schedule. A given schedule may be fixed, or it may vary either at random or according to some plan. Therefore, four major types of schedules of reinforcement exist: fixed ratio, variable ratio, fixed interval, and variable interval.[65] The experiments described in the previous section were conducted using a fixed ratio one (FR-1), sometimes called a continuous reinforcement (CRF) schedule of reinforcement, i.e., reinforcement was presented after each lever-pressing response emitted during the illumination of a stimulus light.

The effect of altering the schedule of reinforcement on drug self-administration behavior in animals has received little attention. Those studies which have been conducted utilizing intermittent schedules of reinforcement have usually involved fixed ratio schedules. Weeks[204], Weeks and Collins[205], and

Collins and Weeks[40], have studied the effect of changing fixed ratio values on opiate self-administration in rats. These authors found that increasing the fixed ratio schedule from 1 to 400 produced a decrease in the amount of the opiate self-administered. However, in many instances the total opiate intake did not decrease significantly until the FR value approached 50. Running rates, i.e., time from first response to nth response on a FR-N schedule, increased with increases in the FR value. Latencies, i.e., time from previous reinforcement until emission of first response or post-reinforcement pause, also increased with increases in FR value. Regardless of the nature of the reinforcer, latencies tend to increase with increases in FR value.[65]

Pickens et. al.[148], Pickens and Thompson[154], and Pickens and Harris[152], have explored fixed ratio schedules in studies involving methamphetamine, cocaine, and d-amphetamine self-administration in rats. These authors varied fixed ratio values from one to eighty. When the FR value was increased, i.e., more responses must be emitted to obtain reinforcement, the subjects showed proportional increases in the frequency of responding. The result was that about the same amount of drug was self-administered at each ratio value. Fixed ratio performance was characterized by long post-reinforcement pauses, followed by a high response rate terminating with drug infusions. These pauses were related to the ratio value. Also, overall response rate varied directly with the size of the ratio over a considerable range of ratio values. Therefore, the rate of responding for psychomotor stimulant administration in the rat varies

inversely as a function of the magnitude of reinforcement and directly as a function of the value of a fixed ratio schedule of reinforcement.

The purpose of this study was to ascertain if the latter relationship occurs with monkeys, as does the former. If total drug intake remains relatively constant with large increases in FR value, then one must assume that either a drug effect or central regulatory system is functioning to limit the amount of a psychomotor stimulant which the subject self-administers.

B. METHODS

1. Subjects. The subjects for this experiment were two adult Rhesus monkeys which had never previously been used in any drug experiment. The animals weighed 4.2 and 4.9 kg. Chronic indwelling jugular catheters were implanted in their internal jugular veins after they had adjusted to their new laboratory environment.

2. Apparatus. The subjects were housed in individual completely enclosed cubicles. These cubicles were identical to those described in the studies on magnitude or reinforcement, except that an aluminum door had been attached to the front of the cubicle. The door was added to provide more rigid control of the subjects' environment and therefore minimize disruption of the subjects' behavior due to actions of laboratory personnel and of other animals housed in the laboratory. The subjects were restrained by a stainless steel harness and arm. A stimulus light, lever and water spout were mounted on a stainless steel panel which was located on the rear wall of the cubicle.

Illumination of the stimulus light occurred when the subject had access to cocaine or, initially, saline. The subjects' task was to depress the lever a given number of times, which was determined by the schedule of reinforcement being studied while the stimulus light was on. This behavior resulted in the intravenous administration of 0.2 mg/kg of body weight of cocaine hydrochloride. Cocaine solutions were replaced every third day to protect against loss of potency due to decomposition.

Lever-pressing was recorded on a Gerbrands Cumulative Recorder. Programming and recording equipment were located in another room adjacent to the room in which the subjects were tested.

Both subjects had unlimited access to water and were fed 10-15 Purina Monkey Chows twice daily, at 8:00 a.m. and 4:00 p.m. All cubicles were cleaned every four hours by means of an automatic cage washing system.

3. General procedure. Following catheterization, the subjects were returned to their experimental cubicles. The stimulus light was turned on and remained on for 12 hours each day for seven days. The light was turned on and off at the same time each day. Every lever press made during this twelve-hour session resulted in the intravenous administration of 0.2cc/kg of physiologic saline. Each injection cycle lasted from 45-60 seconds, depending on the subject's weight; during this time the stimulus light was turned off and lever-pressing had no consequence. The cumulative recorder was also stopped during this injection cycle or time-out period. Following the determination of each subject's

lever-pressing response frequency for saline, a 1.0mg/cc solution of cocaine hydrochloride was substituted for saline. Following this substitution, each lever press resulted in the administration of 0.2mg/kg of cocaine hydrochloride.

Both subjects initiated lever-pressing behavior for cocaine within three days. The drug access period was then reduced to two hours per day. For subject M2161, the period was 10:00 a.m. to 12:00 noon, and for subject M2143, it was from 1:00 p.m. to 3:00 p.m. This was done to reduce any toxic effects resulting from cocaine administration and secondly to provide a stable baseline of daily cocaine intake. After this stable baseline was established, the effect of changing the schedule of reinforcement on this baseline was determined. Only a fixed ratio schedule of reinforcement was used in this study. The value of the schedule was progressively changed from FR-1 (CRF) to FR-10, to FR-25 and to FR-50 at seven-day intervals. The volume and dose of cocaine in each injection was kept constant throughout the study. Latencies, i.e., elapsed time from illumination of stimulus light after previous reinforcement until emission of first lever pressing response, and running rates, i.e., rate of responding during period from first to last respone of a ratio, were recorded for each completed ratio, i.e., self-administration. Only the data obtained from the last five days of exposure to each ratio value were used to demonstrate the results; median latencies and median running rates were obtained from each session, and the mean of these values was used in expressing the results. Medians, rather than means, were used because a very long latency or running rate would heavily influence the means, but not the

medians. Therefore, since this data was asymmetric or skewed, medians were used for data analysis.

C. RESULTS

Figure 20 illustrates cumulative response records of selected sessions from monkey 2143. Each vertical mark on the horizontal line beneath each session record represents one injection or reinforcement. The effect of increasing the FR value from one to fifty on the pattern of responding for cocaine at a unit dosage of 0.2 mg/kg is readily seen. Rate of responding throughout the session increased with increases in ratio value. Latencies or post-reinforcement pause seemed to decrease with increases in ratio value, and running rates increased with increases in ratio value. However, the rate at which the animal self-administered cocaine throughout the session did not change. Following an initial burst of self-administering cocaine, the rate of drug administration was relatively constant throughout the session. Therefore, it appears that, over the values we studied, daily cocaine intake is independent of the value of a fixed ratio schedule of reinforcement. However, rate of responding was a direct function of FR value.

Figure 21 illustrates the relationship between mean cocaine intake per session and the value of the FR schedule of reinforcement. In subject M2161, mean cocaine intake decreased from 8.1 mg/kg to 4.7 mg/kg as the ratio value was increased from 1 to 50; however, the decrease was only from 8.1 to 6.6 mg/kg as the ratio value was increased from 1 to 25. This is only a small decrement in intake when one considers that the subject would

Figure 20. Cumulative response recorders of selected sessions from monkey 2143 showing the effect of increasing the FR value of a fixed ratio schedule of reinforcement on the rate of responding for cocaine hydrochloride (0.2 mg/kg/injection). Each vertical line beneath each response record indicates an injection.

Figure 20

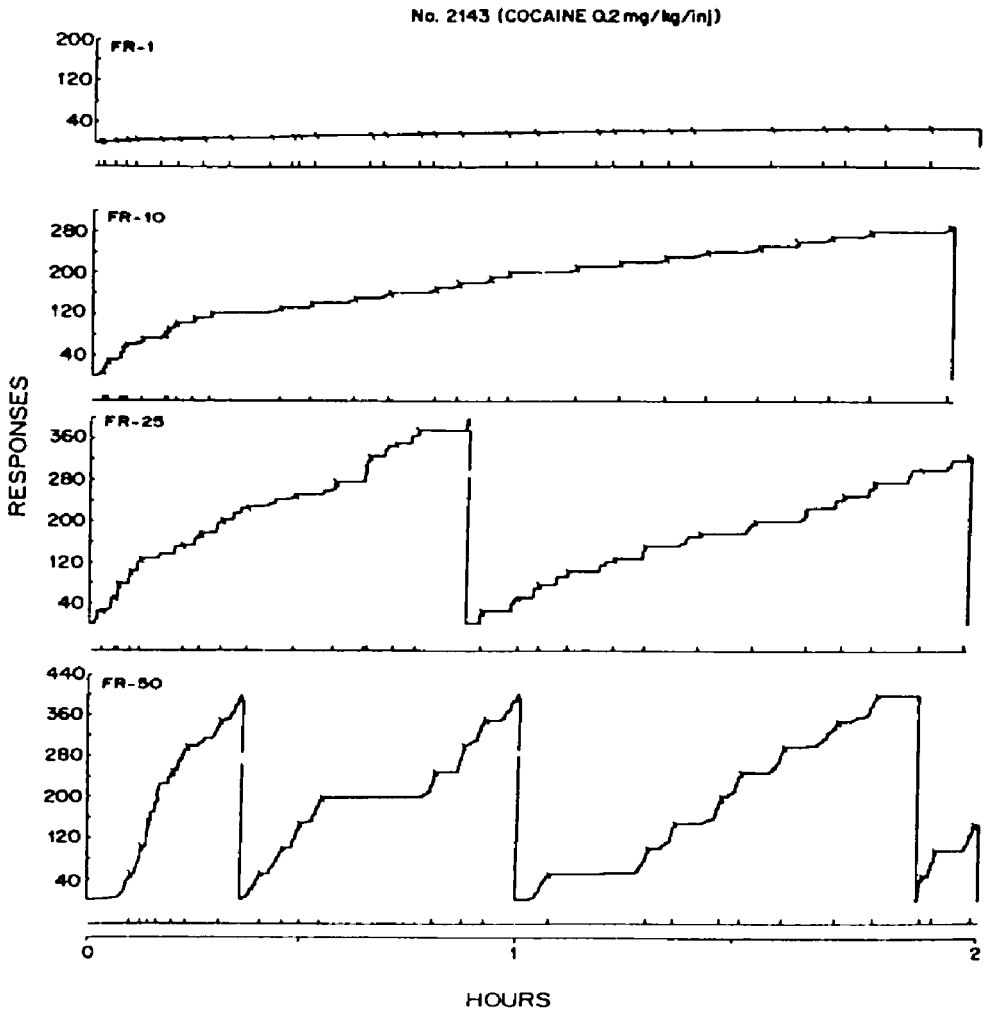
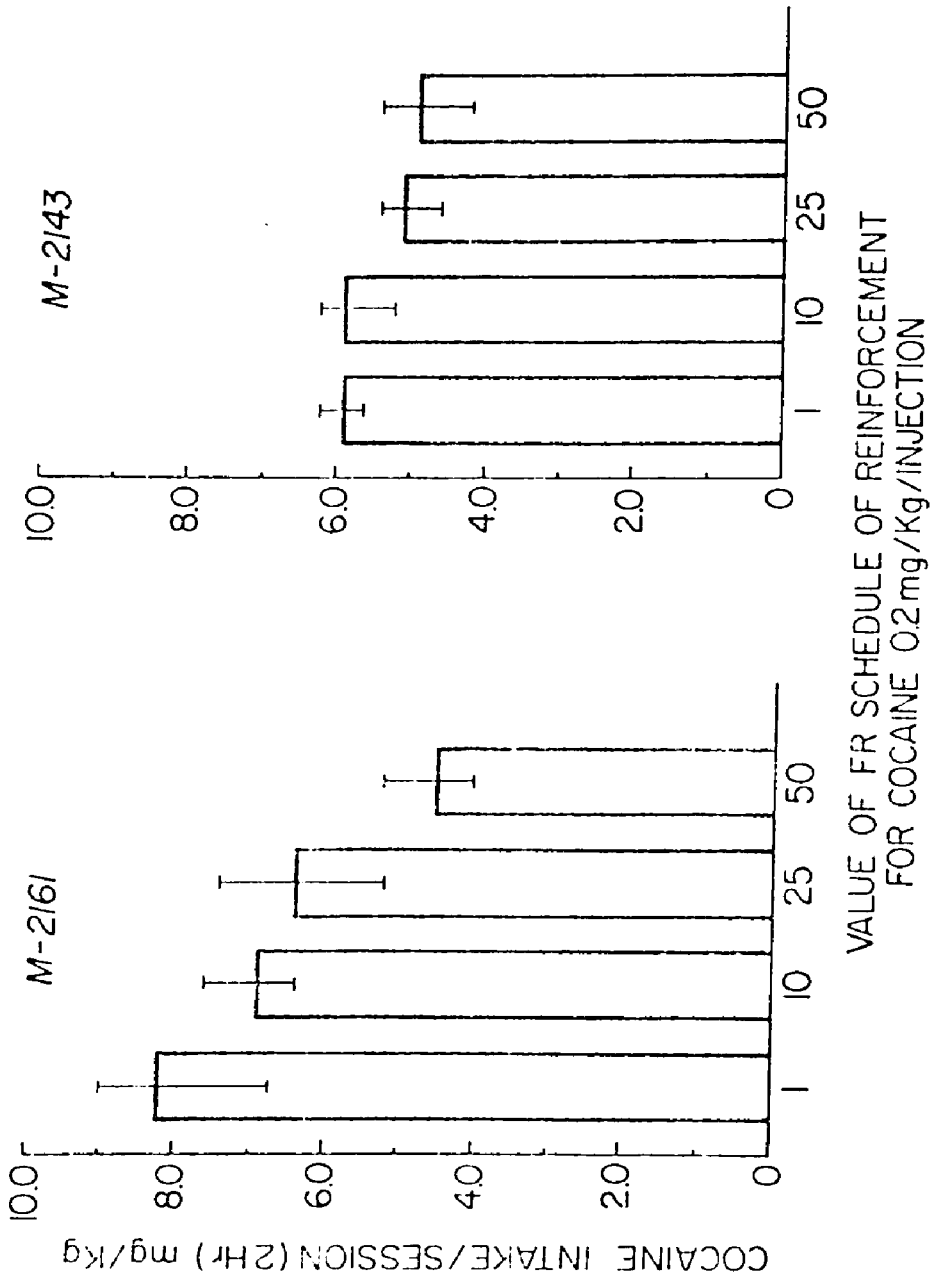

No. 2143 (COCAINE 0.2 mg/kg/inj)
FR-1
FR-10
FR-25
FR-50
RESPONSES
HOURS
200
120
40
280
360
440
0
1
2

Figure 21. Cocaine intake per session as a function of the value of the fixed ratio schedule of reinforcement for subjects M2161 and M2143. The height of the vertical bars represents the mean value obtained from five sessions at each ratio value. Superimposed vertical lines indicate the range.

Figure 21


M-2143
M-2161
COCAINE INTAKE/SESSION (2Hr) mg/kg
10.0
8.0
6.0
4.0
2.0
0
1
10
25
50
VALUE OF FR SCHEDULE OF REINFORCEMENT
FOR COCAINE 0.2mg/Kg/INJECTION

have had to increase his responding 25-fold to maintain normal intake. In subject M2143, cocaine intake and FR value were almost independent. Cocaine intake decreased from only 5.8 to 5.1 mg/kg, even though the ratio value increased by a factor of fifty. Therefore, these subjects compensated for increases in ratio value by increasing their response rates. The end result is that cocaine intake was kept fairly constant.

Figure 22 illustrates the relationship between running rate and fixed ratio value when cocaine administration served as the reinforcement. Running rates increased with increases in ratio value in both subjects; however, the increase was more pronounced in M2161. M2161's running rate more than doubled, whereas M2143's running rate did not increase to this extent. M2161's running rate was higher for all ratio values investigated than M2143's.

Figure 23 shows the relationship between latencies and the value of a fixed ratio schedule of reinforcement in these same two subjects. In subject M2161, the mean latencies increased from 42 secs. at FR-1 to 138 secs. at FR-50. However, opposite results were seen in M2143. Mean latency at FR-1 was 124 seconds and this decreased to 72 seconds as the FR value was increased from one to fifty. There was little change in the mean latency value in both subjects, though, with increases in FR value from one to ten.

Figure 22. Mean of median running rates in responses per second as a function of the value of a fixed ratio schedule of reinforcement for cocaine (0.2 mg/kg/injection) in subjects M2161 and M2143. The height of the vertical bars represents the mean of the median running rates obtained from five sessions at each ratio value. Superimposed vertical lines indicate the range.

Figure 22

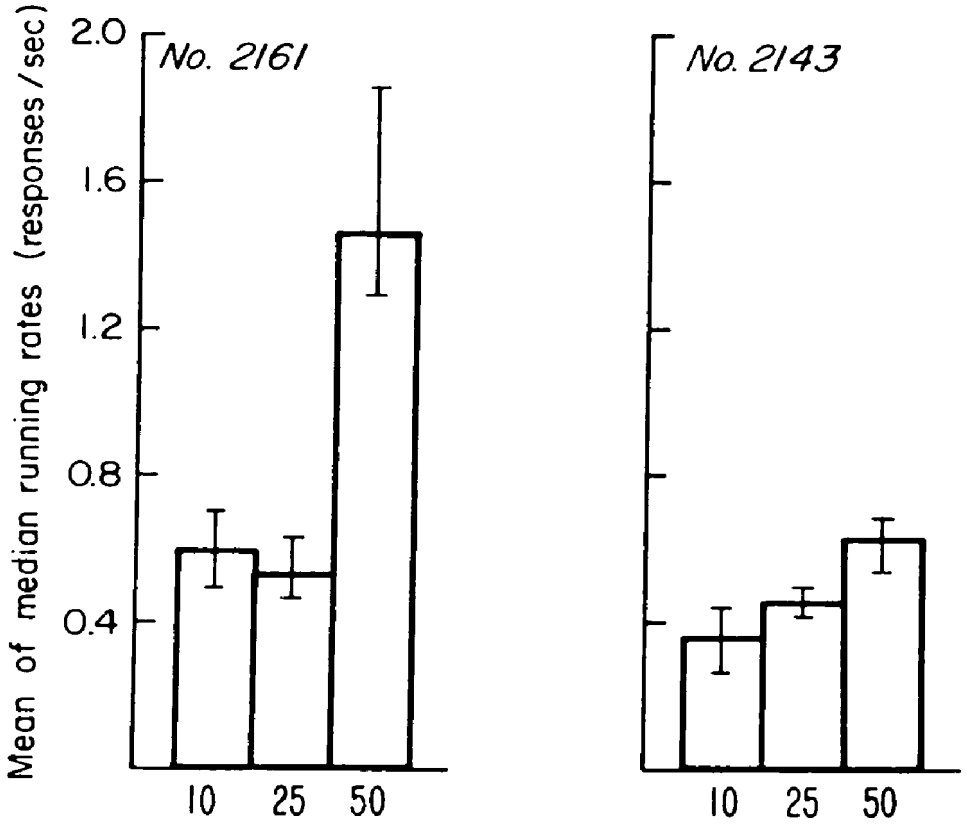
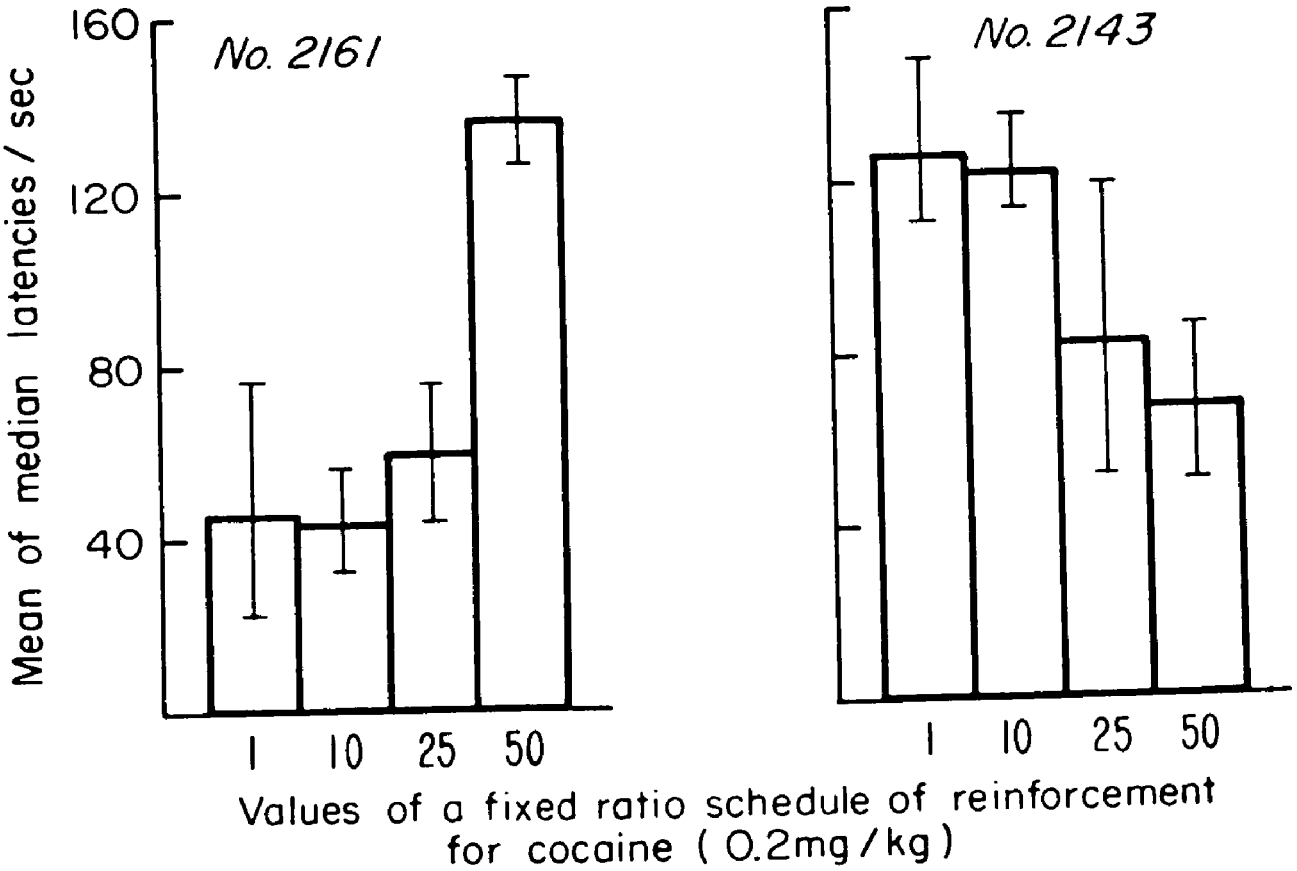

Mean of median running rates (responses / sec)
2.0
1.6
1.2
0.8
0.4
No. 2161
No. 2143
10
25
50
10
25
50
Values of a fixed ratio schedule of reinforcement
for cocaine (0.2 mg / kg)

Figure 23. Mean of median latencies in seconds as a function of the value of a fixed ratio schedule of reinforcement for cocaine (0.2 mg/kg/injection) in subjects M2161 and M2143. The height of the vertical bars represents the mean of the median latencies obtained from five sessions at each ratio value. Superimposed vertical lines indicate the range.

Figure 23


160
120
80
40
Mean of median latencies / sec
No. 2161
No. 2143
1
10
25
50
1
10
25
50
Values of a fixed ratio schedule of reinforcement
for cocaine ( 0.2mg / kg )

## D. DISCUSSION

This study indicates that psychomotor stimulant administration can maintain lever-pressing behavior over a wide range of ratio values on a FR schedule of reinforcement.

The results of this study are in agreement with those obtained by other investigators in rats self-administering psychomotor stimulants[148,152,154] and opiates[205]. These investigators found that increases in FR value from one to eighty produced very little change in total drug intake. The subjects merely increased their rate of responding in proportion to the increases in FR value. Therefore, it appears that total psychomotor stimulant intake is independent of the value (within the limits of 1-80) of the fixed ratio schedule of reinforcement being used. These authors also saw an increase not only in running rates, but also in latencies, i.e., post-reinforcement pause, with increases in ratio value. Similar increases in latencies and response rates are seen with increases in FR value for other types of reinforcers.[65] This study produced similar results, except in the case of the latencies obtained in M2143.

The most interesting result of these studies is the ability of the animals to compensate for schedule changes with alterations in response rate so that the end result is the administration of a given amount of cocaine or any of the other drugs which were studied. It appears that either a given amount of these compounds is desired or is able to be self-administered in a certain period of time. The rate of responding to administer these compounds is greatly influenced by the schedule of reinforcement and the magnitude of reinforcement, i.e., dose per injection; however, total

intake appears to be independent of both of these factors. The results of this study also lead one to postulate that either a central regulatory mechanism or a direct effect of the drug is functioning to limit or regulate the amount of psychomotor stimulants which an animal will self-administer.

## IV. COCAINE INTAKE AS A FUNCTION OF THE DEGREE OF CONCOMITANT FOOD DEPRIVATION CONDITIONS.

### A. INTRODUCTION

Many investigators have postulated that a reward system exists in the brain which functions to regulate reinforcement oriented behavior. If such a system does function in initiating behavior which leads to the acquisition of a reinforcer, then one would speculate that perhaps deprivation of one reinforcer may influence behavior being emitted to obtain a second reinforcer. One could visualize this system perhaps as a common pathway for reinforcement. Food in a hungry animal, sex in a sex-deprived animal, water in a thirsty animal, and drug in a drug-dependent organism, may all increase neural activity in such a system. Perhaps the level of neuronal activity which is produced by the acquisition of one reinforcer is altered by concomitant deprivation of a second reinforcer. In other words, would cocaine be more, as, or less reinforcing to a subject which is food deprived than under conditions of food satiation?

A possible interaction exists between food seeking behavior and drug seeking behavior in subjects which self-administer cocaine. Cocaine has anorexic properties; therefore, it would reduce the motivation for obtaining food in food deprived subjects. The reduction of this food-oriented drive may make cocaine more reinforcing in such a subject under conditions of food deprivation than under free feeding conditions. If this is true, then perhaps the converse, i.e., cocaine is less reinforcing in food satiated subjects, is also a reasonable hypothesis.

Perhaps psychomotor stimulants are only reinforcing because they produce food seeking, i.e., drive-oriented behavior; all psychomotor stimulants which are abused possess this anorexic property. Therefore, in order to determine if the degree of food deprivation alters the reinforcing property of cocaine in subjects psychologically dependent on cocaine, the following experiment was conducted.

B. METHODS

1. Subjects. The subjects for this experiment were three adult Rhesus monkeys: M2121, M2198, and M2170. Chronic indwelling jugular catheters had been implanted in these subjects and each subject had been self-administering cocaine for a month. The subjects had access to cocaine for four hours (11:00 a.m.-3:00 p.m.) daily. The subjects received 0.2 mg/kg of cocaine following each lever-pressing response in the presence of an illuminated stimulus light. Variability in daily cocaine intake rarely exceeded ±10% in any of the subjects.

2. Apparatus. The subjects were individually housed in open-faced experimental cubicles and were restrained by a stainless steel harness and arm. The lower back wall consisted of a stainless steel panel; the sides, top and remainder of the back were made of nontransparent white plastic. The floor was constructed of galvanized steel mesh. A covered food tray was located in one back corner. The stainless steel panel contained apertures for two levers; however, only one lever was utilized in this study. A microswitch was closed whenever 100 grams of force was applied to the lever. Closure of the microswitch

activated an automatic injector which was mounted on a stainless steel shelf which was attached to the outside of the rear wall. A stimulus light and pressure-sensitive water spout were also mounted on the stainless steel panel.

Depression of the lever, in the presence of the discriminative stimulus, i.e., illumination of the stimulus light, resulted in the intravenous administration of 0.2 mg/kg of cocaine hydrochloride. All lever presses were recorded, whether or not they occurred in the presence of the discriminative stimulus, on an Esterline Angus event recorder. Programming and recording equipment were located in an adjacent room.

3. Procedure. The subjects had access to cocaine daily from 11:00 a.m. to 3:00 p.m. Each subject received a programmed injection of cocaine every four hours during the twenty hours between sessions to aid in preventing clots from forming in the catheter. The subjects were normally given fifteen Purina Monkey Chows at 8:00 a.m. and 4:00 p.m. The subjects were run for seven days on this baseline schedule of drug and food access. Water was available to the subject at all times during the study. The subjects were not fed following the experimental session on day seven; the animals received no nourishment until the end of the drug access period on day ten. Therefore, the subjects were completely food deprived for seventy-two hours.

The subjects were then given their normal daily food allotment for seven days. After the experimental session on day seventeen was complete, approximately one hundred monkey chows were placed in each subject's cage. Food was constantly available to the subjects for the next five days. In addition to the

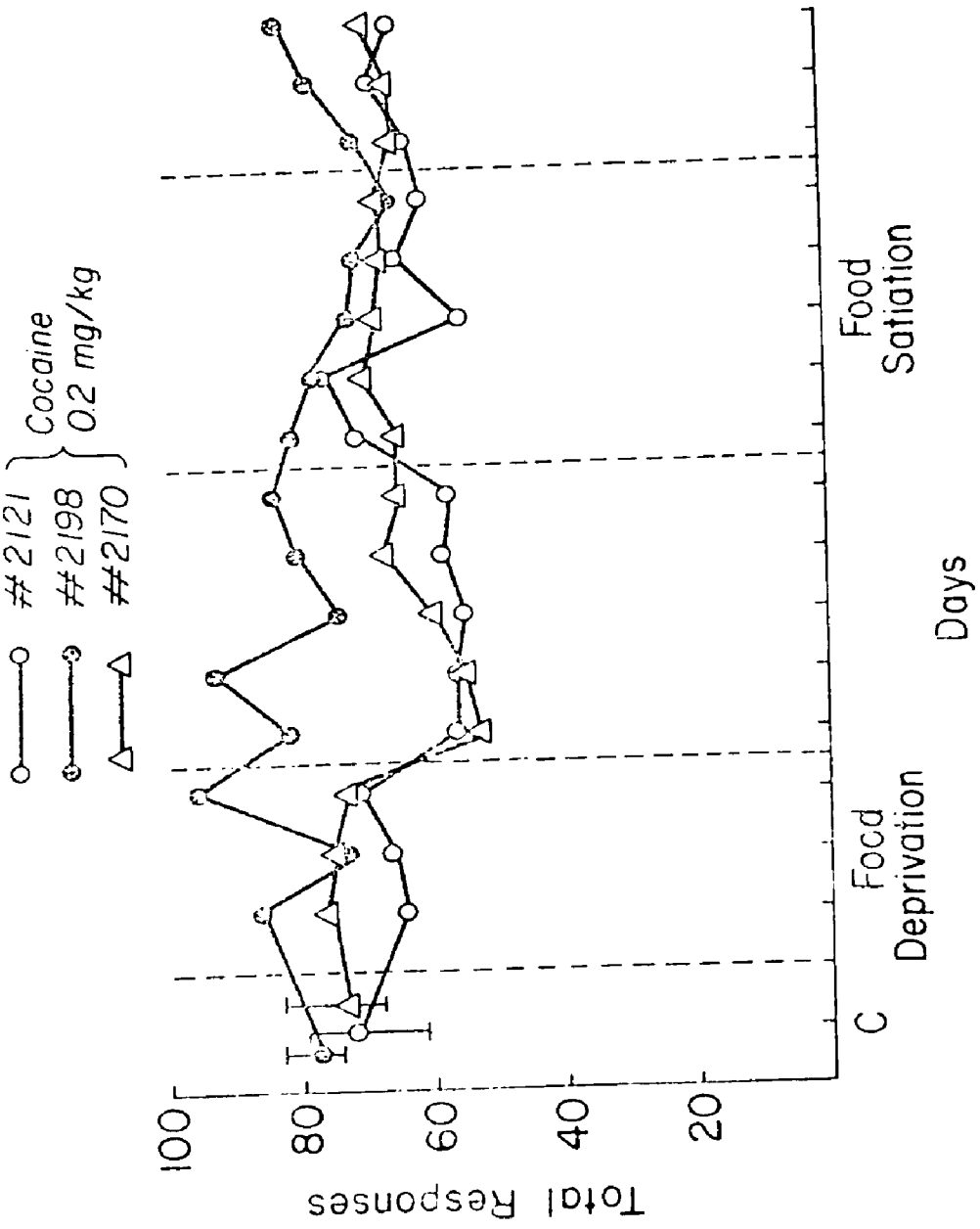
constant access to monkey chows, the subjects were provided with a quantity of fruit one hour before the start of the daily experimental session on each of these five days. After the drug access period on day twenty-two had concluded, all food was removed from the cage. The animals then received their normal food allotment for the remainder of the study. Daily cocaine intake was measured prior to, during, and after these conditions of food deprivation and food satiation.

C. RESULTS

Figure 24 illustrates the effects of three days of food deprivation and of five days of food satiation on daily cocaine intake in subjects M2121, M2198, and M2170. Since the schedule of reinforcement was FR-1 or CRF, each point represents the total number of injections received in a given session. Mean control values were obtained for the seven days prior to conditions of food deprivation. Vertical lines represent the range. M2121 normally received 72 self-administrations of cocaine daily; M2198, 78; and M2170, 75 injections. In two of the three subjects, conditions of food deprivation had no effect on cocaine self-administration. In M2198, no consistent daily effect was observed on cocaine intake; however, variability in cocaine intake increased greatly over that seen normally. The subjects' overall behavior and appearance did not change appreciably during the time in which they were completely food deprived. However, it did appear that locomotor activity had increased during this period, although this was not quantitatively measured.

Figure 24. Effects of three days of food deprivation and five days of food satiation on rate of responding for cocaine (0.2 mg/kg/injection) in M2121, M2198, M2170. The schedule of reinforcement was FR-1, i.e., CRF; therefore, each point represents the total number of injections received in a given session. Mean control values were obtained for the seven days prior to food deprivation. Vertical lines represent the range.

**Figure 24**


#2121
#2198
#2170
Cocaine
0.2 mg/kg
Total Responses
100
80
60
40
20
C
Food
Deprivation
Food
Satiation
Days

Large decrements in responding for cocaine were produced in two of the subjects, i.e., M2121, M2170, when they were returned to a normal feeding schedule. This effect lasted for three to five days. The increased variability in daily cocaine intake seen in M2198 under conditions of food deprivation persisted for three days under a normal feeding schedule. However, mean daily cocaine intake in this animal was always within the range of control values. This variability in responding for cocaine had returned to baseline levels prior to initiation of food satiation conditions.

Under conditions of food satiation, cocaine intake in M2121 and M2170 returned to baseline levels, which had existed prior to imposition of food deprivation conditions. However, cocaine intake decreased during the time in which M2198 was satiated with food. Within five days after conditions of food satiation were terminated, cocaine intake in all subjects had returned to pre-study baseline levels.

## D. DISCUSSION

The increased variability in responding for cocaine injections during conditions of food deprivation seen with M2198 may have been due to two factors. Although gross observations of the subjects did not indicate significant weight loss in the subjects under food deprivation conditions, it is certain that some did occur. The injection volume was kept constant throughout the study. Therefore, a twenty per cent reduction in weight would have had the effect of increasing the unit dosage by a fifth.

Furthermore, food deprivation conditions have been shown to increase locomotor activity.[192,59] Increases in activity have also been shown to potentiate the effects of psychomotor stimulants.[27] Therefore, weight loss and increased activity may have been responsible for, in effect, increasing the unit dosages of cocaine. As previously demonstrated, increases in the magnitude of reinforcement, i.e., unit dosage, decreases the frequency of responding for cocaine.

Food deprivation did not alter the amount of cocaine self-administered in M2121 and M2170. There was also no consistent change in the number of daily responses for cocaine in M2198 under these conditions. Furthermore, there was no consistent change in the rate of responding for cocaine under conditions of food satiation in any of the subjects. Therefore, it appears that there is no interaction between reinforcement produced by the ingestion of food and reinforcement produced by the administration of psychomotor stimulants.

The only significant effect on the frequency of responding for cocaine in this study occurred in two of the three subjects immediately after food deprivation conditions had been terminated. For three days in M2170, and for five days in M2121, cocaine intake, i.e., lever-presses for cocaine, stayed below the control range. The subjects had received food twice prior to the first session in which this change was evident. This would argue against any interpretation of this effect being directly attributable to food deprivation. Also, one could not argue that now the subjects would rather eat than press a lever for cocaine during the experimental session, because food was

not available to them while they had access to cocaine. A possible explanation would be that significant weight loss produced by conditions of food deprivation did not occur until the first day after these conditions had been terminated. Perhaps, then, three to five days on a normal feeding schedule were required to again establish baseline weights in the subjects. A decrease in weight would have had the effect of increasing the unit dosage, since volume of injection was constant. I have demonstrated that increases in unit dosage, i.e., magnitude of reinforcement, results in a decrease in the rate of responding, which was the effect observed in this current study.

## V. MODIFICATION OF COCAINE SELF-ADMINISTRATION BY PRETREATMENT WITH OTHER PHARMACOLOGICAL AGENTS.

### A. INTRODUCTION

The results of the previous studies indicated that some factor limits the amount of psychomotor stimulants which would be self-administered by animals. Changes in the value of a fixed ratio schedule of reinforcement from FR-1 to FR-50 and twenty-five fold changes in the unit dosage produced very little fluctuation in the daily intake of cocaine. Regardless of whether it is a direct effect of the drug, i.e., aversiveness, being produced after a given dosage is administered, or a given dosage suppressing all on going behavior, or whether some central system is functioning to limit intake, one should be able to produce changes in cocaine intake by treatment with other compounds. These drugs may either potentiate or block the effects of cocaine or interact with the regulating mechanism in some manner to produce changes in cocaine intake.

Pickens, Meisch and Dougherty[147] demonstrated that similar results are obtained with rats who self-administer methamphetamine. Daily drug intake was independent of changes in FR value or of changes in unit dosage. The subjects adjusted their response rates accordingly to maintain their baseline level of methamphetamine intake. These investigators studied the effects of methamphetamine, alpha-methyl paratyrosine (AMPT) and l-dopa administration on this behavioral baseline of psychomotor stimulant intake. Methamphetamine pretreatment in dosages of 0.5 and 1.0 mg/kg produced a dose-related decrease in methamphetamine

self-administration. AMPT in dosages of 5.0-80 mg/kg produced an increase in this behavior; whereas, l-dopa in dosages of 20-160 mg/kg produced no change in methamphetamine self-administration. These results tend to implicate central catecholamines as perhaps being the mediators of not only the reinforcing action, but also of the aversive or behavioral disrupting effect of the psychomotor stimulants. This would not at all be surprising, since all of the psychomotor stimulants have been shown to interact with central and peripheral sympathetic systems.

The purpose of the following study was to determine if we could alter the reinforcing property of cocaine or the intake limiting mechanism seen with cocaine self-administration by pretreating the subjects with other drugs with known pharmacological actions. The results of the study would perhaps aid in determining which neurotransmitters are functioning in mediating the reinforcing property of psychomotor stimulants. This study would also provide clinicians with data which would be helpful in determining what compounds may be effective in treating psychomotor stimulant dependence.

B. METHODS

1. Subjects. The subjects were sixteen adult Rhesus monkeys, weighing between 3.6 and 5.8 kg. After each subject had been in the laboratory for one week, to allow time for environmental adjustment, a chronic indwelling catheter was implanted in the right internal jugular vein. If at any time during the study a catheter was removed by the subject, or became clotted, attempts

were made to place another catheter in the same vein. If this attempt failed, a catheter was implanted in the contralateral vein.

The subjects were given fifteen Purina Monkey Chows twice a day, at 8:30 a.m. and 4:30 p.m.

2. Apparatus. The subjects were housed individually in open-faced experimental cubicles. The floor of the cubicles was constructed of one inch galvanized mesh. The sides, top, and upper back wall were constructed of non-transparent white plastic. The lower half of the back wall consisted of stainless steel. A stainless steel panel consisting of two lever apertures, but with only one lever, stimulus light, and water spout, was attached to the larger piece of stainless steel. A covered food tray was located in one lower back corner. A stainless steel shelf was attached to the outside of the back wall; the injector unit, consisting of syringe, syringe driver, drug reservoir, filter, and motor, was placed on this shelf. Cables connected this unit to programming and recording equipment, e.g., Esterline Angus event recorder, located in an adjacent room. The cage floor, i.e., stainless steel pans located beneath the wire mesh, was washed every six hours via an automatic cage washer. The subjects were restrained by a stainless steel harness and arm, which was attached to the back of the cage. The jugular catheter, which exited the subject via a stab wound in the back between the shoulder blades, was attached to an 18 guage needle connector located on the back of the harness. A second catheter was attached to the other side of the connection and passed through the stainless steel arm, out the back of the cubicle, and was

attached to the injector unit.

Depression of the lever with at least 100 grams of force, while the stimulus light was illuminated, activated a microswitch which in turn energized the injector unit. The subject received either an injection of saline or drug. The length of the injection cycle was 45-60 seconds, depending upon the subject's weight. During this period, the stimulus light was turned off and lever presses, although recorded, had no consequence. One could also program injections without requiring illumination of the light and depression of the lever. Each subject in this study received a programmed injection of cocaine every six hours. This aided in preventing clot formation in the catheter. All lever presses which occurred in the absence of the discriminative stimulus, i.e., stimulus light, were recorded, but were without consequence.

3. General procedure. Following catheter implantation, the subjects were returned to the experimental cubicles. The stimulus light was illuminated for twenty-four hours a day for seven days. Each lever press resulted in the administration of 0.2 cc/kg of body weight of sterile physiological saline. Following the determination of each subject's lever-pressing response frequency for saline, cocaine hydrochloride was substituted for the saline. Each lever press now resulted in the administration of 0.2 cc/kg of a 1.0 mg/cc solution of cocaine hydrochloride in sterile physiological saline. Each injection resulted in the administration of 0.2 mg/kg of cocaine. Cocaine solutions were prepared every three days to prevent potency loss due to decomposition.

If a subject did not respond significantly for cocaine within

three days after this substitution, either raisins were taped to the lever or a 2" x 2" plexiglass extension was attached. These two procedures, though very seldom necessary, were used to increase the chance of a subject depressing the lever resulting in cocaine administration. All subjects initiated this self-administration behavior within five days after substituting the cocaine for the saline. After each subject had administered cocaine for twenty-four hours, the drug access period was limited to a four-hour session daily between 11:00 a.m. and 3:00 p.m. This was done to reduce the toxic effects of cocaine self-administration, which occurs with unlimited access to the drug, and also to provide a stable daily baseline of cocaine intake. Monkeys which have unlimited access to cocaine administer cocaine for two to four days without sleeping; they then totally abstain from drug-seeking behavior for one to three days, during which time they sleep and eat. This cycle is then repeated, etc. However, monkeys with limited access to cocaine self-administer the same amount, ±10% of cocaine on a mg/kg basis, daily for many months.

Each subject self-administered cocaine under these access conditions for two weeks prior to the beginning of the pretreatment studies. Both acute and chronic pretreatment studies were conducted.

a. Acute pretreatment. In these studies, each drug was studied in four subjects. At least four different dosages of the drug was administered to each subject. Each dosage was tested once in each subject. All drugs used as pretreatment agents were dissolved in sterile physiological saline. Drug

solutions were prepared on the day in which they were administered. The drugs were administered intramuscularly five minutes prior to the onset of the experimental session. The volume of the injection was 1.0 cc, and this was kept constant throughout the study. At least three days elapsed between drug pretreatment sessions to allow for drug intake to return to baseline levels following the previous pretreatment session, and also to allow time for metabolism of the previously administered compound. Five saline control pretreatment sessions were conducted in each subject throughout the course of the study.

More than one pretreatment drug was studied in each subject. Studies with one drug were completed in a subject and two weeks allowed to pass before studies with a second drug were initiated in that subject.

The effects of the acute administration of chlorpromazine hydrochloride (CPZ), pentobarbital sodium, morphine sulfate, trifluoperazine hydrochloride, phentolamine hydrochloride, phenoxybenzamine hydrochloride, pargyline hydrochloride, methyl ester of alpha-methylparatyrosine (AMPT), d-amphetamine sulfate, phenmetrazine hydrochloride, imipramine hydrochloride, atropine sulfate, atropine methylnitrate and physostigmine salicylate on cocaine self-administration was studied in Rhesus monkeys.

The effect of acute chlorpromazine pretreatment on the self-administration of cocaine in two subjects who were working on fixed ratio, FR-10 and FR-25, schedule of reinforcement was also studied. The unit dosage of cocaine was 0.1 mg/kg/injection in the subject on the FR-25 schedule and 0.2 mg/kg/injection in the

subject on the FR-10 schedule. The effect of acute chlorpromazine pretreatment in five subjects which self-administered four different unit dosages of cocaine was also studied. Three pretreatment dosages of CPZ were studied in each subject during exposure to each of the four unit dosages of cocaine.

b. Chronic pretreatment. The effects of chronic pretreatment with chlorpromazine hydrochloride and reserpine hydrochloride on cocaine self-administration were studied. The effects of chronic pretreatment with chlorpromazine (CPZ) was studied in two subjects. CPZ in a dosage of 2.0 mg/kg was administered intramuscularly five minutes prior to the onset of the experimental session for five successive days. The CPZ was dissolved in sterile physiological saline and solutions were prepared on the day in which they were used. The volume of all injections was 1.0 cc. Saline control pretreatment sessions were conducted before and after the chronic treatment regimen with chlorpromazine.

The chronic pretreatment studies with reserpine were conducted in seven subjects. Three dosages of reserpine were studied, i.e., 0.1, 0.3, and 1.0 mg/kg. The lowest and highest dosages were studied in two subjects each, and the 0.3 mg/kg dosage was studied in three subjects. The 0.1 and 0.3 mg/kg dosages were administered intramuscularly five minutes following the experimental session for ten days in succession. The 1.0 mg/kg dosage was administered similarly, but only for five consecutive days. Reserpine was administered following the session in an attempt to prevent the acute depressant effects of reserpine from

masking any effects seen due to catecholamine depletion if these are unrelated. The drug was dissolved in sterile physiological saline and solutions were prepared on the day of usage. The volume of the injection was 1.0 cc. Saline control pretreatment sessions were conducted in these subjects before and after they were exposed to this treatment regimen.

C. RESULTS

Figure 25 illustrates the mean percentage change in cocaine self-administration as a function of the pretreatment dosage of chlorpromazine (CPZ). The points represent the mean of four subjects and the vertical lines indicate the range. The brackets at the left represent the range for twenty saline control pretreatment sessions, five conducted in each subject. CPZ in dosages of 0.125-4.0 mg/kg produced a mean increase (15-55%) in cocaine self-administration. This increase did not appear to be dose-related, since the dosage range of 0.5-2.0 mg/kg produces the same magnitude of effect. When the pretreatment dosage of CPZ was increased to 8.0 mg/kg, there was evidence of marked CNS depression, and cocaine self-administration was significantly depressed.

Figure 26 illustrates the effects of CPZ pretreatment on cocaine self-administration in subject M2068, which was self-administering cocaine at a unit dosage of 0.2 mg/kg/injection on a FR-1 schedule of reinforcement. The figure is divided into four parts; each part represents the data obtained from one hour of the four hour experimental session. The heights of the vertical bars indicate cocaine intake (mg/kg) for that hour. The

Figure 25. Mean percentage change in cocaine self-administration as a function of the pretreatment dosage of chlorpromazine. Each point represents the mean of four subjects and the vertical lines illustrate the range. The brackets at the left represent the range of change in cocaine self-administration which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 25

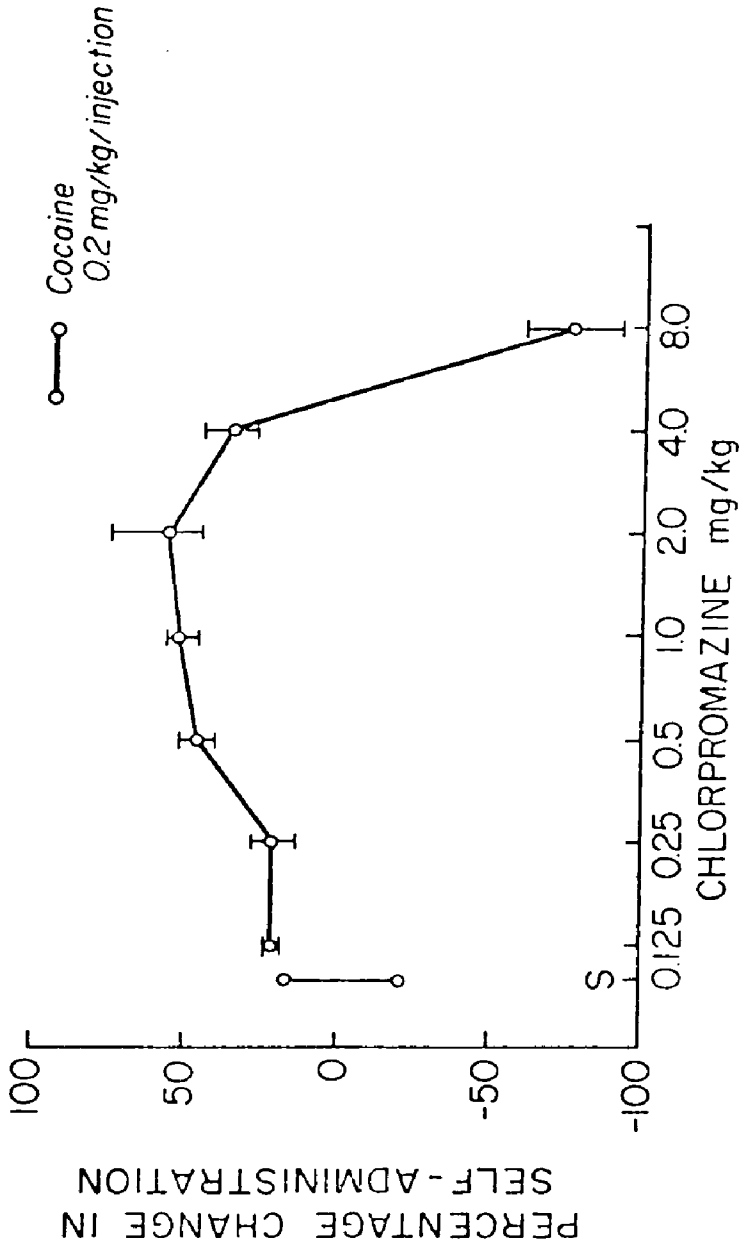
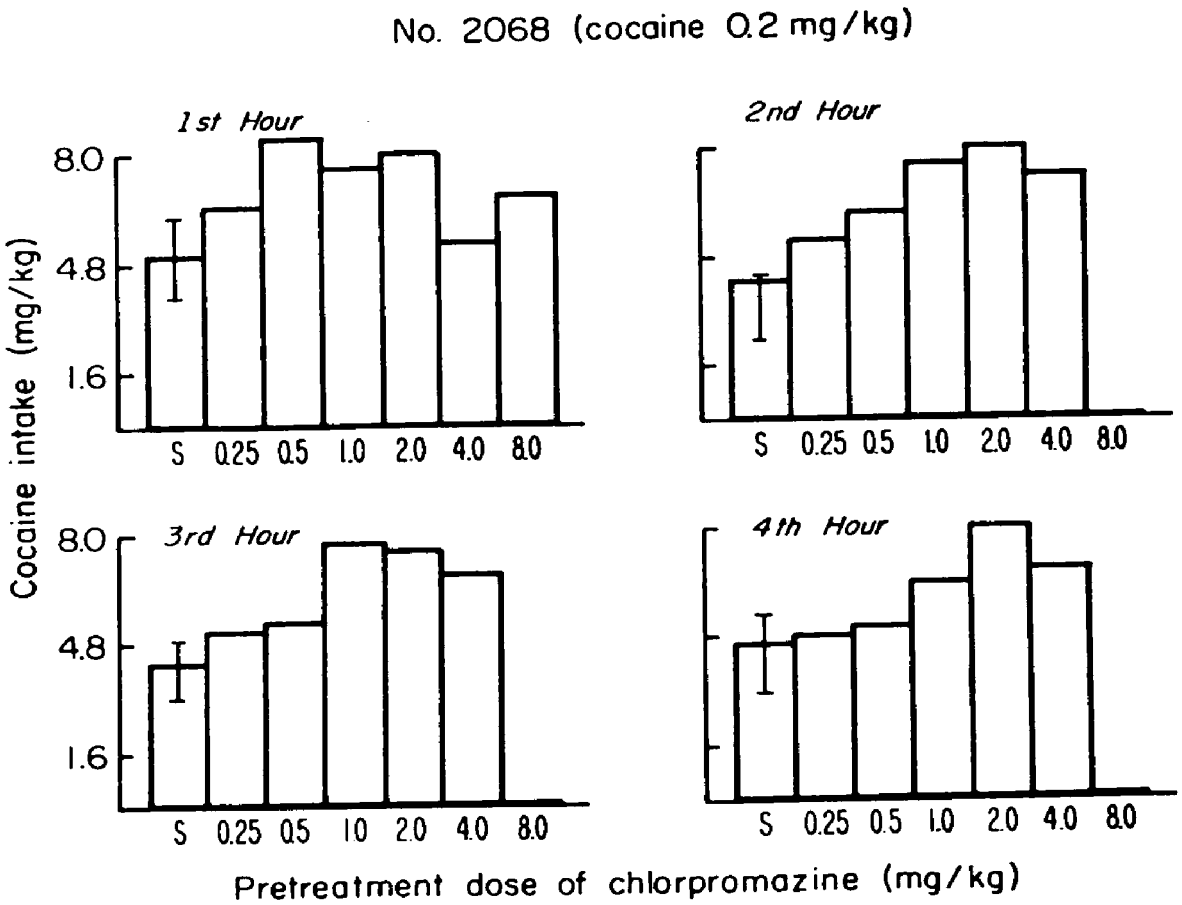

Cocaine
0.2 mg/kg/injection
PERCENTAGE CHANGE IN
SELF-ADMINISTRATION
100
50
0
-50
-100
S
0.125
0.25
0.5
1.0
2.0
4.0
8.0
CHLORPROMAZINE mg/kg

Figure 26. Alteration in cocaine intake in M2068 as a function of the pretreatment dosage of chlorpromazine. The heighth of the bars indicates cocaine intake during that period, following pretreatment with a given dosage of chlorpromazine. The heighth of the bars over the letter "S" indicates mean cocaine intake in that period, after pretreatment with saline on five different occasions. The vertical lines represent the range of cocaine intake for these five control sessions.

Figure 26

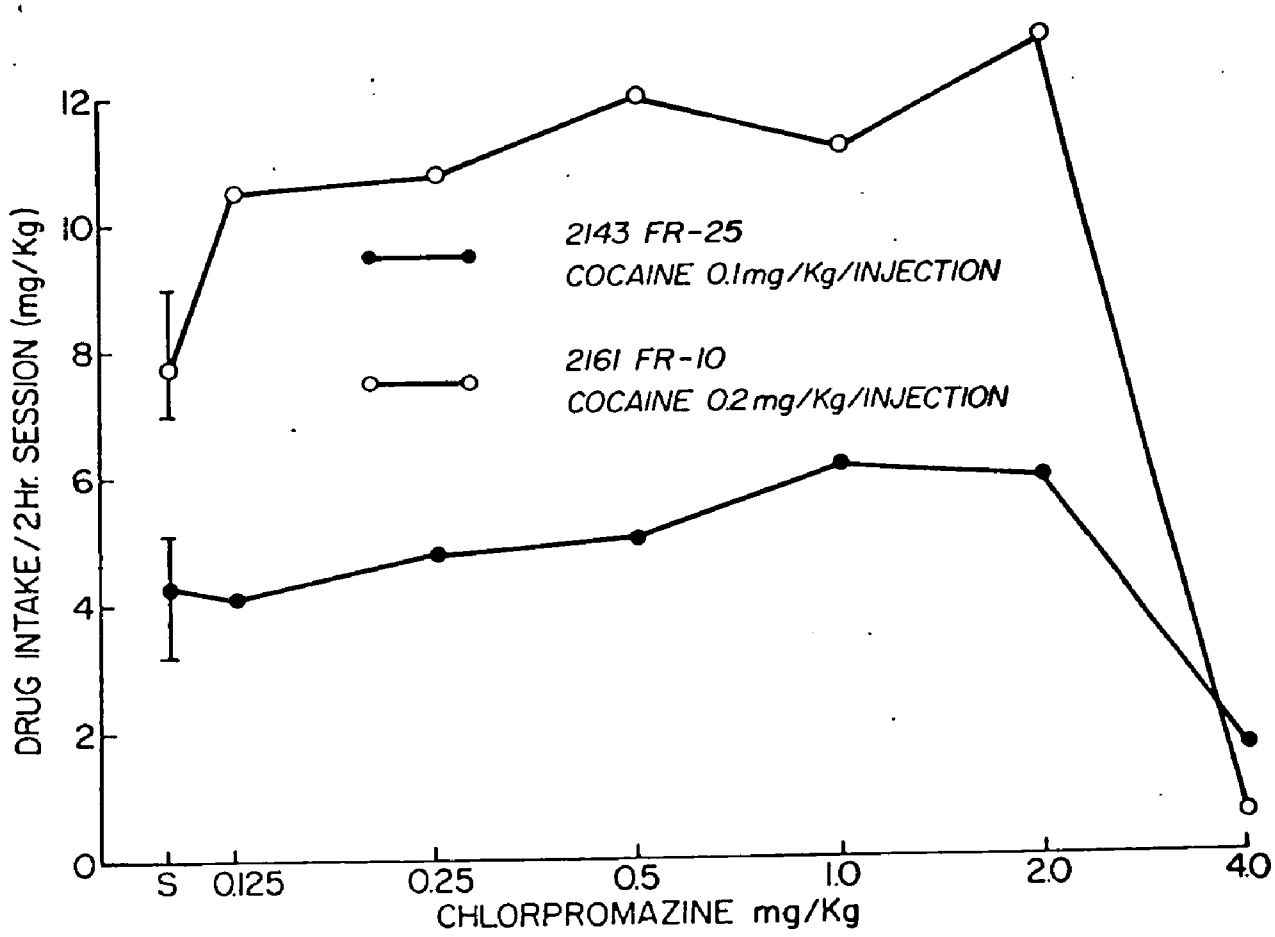

No. 2068 (cocaine 0.2 mg/kg)
1st Hour
2nd Hour
3rd Hour
4th Hour
8.0
4.8
1.6
Cocaine intake (mg/kg)
S 0.25 0.5 1.0 2.0 4.0 8.0
Pretreatment dose of chlorpromazine (mg/kg)

letter "S" designates saline control pretreatment sessions, and the brackets indicate the range for five of these sessions. The height of the bar over the "S" indicates mean cocaine intake for the control sessions. Mean control cocaine intake was almost identical for all four one-hour periods. All pretreatment dosages of CPZ produced an increase in cocaine intake in the first hour of the session. In the second hour, a similar increase, which appeared to be dose-related, was seen with dodages of CPZ from 0.25 to 4.0 mg/kg. The 8.0 mg/kg dose of CPZ completely suppressed cocaine self-administraion during the second, third, and fourth hours of the session. Dosages of 0.25-4.0 mg/kg continued to increase cocaine self-administration during the third hour of the session. However, during the fourth hour, only dosages of 1.0-4.0 mg/kg of CPZ were effective in increasing cocaine intake. Cocaine intake had returned to control levels with lower dosages of CPZ, i.e., 0.25 and 0.5 mg/kg, by this time.

The effect of CPZ pretreatment in dosages of 0.125-4.0 mg/kg on cocaine self-administration in two subjects, one on a FR-10 and another on a FR-25 schedule of reinforcement, is illustrated in Figure 27. CPZ in dosages of 0.125-2.0 mg/kg increased cocaine self-administration in M2161, who was on the FR-10 schedule of reinforcement for cocaine at a unit dosage of 0.2 mg/kg/injection. However, in M2143, who was self-administering cocaine on a FR-25 schedule of reinforcement at a unit dosage of 0.1 mg/kg/injection, increases in cocaine intake were seen only when the pretreatment dosage of CPZ was 1.0 and 2.0 mg/kg. Increases in pretreatment dosage of CPZ to 4.0 mg/kg almost completely suppressed cocaine reinforced behavior in both subjects. At this dosage they

Figure 27. Cocaine intake as a function of the pretreatment dosage of chlorpromazine in two subjects self-administering cocaine. M2143 was working on a FR-25 schedule and M2161 on a FR-10 schedule of reinforcement. Each point represents total cocaine intake for that session in one subject. Vertical lines at the left represent the range of cocaine intake which occurred during five control, i.e., saline pretreatment, sessions. The superimposed point represents mean cocaine intake for these control sessions.

Figure 27


DRUG INTAKE/2Hr. SESSION (mg/Kg)
12
10
8
6
4
2
0
2143 FR-25
COCAINE 0.1mg/Kg/INJECTION
2161 FR-10
COCAINE 0.2mg/Kg/INJECTION
S
0.125
0.25
0.5
1.0
2.0
4.0
CHLORPROMAZINE mg/Kg

exhibited marked CNS depression, but could be aroused by sensory stimulation.

Figures 28 and 29 illustrate the effects of this CPZ pretreatment on median running rates and median latencies in these same two subjects. In M2143, running rate, i.e., time from first to nth response on a FR-N schedule, was increased two to three times that of control sessions, with CPZ pretreatment in dosages of 0.125-2.0 mg/kg. A similar increase in running rate was seen in M2161. Median running rates were greatly reduced in both subjects when the pretreatment dosage of CPZ was increased to 4.0 mg/kg. Median latencies, i.e., time from last reinforcement to emission of first appropriate response, decreased in both subjects as the pretreatment dosage was increased from 0.5 to 2.0 mg/kg. Pretreatment with 4.0 mg/kg of CPZ increased median latencies; in M2143 the increase was back toward control values; however, in M2161 the increase was greater than that seen during control sessions.

The effect of CPZ pretreatment in dosages of 1.0, 2.0, and 4.0 mg/kg on cocaine self-administration at five different unit dosage levels, in subject M2170, is represented in Figures 30, 31, and 32. The height of the open vertical bars in the figure on the left represents mean cocaine intake in mg/kg, at each unit dose level of cocaine studied. Vertical lines represent the range for seven control sessions. The height of the open bars in the right-hand figures represent the mean number of responses seen at each unit dosage of cocaine studied. The vertical lines represent the range for seven control sessions. The height of the cross-hatched bars illustrate cocaine intake (left-hand graph) and lever-pressing

Figure 28. Median running rates (responses per sec.) in two subjects self-administering cocaine on a FR-10 and FR-25 schedule of reinforcement as a function of the pretreatment dosage of chlorpromazine. The vertical lines and superimposed points at the left indicate the range and mean respectively, obtained from five control, i.e., saline pretreatment, sessions in each subject.

Figure 28

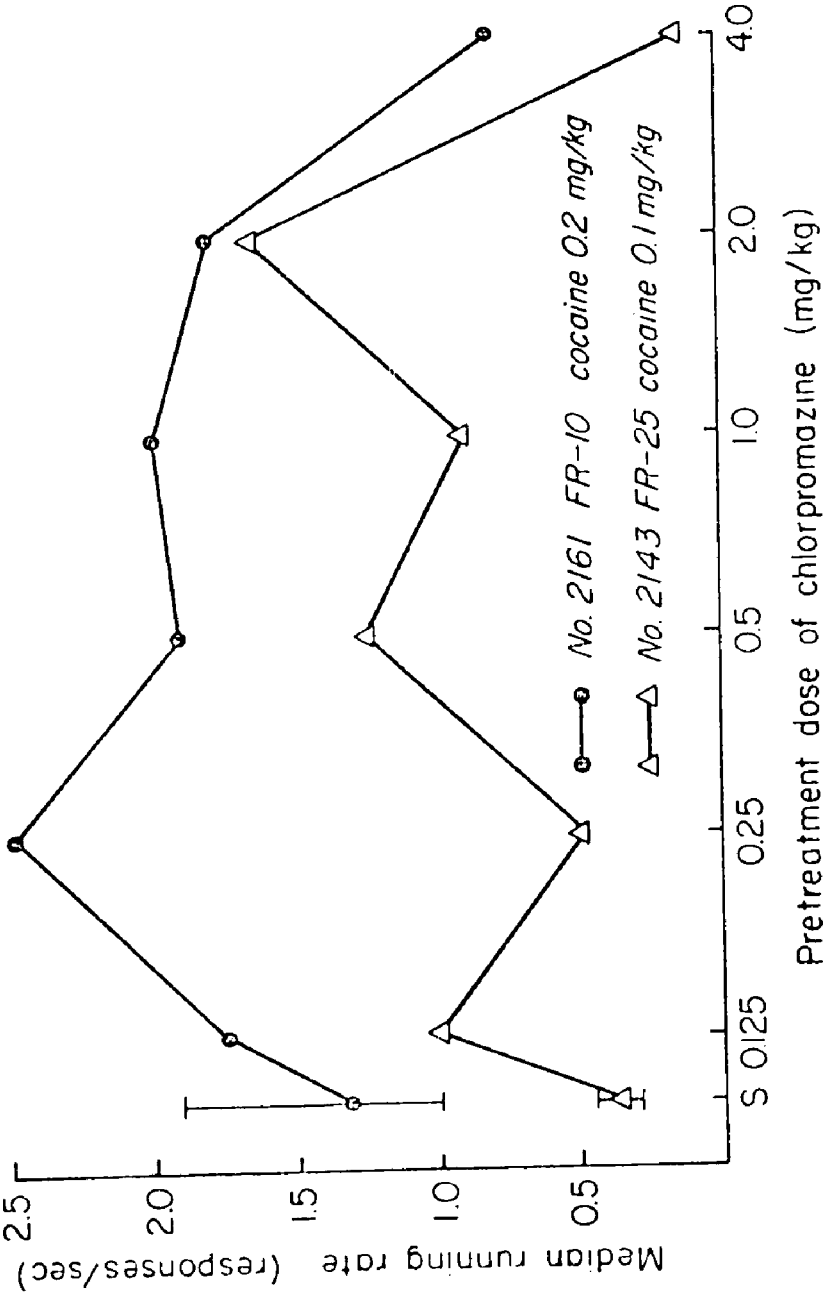

Median running rate (responses/sec)
2.5
2.0
1.5
1.0
0.5
S 0125
0.25
0.5
1.0
2.0
4.0
Pretreatment dose of chlorpromazine (mg/kg)
No. 2161 FR-10 cocaine 0.2 mg/kg
No. 2143 FR-25 cocaine 0.1 mg/kg

Figure 29. Median latencies (secs.) in two subjects self-administering cocaine on a FR-10 and FR-25 schedule of reinforcement as a function of the pretreatment dosage of chlorpromazine. The vertical lines and superimposed points at the left indicate the range and mean respectively obtained from five control, i.e., saline pretreatment, sessions in each subject.

Figure 29

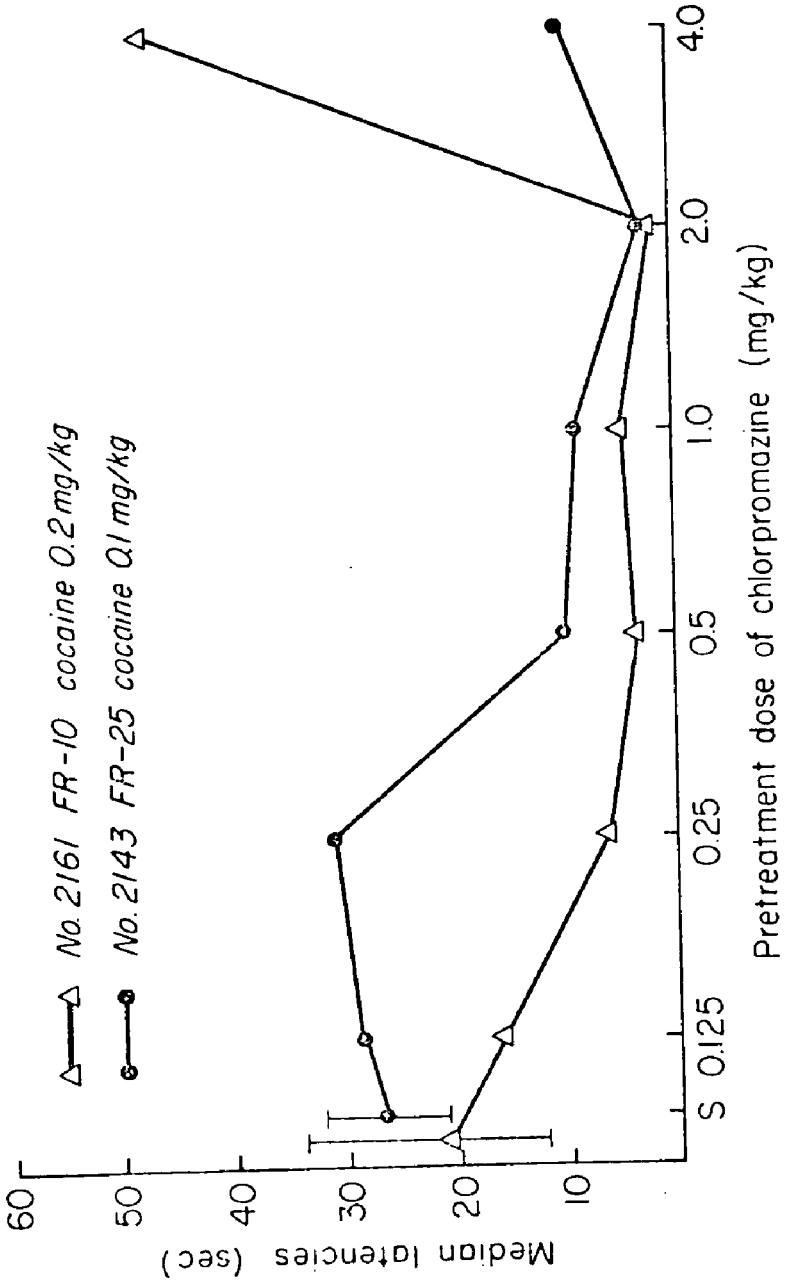

No. 2161 FR-10 cocaine 0.2 mg/kg
No. 2143 FR-25 cocaine 0.1 mg/kg
Median latencies (sec)
60
50
40
30
20
10
S 0.125
0.25
0.5
1.0
2.0
4.0
Pretreatment dose of chlorpromazine (mg/kg)

Figure 30. Cocaine intake in M2170 following pretreatment with chlorpromazine, 1.0 mg/kg, as a function of the unit dosage of cocaine. The height of the open bars represents the mean cocaine intake for five sessions at a given unit dosage. The vertical lines indicate the range of intake for these control sessions. The height of the cross-hatched bars represents cocaine intake seen following chlorpromazine pretreatment at a given unit dosage.

Figure 30

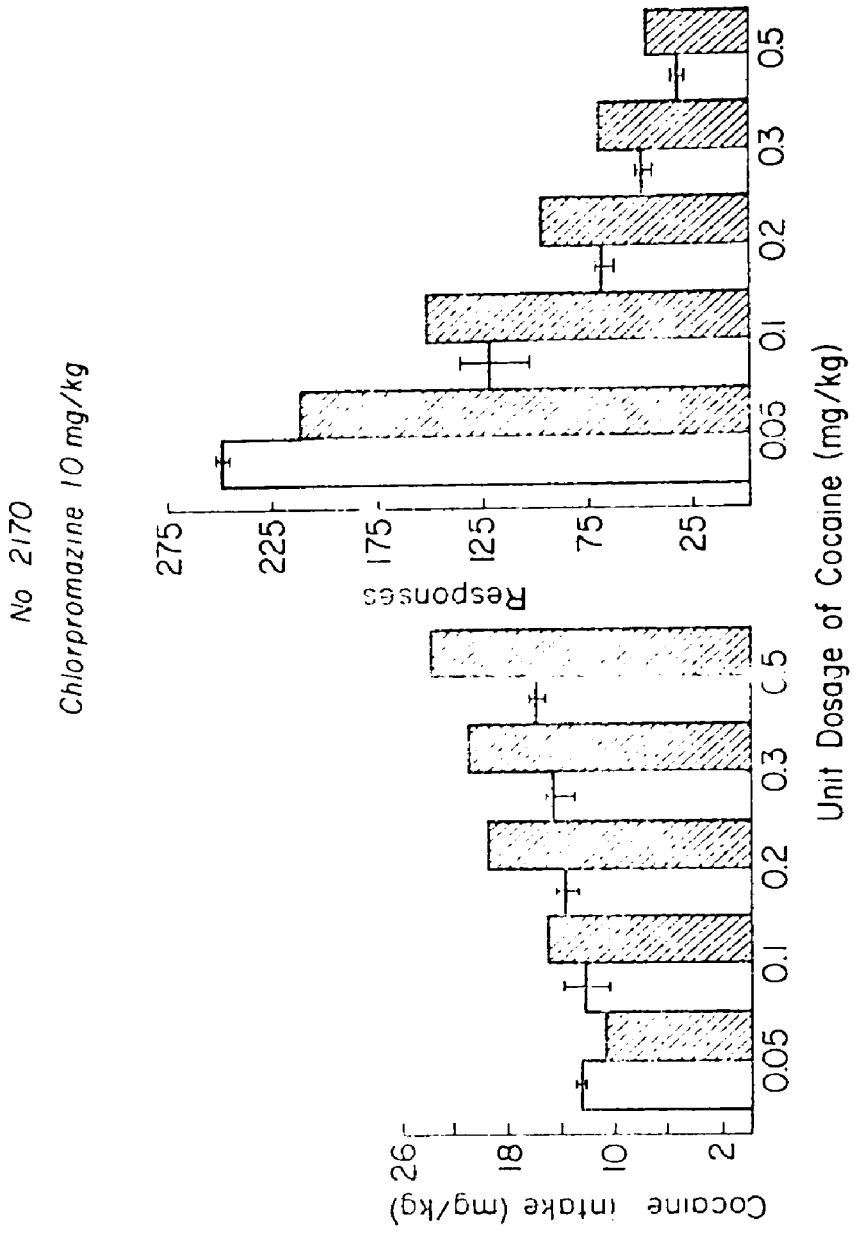

No 2170
Chlorpromazine 10 mg/kg
Responses
275
225
175
125
75
25
0.05
0.1
0.2
0.3
0.5
Cocaine intake (mg/kg)
26
18
10
2
0.05
0.1
0.2
0.3
0.5
Unit Dosage of Cocaine (mg/kg)

Figure 31. Cocaine intake in M2170 following pretreatment with chlorpromazine, 2.0 mg/kg, as a function of the unit dosage of cocaine. The height of the open bars represents the mean cocaine intake for five sessions at a given unit dosage. The vertical lines indicate the range of intake for these control sessions. The height of the cross-hatched bars represents cocaine intake seen following chlorpromazine pretreatment at a given unit dosage.

Figure 31

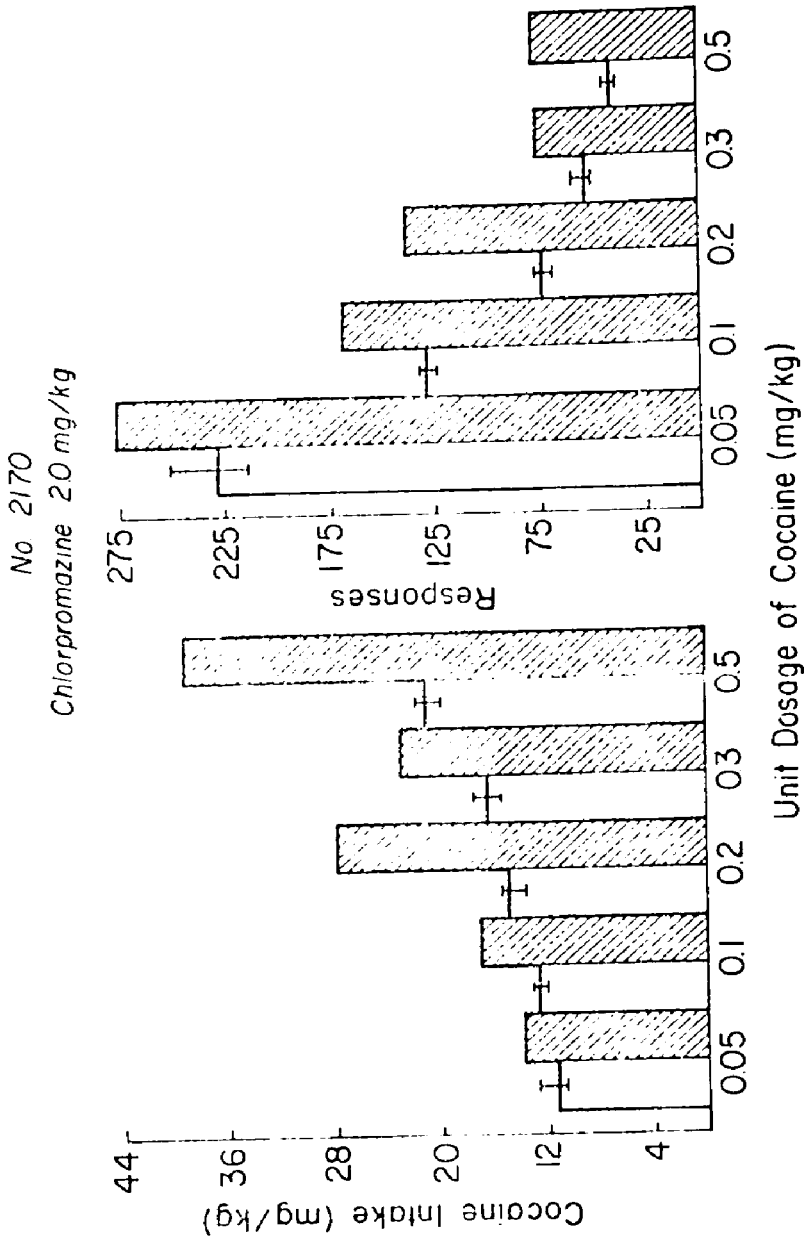
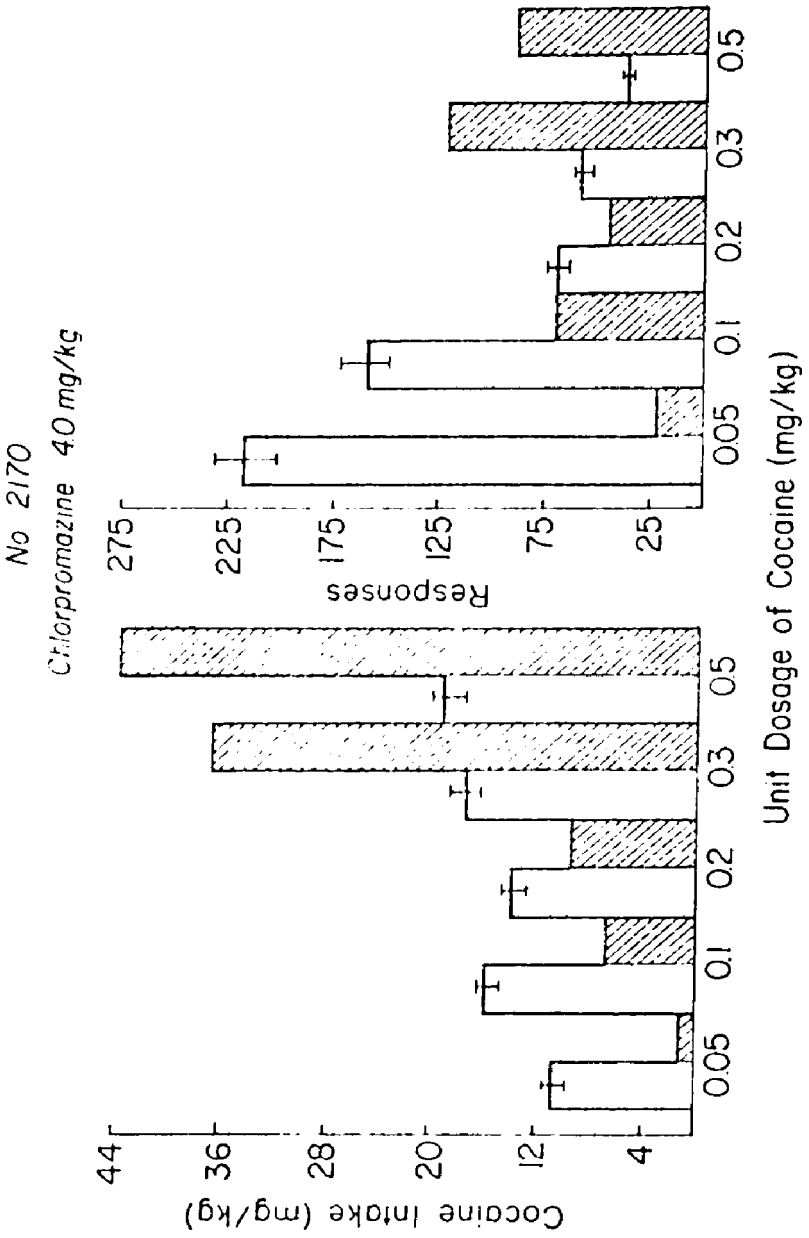

No 2170
Chlorpromazine 20 mg/kg
Responses
275
225
175
125
75
25
0.5
0.3
0.2
0.1
0.05
Unit Dosage of Cocaine (mg/kg)
Cocaine Intake (mg/kg)
44
36
28
20
12
4

Figure 32. Cocaine intake in M2170 following pretreatment with chlorpromazine, 4.0 mg/kg, as a function of the unit dosage of cocaine. The height of the open bars represents the mean cocaine intake for five sessions at a given unit dosage. The vertical lines indicate the range of intake for these control sessions. The height of the cross-hatched bars represents cocaine intake seen following chlorpromazine pretreatment at a given unit dosage.

Figure 32

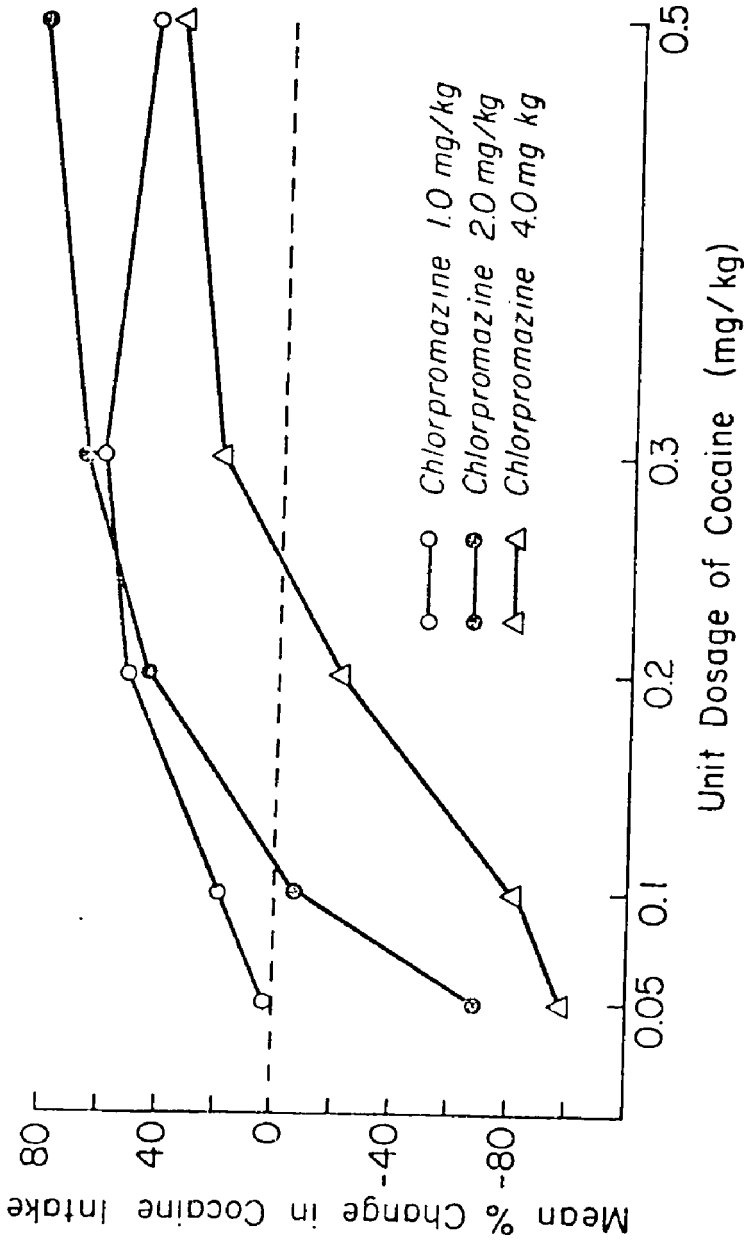

No 2170
Chlorpromazine 40 mg/kg
Responses
275
225
175
125
75
25
0.5
0.3
0.2
0.1
0.05
Unit Dosage of Cocaine (mg/kg)
Cocaine Intake (mg/kg)
44
36
28
20
12
4

responses (right-hand graph) seen in sessions following chlorpromazine pretreatment. Figure 30 illustrates the effects of pretreatment with 1.0 mg/kg of CPZ; Figure 31, pretreatment with 2.0 mg/kg of CPZ; and Figure 32, pretreatment with 4.0 mg/kg of CPZ. Pretreatment with 1.0 mg/kg of CPZ caused progressively larger increments in cocaine intake as the unit dosage of cocaine was increased from 0.1 to 0.5 mg/kg. This was also true when the pretreatment dosage was 2.0 mg/kg; however, when the dosage of CPZ was increased to 4.0 mg/kg, cocaine intake decreased at the lower unit dosages, e.g., 0.05, 0.1, and 0.2 mg/kg/injection, but progressively increased at higher unit dosages, e.g., 0.3 and 0.5 mg/kg/injection. At a given unit dosage of cocaine, increases in CPZ pretreatment dosage from 1.0 to 4.0 mg/kg produced less of an increase in cocaine intake, e.g., unit dosages of 0.3 and 0.5 mg/kg/injection, or initially an increase and then a decrease below control values, e.g., unit dosages of 0.1 and 0.2 mg/kg/injection, or a progressive decrease in cocaine intake, e.g., unit dosage of 0.05 mg/kg/injection.

Figure 33 illustrates the mean percentage change in cocaine intake as a function of the unit dosage of cocaine and the pretreatment dosage of CPZ. Each point represents the mean for five subjects. As the unit dosage of cocaine is increased from 0.05 to 0.5 mg/kg/injection, pretreatment with a given dosage of CPZ may depress intake at lower unit dosages, but increase intake at higher unit dosages of cocaine. The unit dosage at which this effect changes from a decrease to an increase, increases in value with increases in CPZ pretreatment dosage. At a given unit dosage of cocaine, increases in CPZ pretreatment dosage produce

Figure 33. Mean percentage change in cocaine intake in five subjects as a function of the unit dosage of cocaine and of the pretreatment dosage of chlorpromazine.

Figure 33


Mean % Change in Cocaine Intake
80
40
0
-40
-80
0.05
0.1
0.2
0.3
0.5
Unit Dosage of Cocaine (mg/kg)
Chlorpromazine 1.0 mg/kg
Chlorpromazine 2.0 mg/kg
Chlorpromazine 4.0 mg kg

less of an increase or more of a decrease in cocaine self-administration.

Figure 34 shows the effects of chronic CPZ pretreatment, i.e., 5 days at a dosage of 2.0 mg/kg, in two subjects which were self-administering cocaine at a unit dosage of 0.2 mg/kg/injection on a FR-1 schedule. Chlorpromazine increased cocaine administration on all five days in M2121 and on four of the five days in M2068. On the other day, in M2068, a large decrement in cocaine responding occurred and there was profound evidence of CNS depression. In both subjects, cocaine intake returned to baseline levels on the day following cessation of CPZ pretreatment; therefore, there was no evidence that this increase in cocaine intake, seen with chronic CPZ pretreatment, had been conditioned.

The mean percentage change in cocaine self-administration produced by pretreatment with morphine is shown in Figure 35. No change in cocaine intake was observed at dosages of 0.25 and 0.5 mg/kg; however, as the pretreatment dosage of morphine was increased from 1.0 to 8.0 mg/kg, cocaine self-administration was progressively decreased. At these dosages the subjects exhibited signs of marked motor incapacitation. The effects of morphine pretreatment on cocaine self-administration in M1095 is illustrated in Figure 36. Decrements in cocaine intake occur during every hour of the four hour session. The magnitude of this decrement was dependent on the pretreatment dosage of morphine.

Figure 37 demonstrates the effect of pentobarbital pretreatment on cocaine intake. No changes in cocaine intake were produced until the pretreatment dosage was 15.0 mg/kg. Dosages of

Figure 34. Daily cocaine self-administrations in two subjects prior to, during, and after chronic, i.e., five day, pretreatment with chlorpromazine, 2.0 mg/kg.

Figure 34

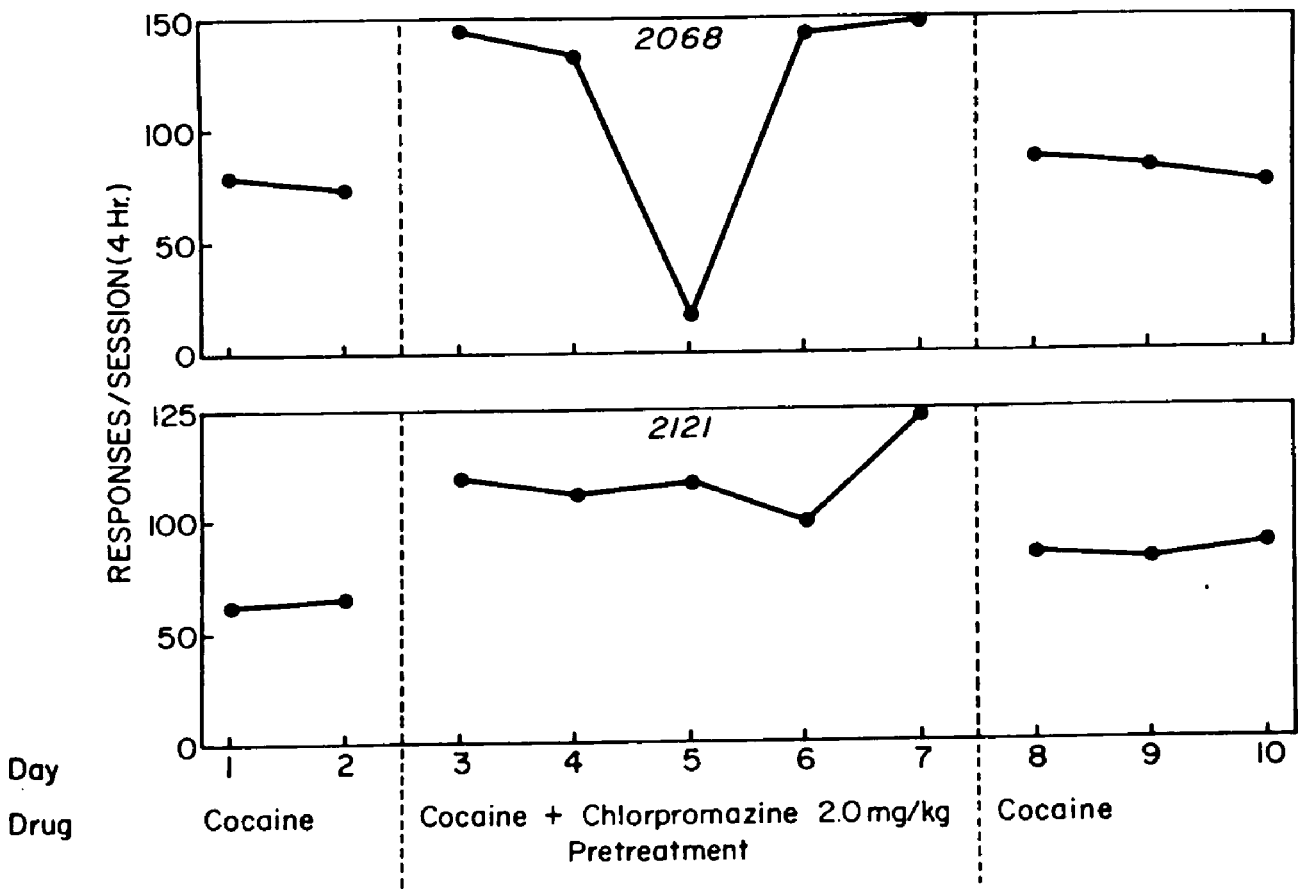

2068
2121
RESPONSES/SESSION (4 Hr.)
150
100
50
0
125
100
50
0
Day
1
2
3
4
5
6
7
8
9
10
Drug
Cocaine
Cocaine + Chlorpromazine 2.0 mg/kg
Pretreatment
Cocaine

Figure 35. Mean percentage change in cocaine self-administration as a function of the pretreatment dosage of morphine. Each point represents the mean of four subjects and the vertical lines illustrate the range. The brackets at the left represent the range of change in cocaine self-administration, which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 35

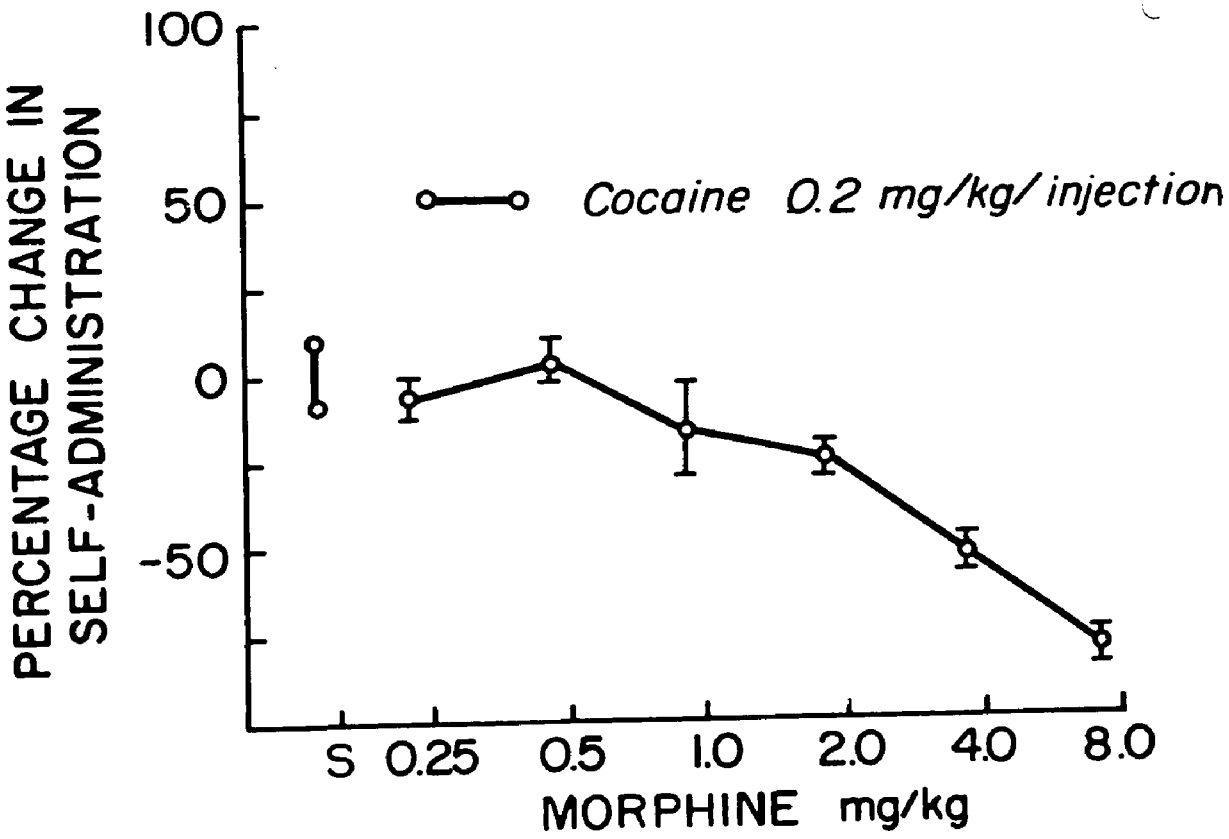

100
50
0
-50
PERCENTAGE CHANGE IN SELF-ADMINISTRATION
Cocaine 0.2 mg/kg/injection
S
0.25
0.5
1.0
2.0
4.0
8.0
MORPHINE mg/kg

Figure 36. Alteration in cocaine intake in M1095 as a function of the pretreatment dosage of morphine. The height of the bars illustrates cocaine intake during that period, following pretreatment with a given dosage of morphine. The height of the vertical bars over the letter "S" represents mean cocaine intake in that period after pretreatment with saline on five different occasions. The vertical lines represent the range of cocaine intake for these five control sessions.

Figure 36

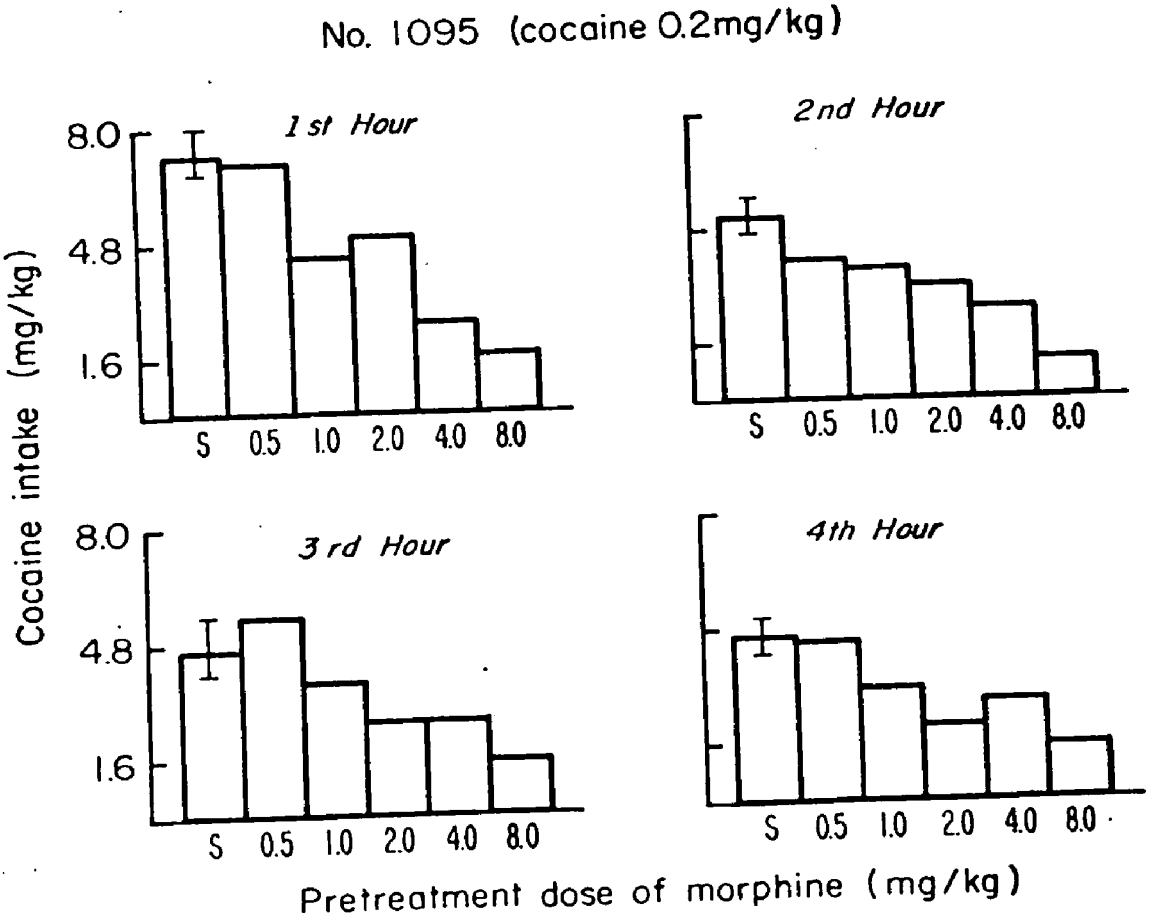
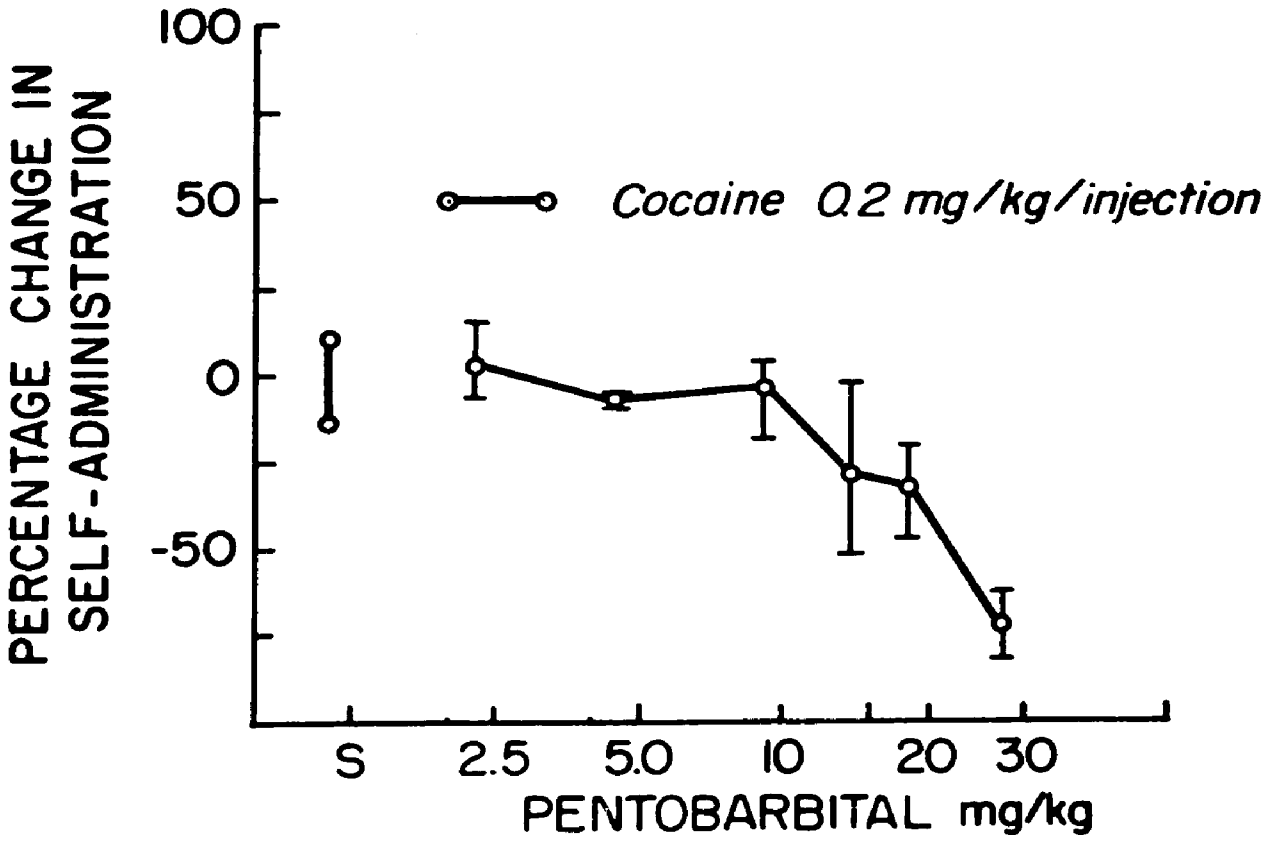

No. 1095 (cocaine 0.2mg/kg)
1st Hour
2nd Hour
3rd Hour
4th Hour
8.0
4.8
1.6
S 0.5 1.0 2.0 4.0 8.0
Cocaine intake (mg/kg)
Pretreatment dose of morphine (mg/kg)

Figure 37. Mean percentage change in cocaine self-administration as a function of the pretreatment dosage of pentobarbital. Each point represents the mean of four subjects and the vertical lines illustrate the range. The brackets at the left represent the range of change in cocaine self-administration, which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 37


100
50
0
-50
PERCENTAGE CHANGE IN SELF-ADMINISTRATION
Cocaine 0.2 mg/kg/injection
S
2.5
5.0
10
20
30
PENTOBARBITAL mg/kg

15, 20 and 30 mg/kg produced a dose-related decrease in cocaine self-administration. These dosages also produced marked CNS depression and motor incapacitation from which the subjects could not be aroused. Figure 38 represents the data obtained from M2068. The 15 mg/kg pretreatment dosage greatly depressed cocaine self-administration during the first hour of the session; however, cocaine intake returned to baseline levels during the second hour, and no change in intake was seen in the last two hours. The 20 mg/kg dosage significantly depressed cocaine self-administration during the first two hours of the session, but intake was normal for the last two hours.

Figure 39 illustrates the effects of trifluoperazine pretreatment on cocaine self-administration. Pretreatment dosages of 10-100 mcg/kg produced a dose-related increase in cocaine self-administration; further increases in pretreatment dosage decreased cocaine intake. The subjects were severely depressed and exhibited signs of dystonia for 24 hours with pretreatment dosages of 200 and 400 mcg/kg. The effect of trifluoperazine pretreatment on cocaine intake in M2068 is shown in Figure 40. Pretreatment with dosages of 0.025 to 0.1 mg/kg produced dose-related increases in cocaine intake in all four hours of the session. Pretreatment with 0.01 mg/kg produced increases in the second and third hour. Pretreatment with 0.2 and 0.4 mg/kg completely suppressed cocaine intake in the last three hours of the session.

The effect of phentolamine pretreatment on cocaine self-administration is demonstrated in Figure 41. Pretreatment with dosages of 0.5-8.0 mg/kg produced no change in cocaine intake.

Figure 38. Alteration in cocaine intake in M2068 as a function of the pretreatment dosage of pentobarbital. The height of the bars indicates cocaine intake during that period, following pretreatment with a given dosage of pentobarbital. The height of the vertical bars over the letter "S" illustrates mean cocaine intake in that period after pretreatment with saline on five different occasions. The vertical lines represent the range of cocaine intake for these five control sessions.

**Figure 38**

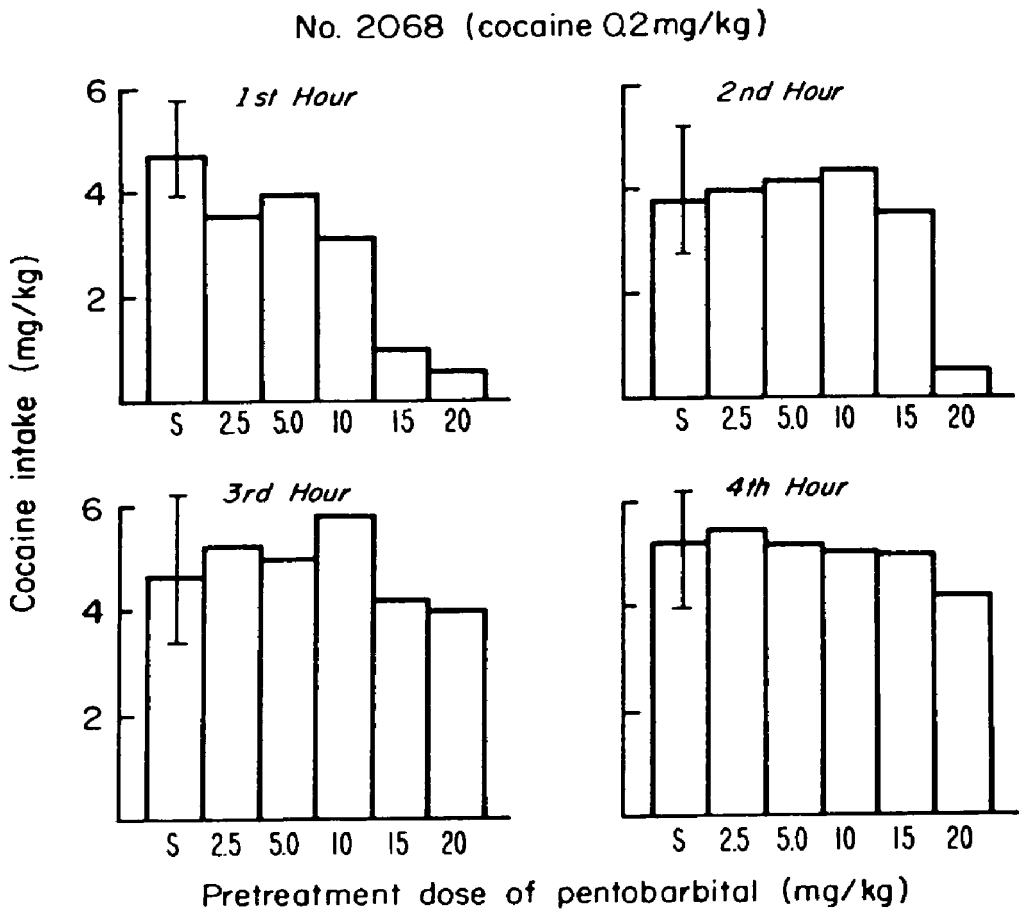

No. 2068 (cocaine 0.2mg/kg)
1st Hour
2nd Hour
3rd Hour
4th Hour
Cocaine intake (mg/kg)
6
4
2
S 2.5 5.0 10 15 20
Pretreatment dose of pentobarbital (mg/kg)

Figure 39. Mean percentage change in cocaine self-administration as a function of the pretreatment dosage of trifluoperazine. Each point represents the mean of four subjects and the vertical lines represent the range. The brackets at the left illustrate the range of change in cocaine self-administration, which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 39

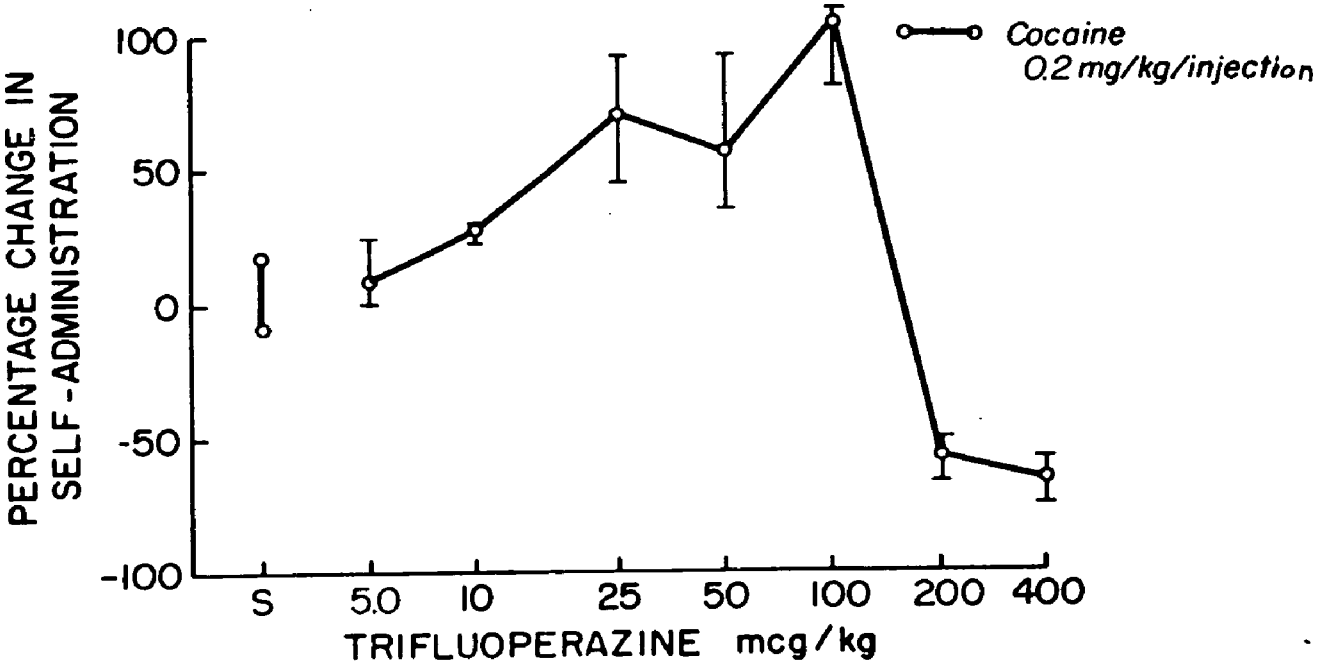

PERCENTAGE CHANGE IN SELF-ADMINISTRATION
100
50
0
-50
-100
S
5.0
10
25
50
100
200
400
TRIFLUOPERAZINE mcg/kg
Cocaine
0.2 mg/kg/injection

Figure 40. Alteration in cocaine intake in M2068 as a function of the pretreatment dosage of trifluoperazine. The height of the bars illustrates cocaine intake during that period, following pretreatment with a given dosage of trifluoperazine. The height of the vertical bars over the letter "S" represents mean cocaine intake in that period, after pretreatment with saline on five different occasions. The vertical lines represent the range of cocaine intake for these five control sessions.

**Figure 40**

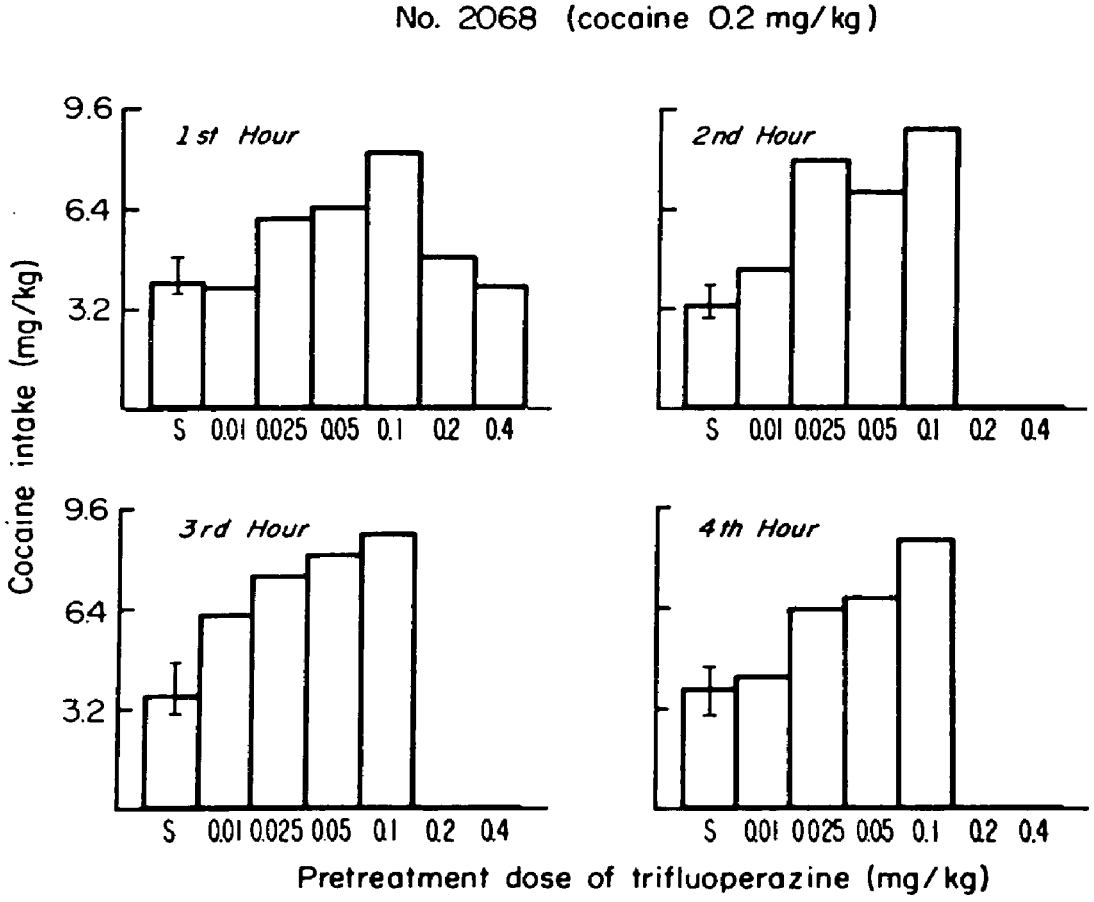

No. 2068 (cocaine 0.2 mg/kg)
1st Hour
2nd Hour
3rd Hour
4th Hour
9.6
6.4
3.2
S 0.01 0.025 0.05 0.1 0.2 0.4
Cocaine intake (mg/kg)
Pretreatment dose of trifluoperazine (mg/kg)

Figure 41. Mean percentage change in cocaine self-administration as a function of the pretreatment dosage of phentolamine. Each point represents the mean of four subjects and the vertical lines indicate the range. The brackets at the left represent the range of change in cocaine self-administration which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 41

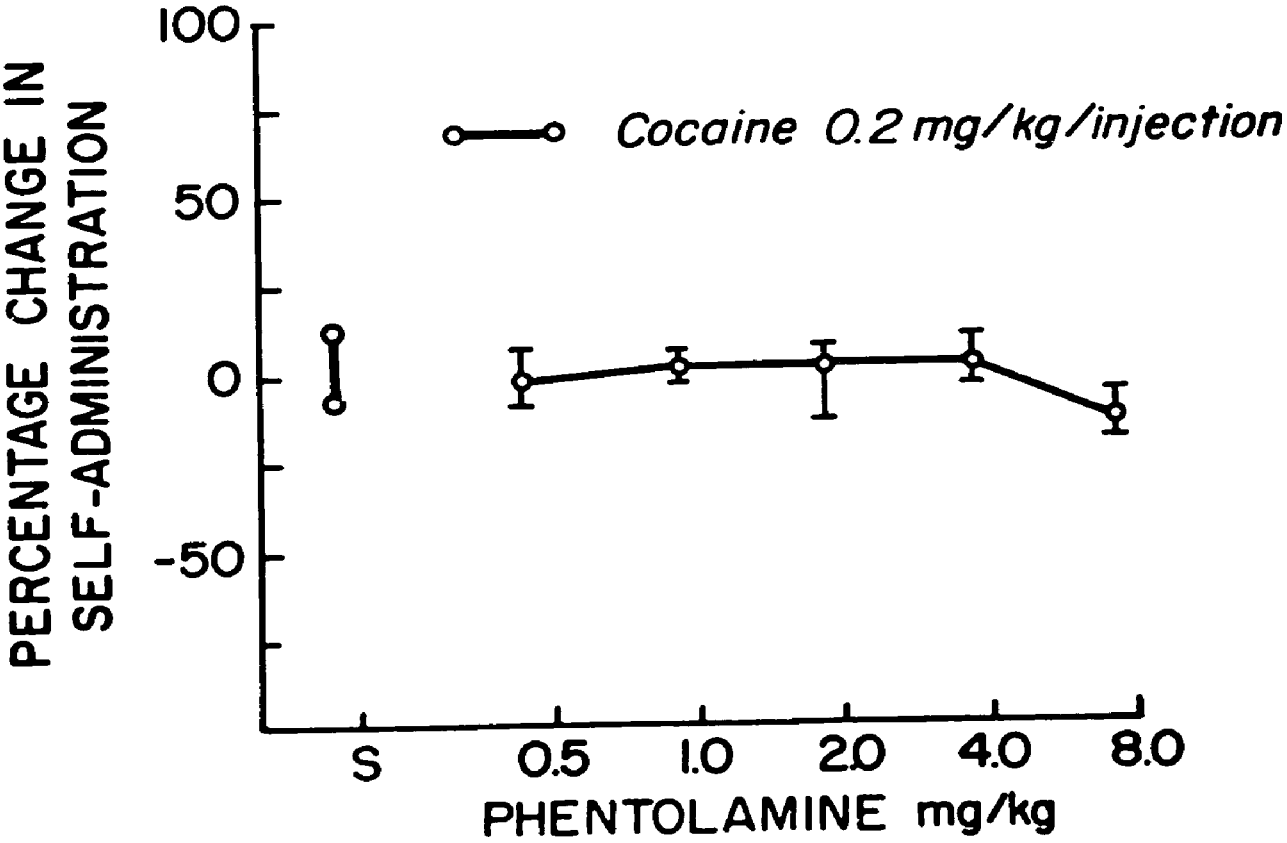

PERCENTAGE CHANGE IN SELF-ADMINISTRATION
100
50
0
-50
Cocaine 0.2 mg/kg/injection
S
0.5
1.0
2.0
4.0
8.0
PHENTOLAMINE mg/kg

Figure 42 shows the effects of phentolamine pretreatment in M2069. There was never any change in cocaine intake seen during any hour of the session, with any pretreatment dosage.

Similar results were seen with phenoxybenzamine pretreatment and these are demonstrated in Figure 43. Phenoxybenzamine pretreatment in dosages of 0.5 to 8.0 mg/kg produced no changes in cocaine intake. The effects of this pretreatment drug on cocaine intake in M2121 are illustrated in Figure 44. There were no changes in cocaine intake seen with any pretreatment dosage of cocaine during any hour of the session. All signs of peripheral sympathetic activity, e.g., salivation, mydriasis, seen during sessions of normal cocaine intake were abolished after pretreatment with phentolamine and phenoxybenzamine.

Figure 45 illustrates the effect of pargyline pretreatment on cocaine self-administration. Pargyline in dosages of 1.0 to 25 mg/kg produced little change in cocaine intake; however, pretreatment with 50 and 100 mg/kg of pargyline did depress cocaine self-administration. The effects of pargyline pretreatment in M331 are demonstrated in Figure 46. Pretreatment with 25, 50, and 100 mg/kg depressed cocaine intake during the first hour of the session, and to a much lesser extent in the second hour of the session. However, cocaine intake with all pretreatment dosages was normal during the third and fourth hours of the session. During those sessions in which cocaine intake was depressed, the subjects exhibited peripheral signs of sympathetic activity of the same magnitude as occurred when the subjects self-administered their normal amount of cocaine.

The effects of pretreatment with alpha-methylparatyrosine

Figure 42. Alteration in cocaine intake in M2069 as a function of the pretreatment dosage of phentolamine. The height of the bars indicates cocaine intake during that period, following pretreatment with a given dosage of phentolamine. The height of the bars over the letter "S" indicates mean cocaine intake in that period, after pretreatment with saline on five different occasions. The vertical lines represent the range of cocaine intake for these five control sessions.

**Figure 42**

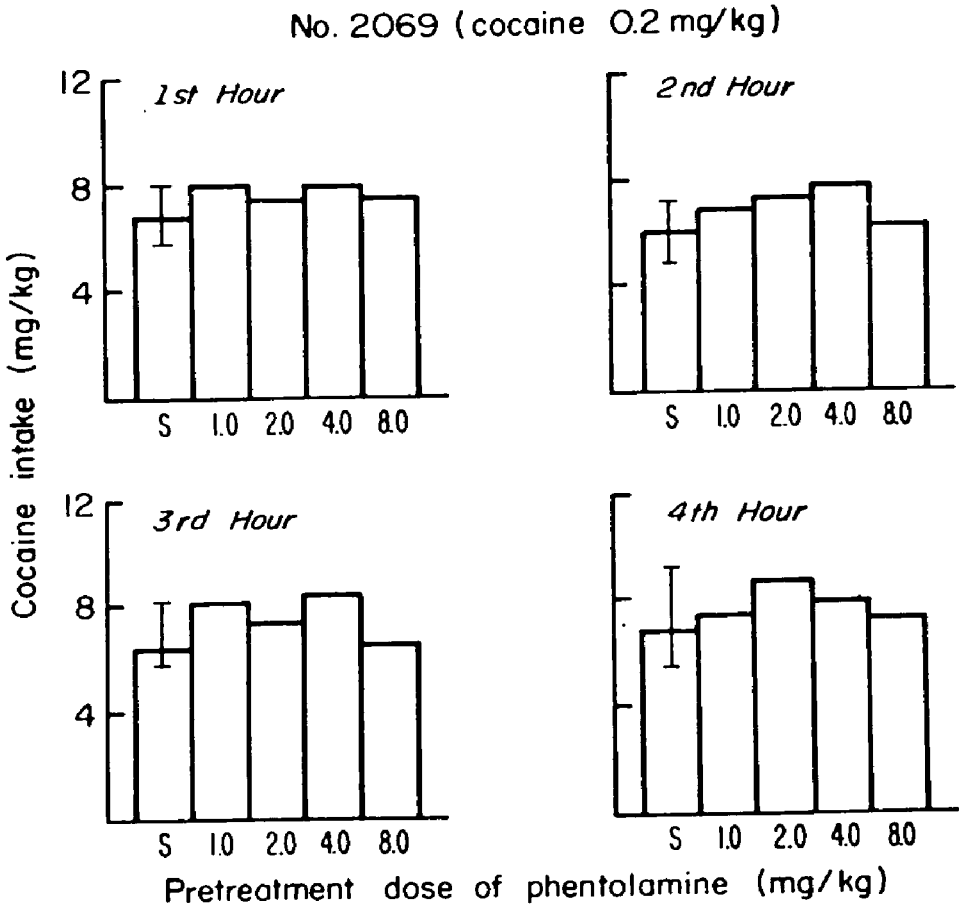

No. 2069 (cocaine 0.2 mg/kg)
1st Hour
2nd Hour
3rd Hour
4th Hour
12
8
4
S
1.0
2.0
4.0
8.0
Cocaine intake (mg/kg)
Pretreatment dose of phentolamine (mg/kg)

Figure 43. Mean percentage change in cocaine self-administration as a function of the pre-treatment dosage of phenoxybenzamine. Each point represents the mean of four subjects, and the vertical lines illustrate the range. The brackets at the left represent the range of change in cocaine self-administration, which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 43

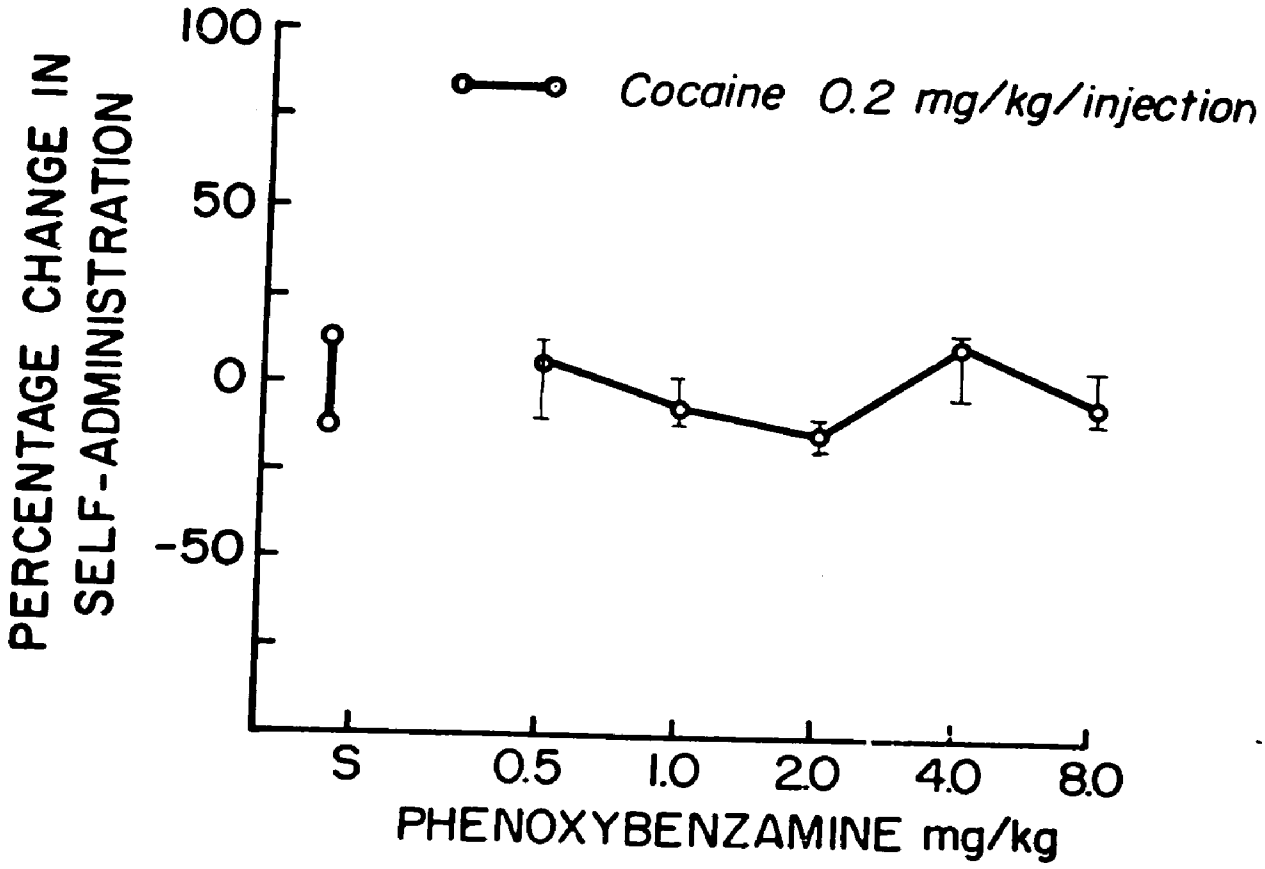

100
50
0
-50
PERCENTAGE CHANGE IN SELF-ADMINISTRATION
Cocaine 0.2 mg/kg/injection
S
0.5
1.0
2.0
4.0
8.0
PHENOXYBENZAMINE mg/kg

Figure 44. Alteration in cocaine intake in M2121 as a function of the pretreatment dosage of phenoxybenzamine. The height of the bars indicates cocaine intake during that period, following pretreatment with a given dosage of phenoxybenzamine. The height of the vertical bars over the letter "S" indicates mean cocaine intake in that period after pretreatment with saline on five different occasions. The vertical lines represent the range of cocaine intake for these five control sessions.

**Figure 44**

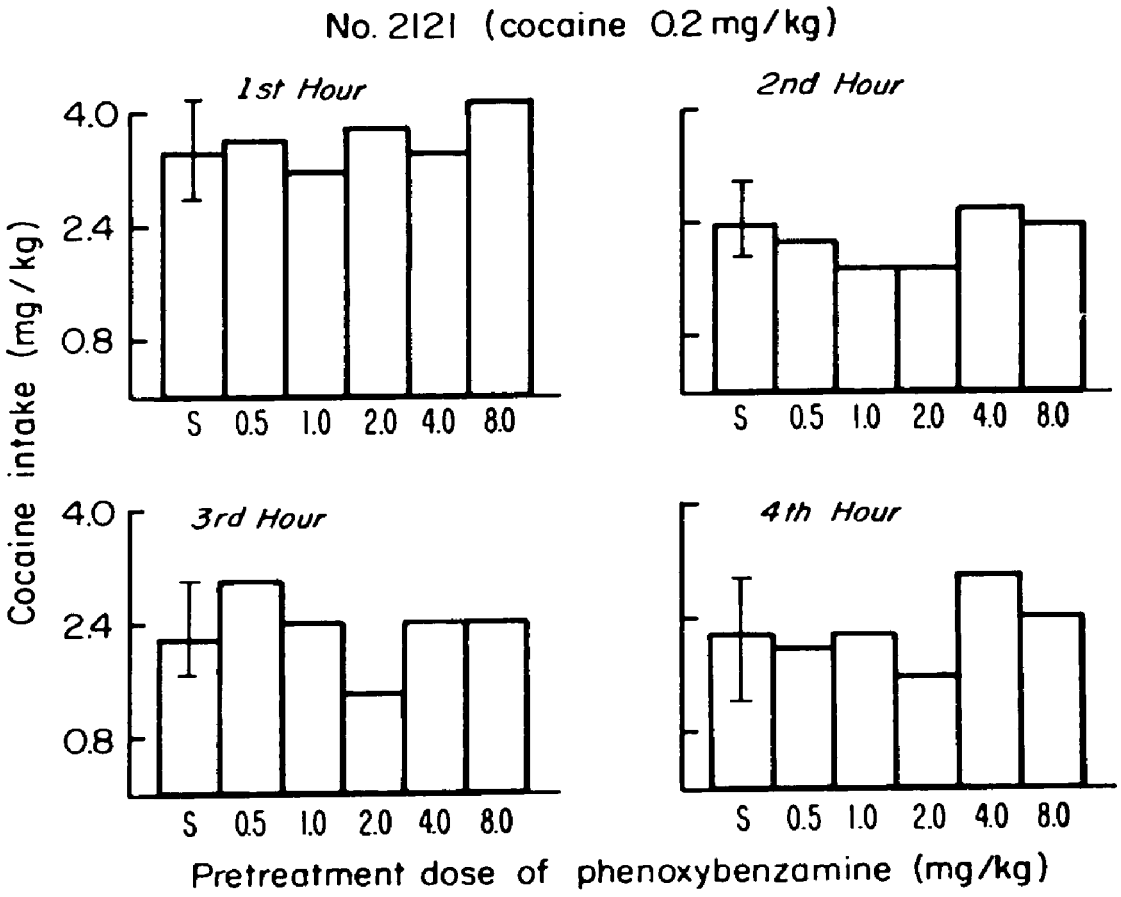

No. 2121 (cocaine 0.2 mg/kg)
1st Hour
2nd Hour
3rd Hour
4th Hour
Cocaine intake (mg/kg)
4.0
2.4
0.8
S 0.5 1.0 2.0 4.0 8.0
Pretreatment dose of phenoxybenzamine (mg/kg)

Figure 45. Mean percentage change in cocaine self-administration as a function of the pretreatment dosage of pargyline. Each point represents the mean of four subjects, and the vertical lines illustrate the range. The brackets at the left indicate the range of change in cocaine self-administration, which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 45

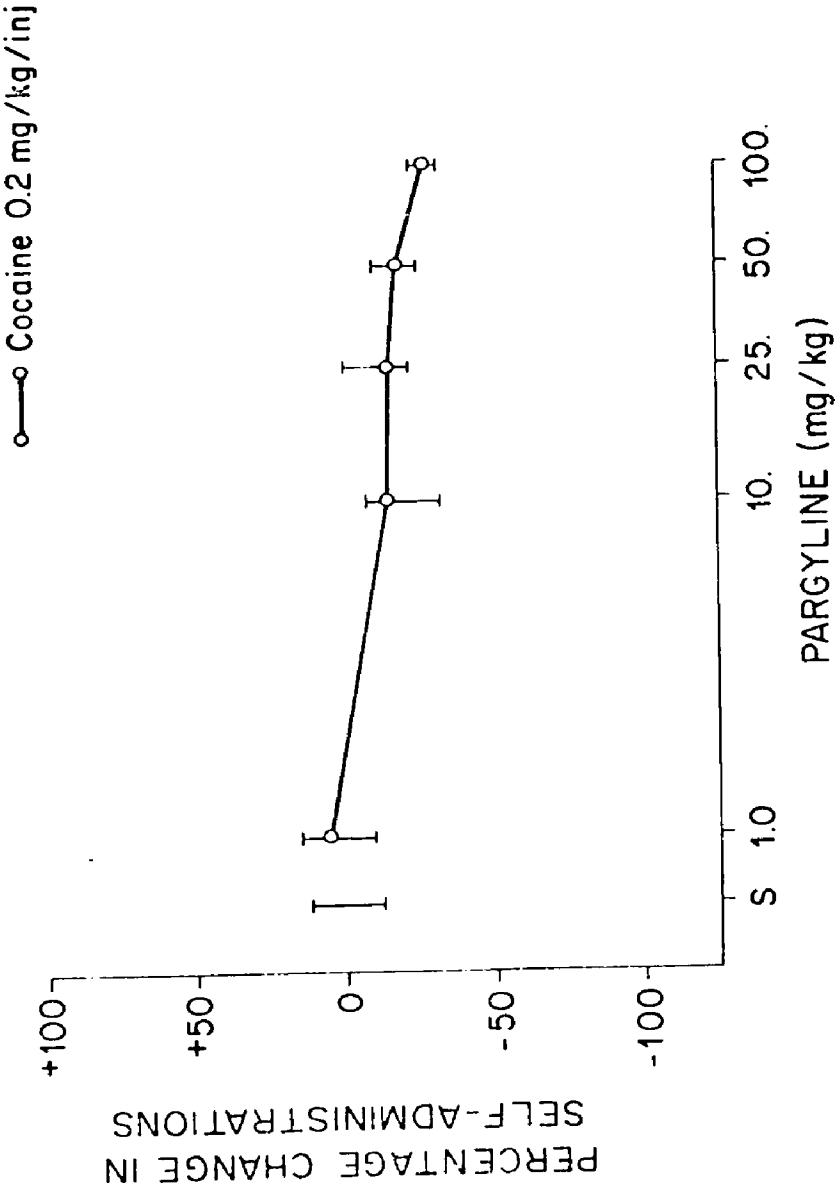
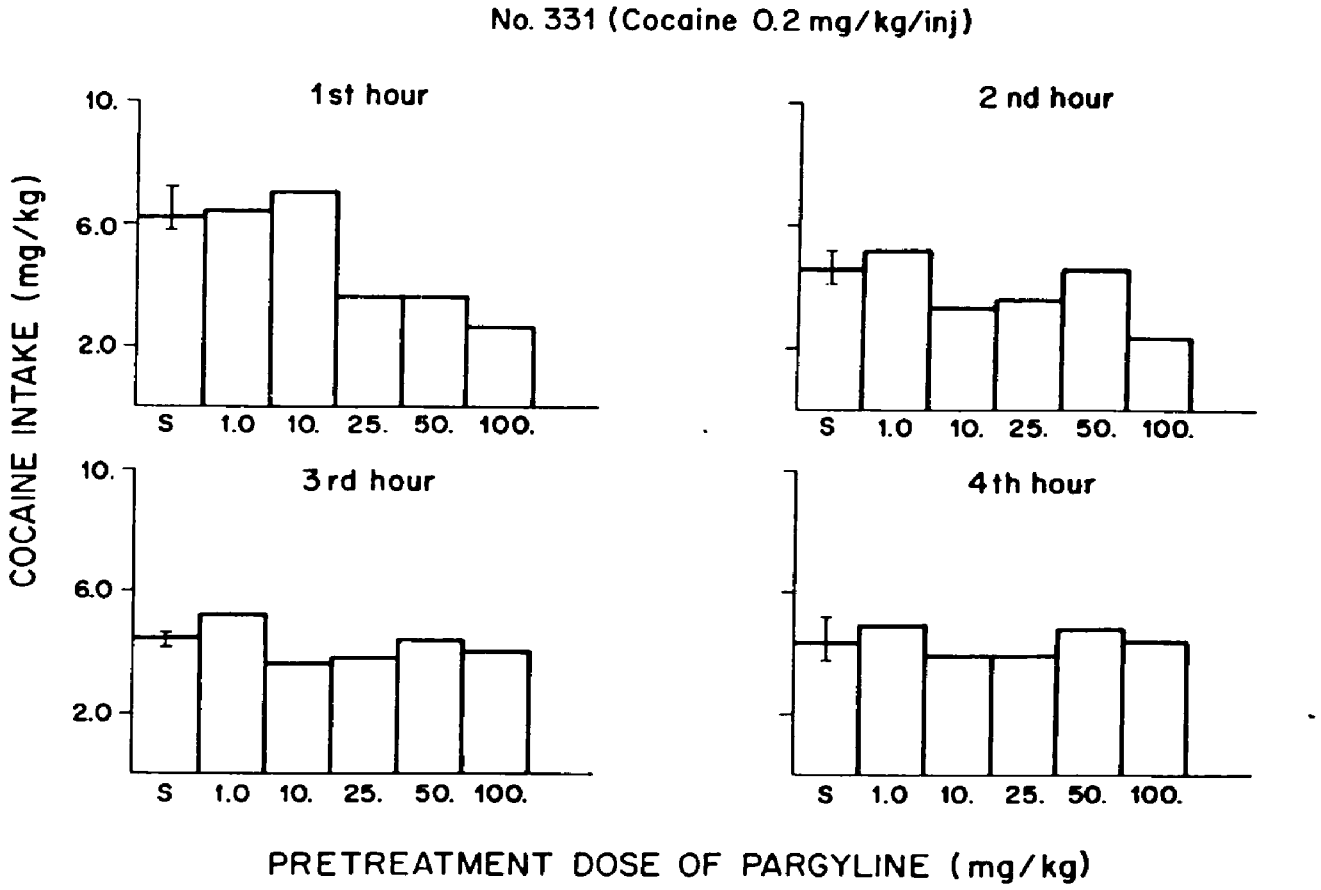

Cocaine 0.2 mg/kg/inj
PERCENTAGE CHANGE IN SELF-ADMINISTRATIONS
+100
+50
0
-50
-100
S
1.0
10.
25.
50.
100.
PARGYLINE (mg/kg)

Figure 46. Alteration in cocaine intake in M331 as a function of the pretreatment dosage of pargyline. The height of the bars indicates cocaine intake during that period, following pretreatment with a given dosage of pargyline. The height of the bars over the letter "S" indicates mean cocaine intake in that period, after pretreatment with saline on five different occasions. The vertical lines represent the range of cocaine intake for these five control sessions.

Figure 46


No. 331 (Cocaine 0.2 mg/kg/inj)
1st hour
2 nd hour
3rd hour
4th hour
10.
6.0
2.0
S
1.0
10.
25.
50.
100.
COCAINE INTAKE (mg/kg)
PRETREATMENT DOSE OF PARGYLINE (mg/kg)

(AMPT) on cocaine self-administration are shown in Figure 47. Pretreatment with 10 and 25 mg/kg of AMPT increased cocaine self-administration in two of the four subjects; however, pretreatment with 50 mg/kg of AMPT increased cocaine intake in all four subjects. Figure 48 illustrates the effects of AMPT pretreatment in M280. Pretreatment with 25 mg/kg of AMPT increased cocaine self-administration in the fourth hour of the session; whereas 50 mg/kg of AMPT increased intake in the second, third and fourth hours of the session. The increase seen in the fourth hour with 50 mg/kg of AMPT was larger than that seen with 25 mg/kg of AMPT.

Figure 49 illustrates the effects of d-amphetamine pretreatment on cocaine self-administration. Increases in pretreatment dosage from 0.5 to 4.0 mg/kg produced a dose-related decrease in cocaine self-administration. The magnitude of the peripheral effects, e.g., mydriasis, salivation, closely resembled those seen on control sessions. The effects of d-amphetamine pretreatment in M2171 are shown in Figure 50. Dose-related decreases in cocaine intake were seen during all four hours of the session. Pretreatment with 2.0 mg/kg completely suppressed lever-pressing behavior during the second and third hours; whereas pretreatment with 4.0 mg/kg resulted in no cocaine intake during the last three hours of the session.

Phenmetrazine pretreatment produced the same results as d-amphetamine pretreatment. Figure 51 illustrates the effect of phenmetrazine pretreatment on cocaine self-administration. As the pretreatment dose of phenmetrazine was increased from 2.0 to 12.0 mg/kg, cocaine intake was progressively decreased. Even though cocaine intake had decreased, the subjects' appearance was

Figure 47. Mean percentage change in cocaine self-administration as a function of the pretreatment dosage of alpha methylparatyrosine (AMPT). Each point represents the mean of four subjects, and the vertical lines illustrate the range. The brackets at the left represent the range of change in cocaine self-administration which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 47

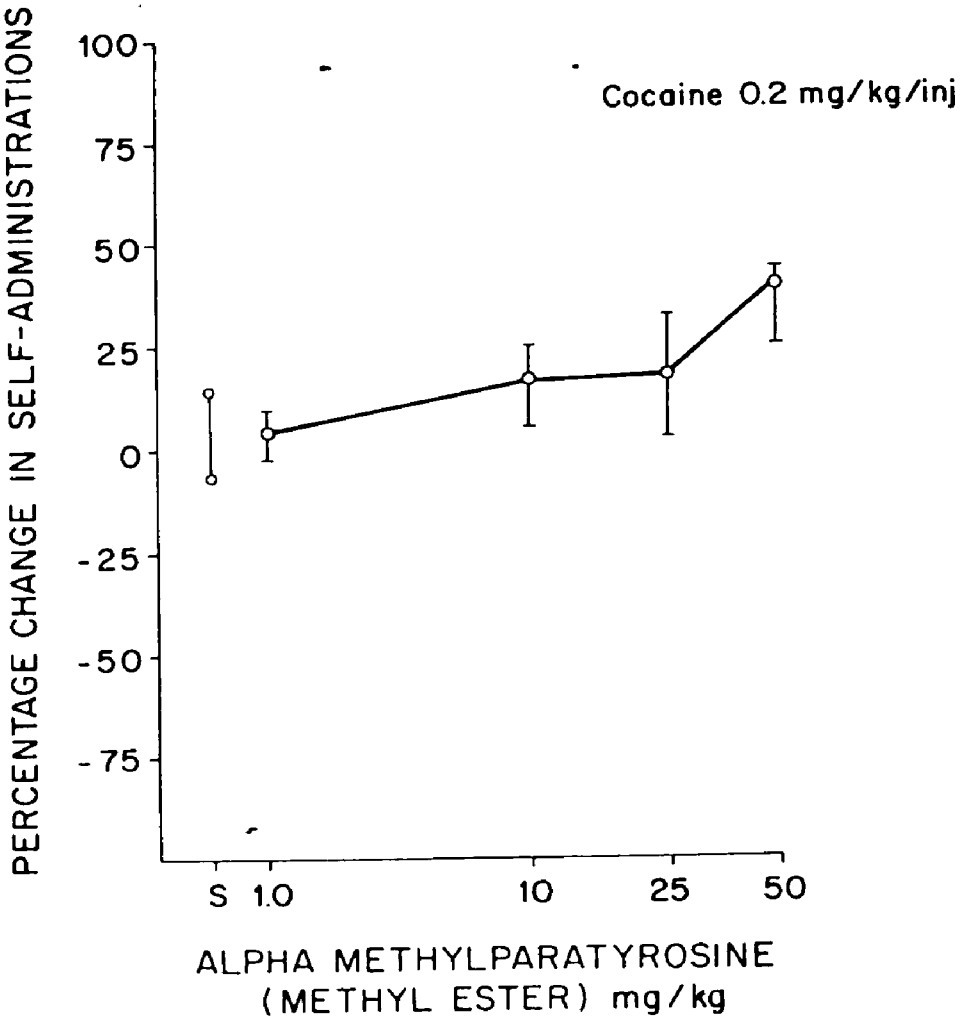

PERCENTAGE CHANGE IN SELF-ADMINISTRATIONS
100
75
50
25
0
-25
-50
-75
Cocaine 0.2 mg/kg/inj
S
1.0
10
25
50
ALPHA METHYLPARATYROSINE
(METHYL ESTER) mg/kg

Figure 48. Alteration in cocaine intake in M280 as a function of the pretreatment dosage of alpha methylparatyrosine (AMPT). The height of the bars indicates cocaine intake during that period, following pretreatment with a given dosage of AMPT. The height of the bars over the letter "S" indicates mean cocaine intake in that period, after pretreatment with saline on five different occasions. The vertical lines represent the range of cocaine intake for these five control sessions.

Figure 48

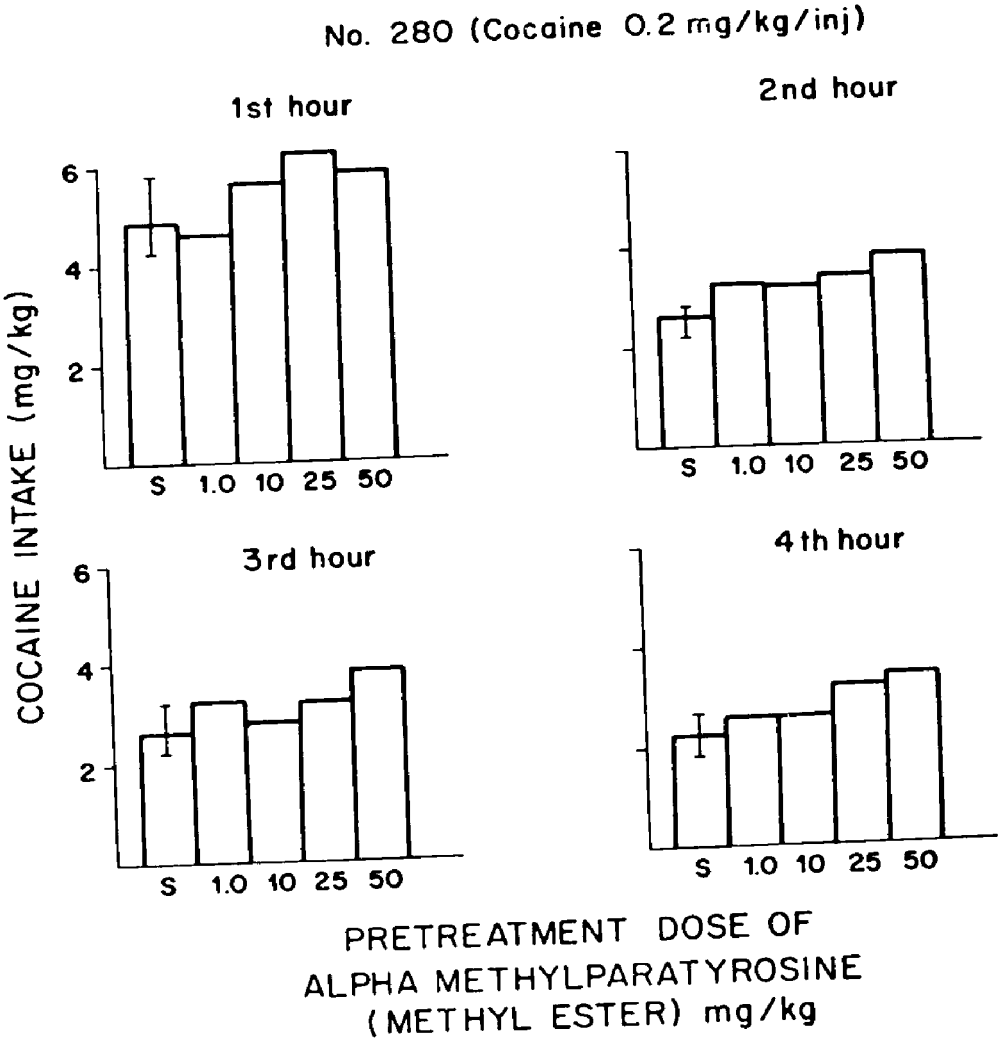

No. 280 (Cocaine 0.2 mg/kg/inj)
1st hour
2nd hour
3rd hour
4th hour
COCAINE INTAKE (mg/kg)
6
4
2
S 1.0 10 25 50
PRETREATMENT DOSE OF
ALPHA METHYLPARATYROSINE
(METHYL ESTER) mg/kg

Figure 49. Mean percentage change in cocaine self-administration as a function of the pretreatment dosage of d-amphetamine. Each point represents the mean of four subjects, and the vertical lines illustrate the range. The brackets at the left represent the range of change in cocaine self-administration which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 49

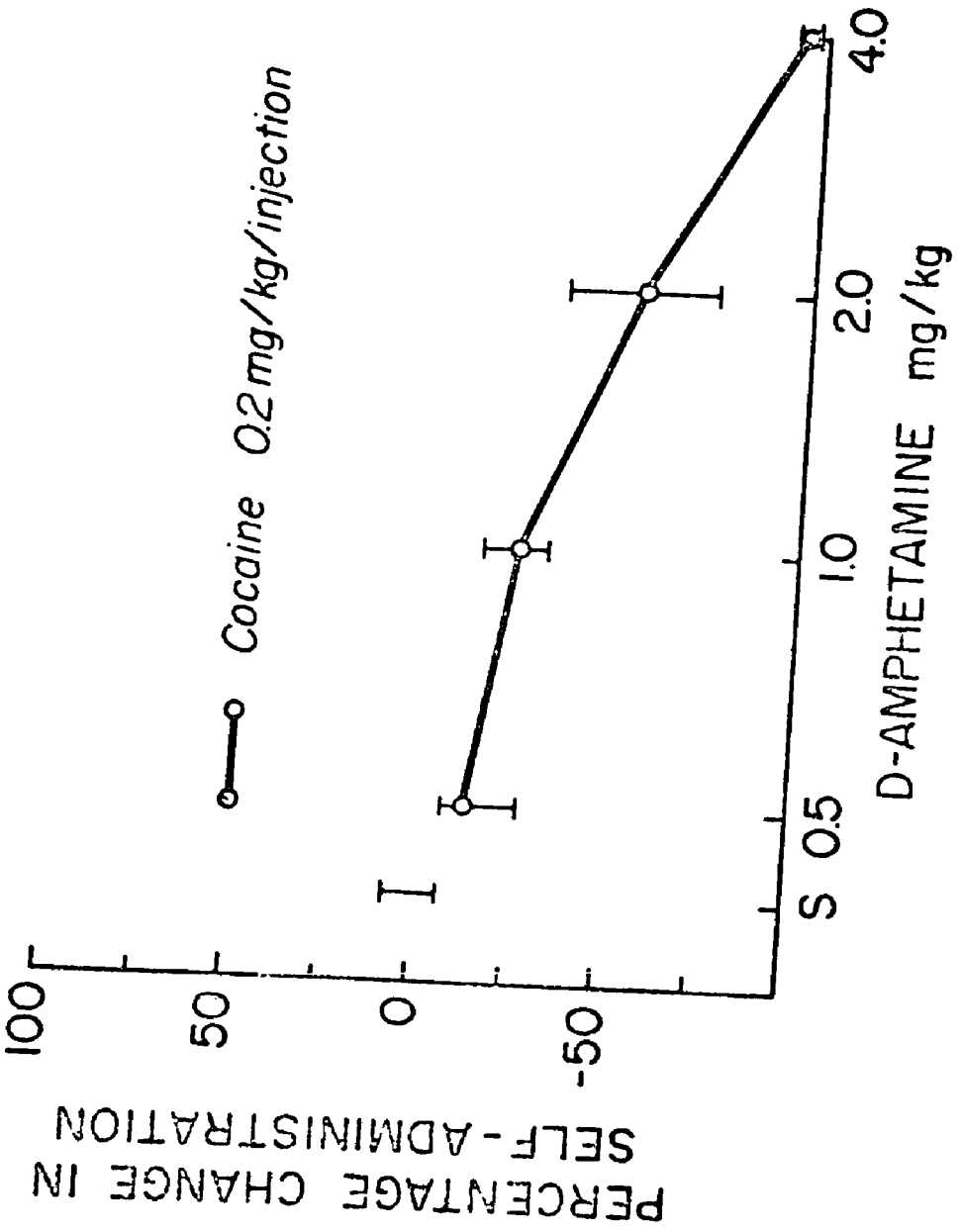

PERCENTAGE CHANGE IN
SELF-ADMINISTRATION
100
50
0
-50
S 0.5
1.0
2.0
4.0
D-AMPHETAMINE mg/kg
Cocaine 0.2 mg/kg/injection

Figure 50. Alteration in cocaine intake in M2171 as a function of the pretreatment dosage of d-amphetamine. The height of the bars indicates cocaine intake during that period, following pretreatment with a given dosage of d-amphetamine. The height of the bars over the letter "S" indicates mean cocaine intake in that period, after pretreatment with saline on five different occasions. The vertical lines represent the range of cocaine intake for these five control sessions.

Figure 50

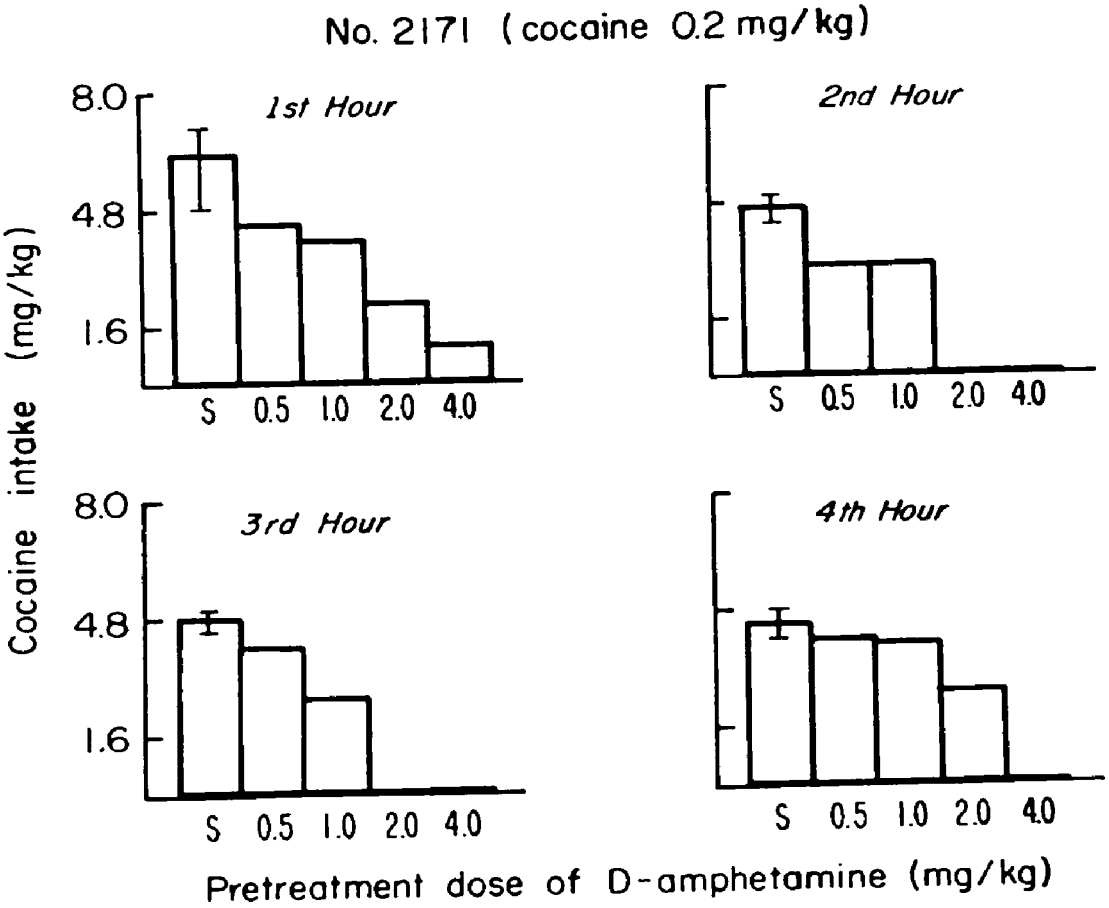
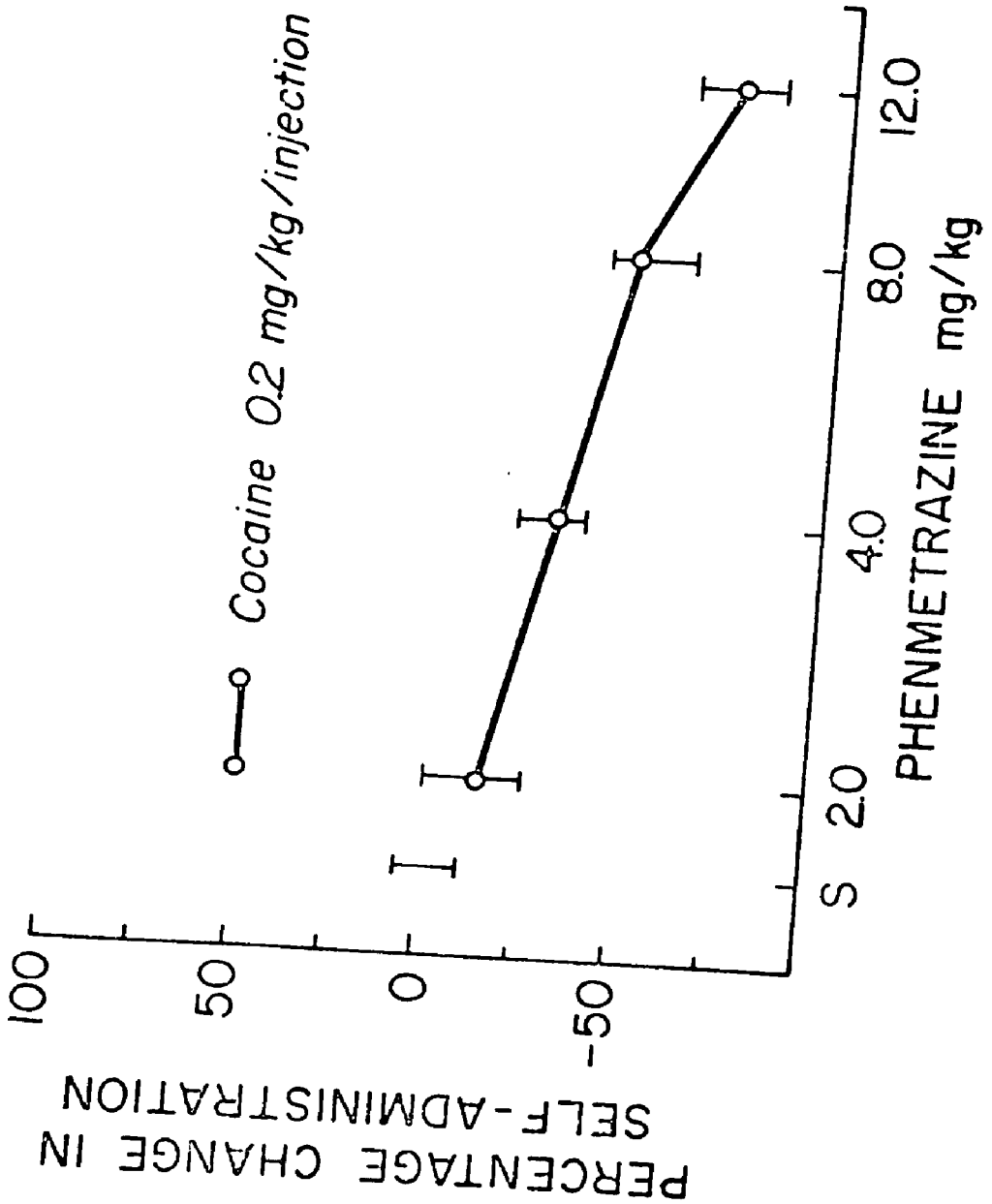

No. 2171 (cocaine 0.2 mg/kg)
1st Hour
2nd Hour
3rd Hour
4th Hour
8.0
4.8
1.6
S 0.5 1.0 2.0 4.0
Cocaine intake (mg/kg)
Pretreatment dose of D-amphetamine (mg/kg)

Figure 51. Mean percentage change in cocaine self-administration as a function of the pretreatment dosage of phenmetrazine. Each point represents the mean of four subjects, and the vertical lines illustrate the range. The brackets at the left represent the range of change in cocaine self-administration which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 51


PERCENTAGE CHANGE IN SELF-ADMINISTRATION
100
50
0
-50
S
2.0
4.0
8.0
12.0
PHENMETRAZINE mg/kg
Cocaine 0.2 mg/kg/injection

identical to that of control sessions. Figure 52 shows the effect of phenmetrazine pretreatment in M2069. In the first and second hours of the session, there was a dose-dependent decrease in cocaine intake as the pretreatment dosage was increased from 2.0 to 12.0 mg/kg. The 12 mg/kg dosage completely suppressed cocaine intake in the second hour. Cocaine intake returned to normal in the third and fourth hours when the pretreatment dosage was 2.0 and 4.0 mg/kg. Cocaine intake was still depressed in the latter half of the session, but to a lesser extent than in the first half with the higher pretreatment dosages, i.e., 8.0 and 12.0 mg/kg.

Figure 53 illustrates the results seen with imipramine pretreatment in four subjects which were self-administering cocaine. As the pretreatment dosage of imipramine was increased from 5.0 to 50.0 mg/kg, cocaine self-administration was progressively decreased. Only one subject was pretreated with the 50 mg/kg dosage due to the potential lethality of the combination of cocaine and imipramine. The subject's general appearance during pretreatment sessions, in which cocaine intake was markedly depressed, was identical to that seen during control sessions. One of the four subjects showed an increase in cocaine intake with the pretreatment dosage of 10.0 mg/kg; however, dosages of 5.0 and 25.0 mg/kg had produced a decrease in cocaine intake in the same subject. The effect of imipramine pretreatment on cocaine intake in M2198 is shown in Figure 54. Pretreatment with 1.0 mg/kg produced no change in cocaine intake at any time during the session. Pretreatment with 5.0, 10.0, and 25.0 mg/kg produced dose-related decrements in each hour of the four-hour session. The greatest decrease in

Figure 52. Alteration in cocaine intake in M2069 as a function of the pretreatment dosage of phenmetrazine. The height of the bars indicates cocaine intake during that period, following pretreatment with a given dosage of phenmetrazine. The height of the bars over the letter "S" indicates mean cocaine intake in that period, after pretreatment with saline on five different occasions. The vertical lines represent the range of cocaine intake for these five control sessions.

**Figure 52**

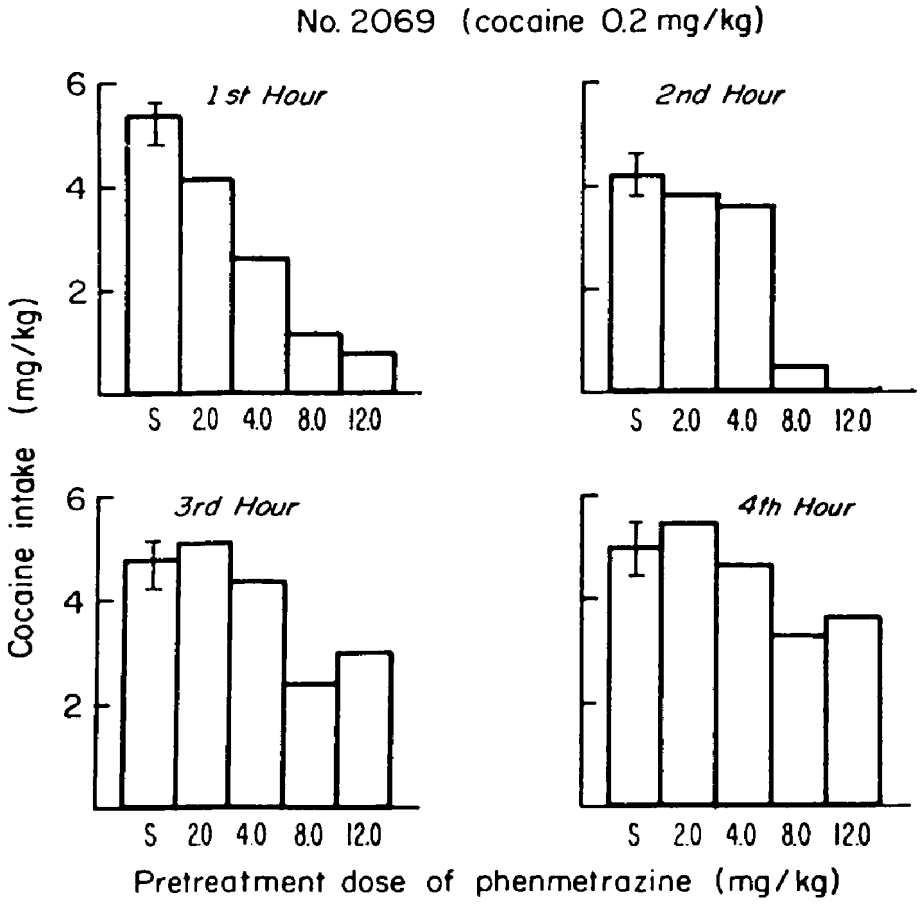

No. 2069 (cocaine 0.2 mg/kg)
1st Hour
2nd Hour
3rd Hour
4th Hour
Cocaine intake (mg/kg)
6
4
2
S 2.0 4.0 8.0 12.0
Pretreatment dose of phenmetrazine (mg/kg)

Figure 53. Mean percentage change in cocaine self-administration as a function of the pretreatment dosage of imipramine. Each point represents the mean of four subjects and the vertical lines illustrate the range. The brackets at the left represent the range of change in cocaine self-administration which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 53

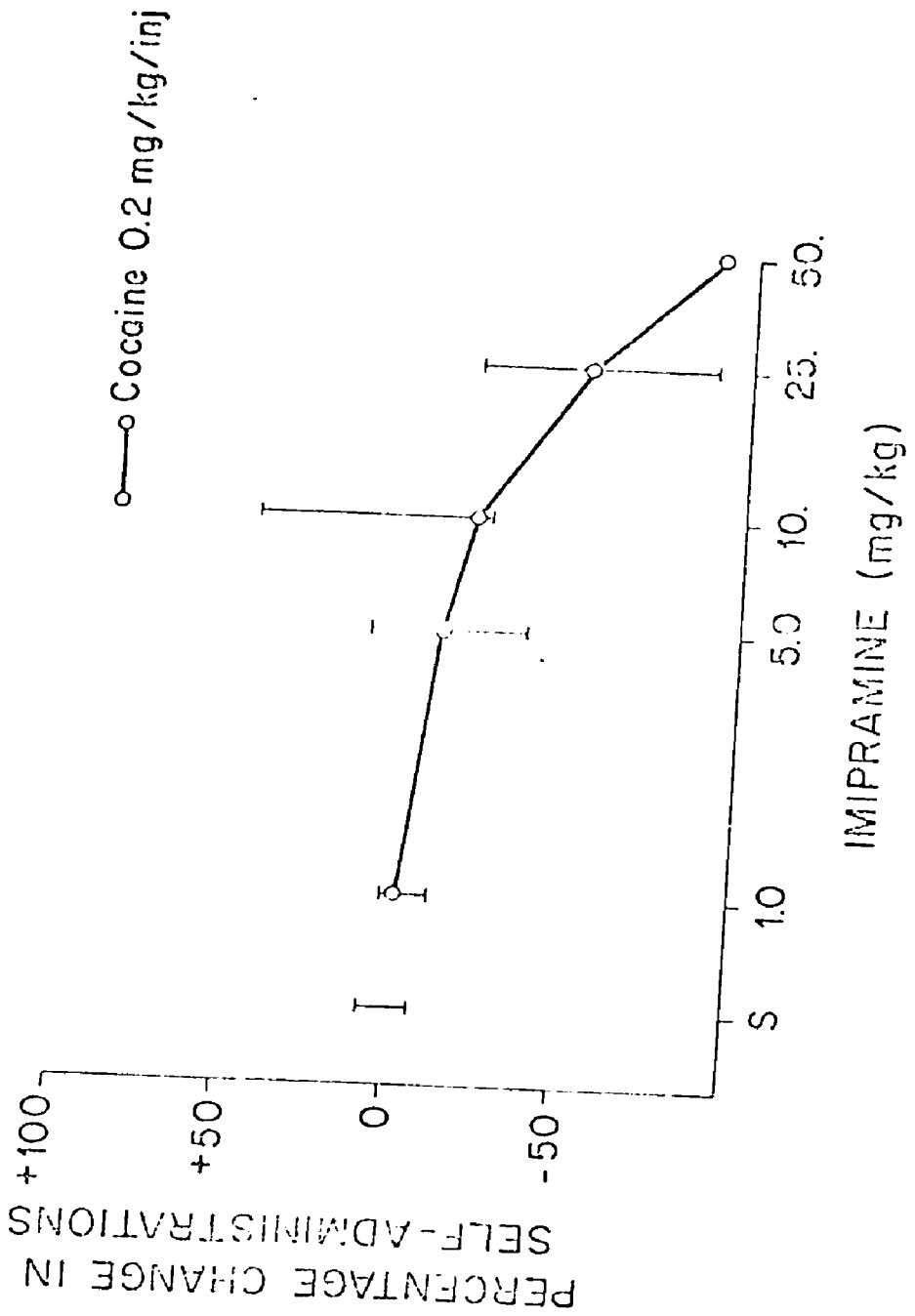
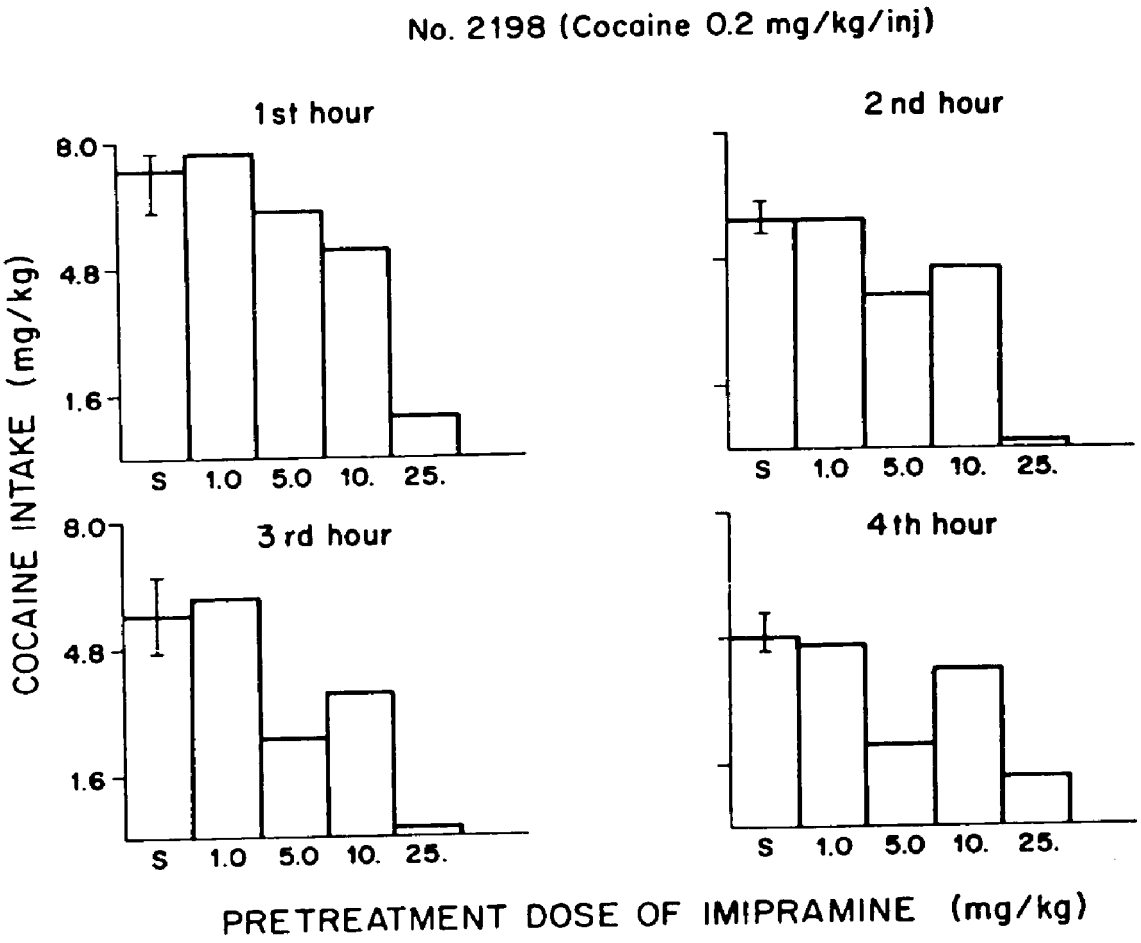

Cocaine 0.2 mg/kg/inj
PERCENTAGE CHANGE IN SELF-ADMINISTRATIONS
+100
+50
0
-50
S
1.0
5.0
10.
25.
50.
IMIPRAMINE (mg/kg)

Figure 54. Alteration in cocaine intake in M2198 as a function of the pretreatment dosage of imipramine. The height of the bars indicates cocaine intake during that period, following pretreatment with a given dosage of imipramine. The height of the bars over the letter "S" indicates mean cocaine intake in that period, after pretreatment with saline on five different occasions. The vertical lines represent the range of cocaine intake for these five control sessions.

Figure 54


No. 2198 (Cocaine 0.2 mg/kg/inj)
1st hour
2nd hour
3rd hour
4th hour
8.0
4.8
1.6
S
1.0
5.0
10.
25.
COCAINE INTAKE (mg/kg)
PRETREATMENT DOSE OF IMIPRAMINE (mg/kg)

cocaine intake was seen in the third hour.

The effects of atropine pretreatment on cocaine self-administration are illustrated in Figure 55. Pretreatment with 0.125 mg/kg produced no change in cocaine intake; however, a dose-related increase in cocaine self-administration occurred as the pretreatment dosage was increased from 0.25 to 2.0 mg/kg. Further increases in pretreatment dosage decreased cocaine intake toward control values. Even when the pretreatment dosage was increased to 3.0 mg/kg, there was no decrement in cocaine intake produced in any of the subjects. Figure 56 shows the effects of atropine pretreatment on cocaine self-administration in M2121. Pretreatment with 0.125 mg/kg produced no changes in cocaine intake at anytime during the session. Pretreatment with 0.25 mg/kg produced increases in cocaine intake during the third and fourth hours of the sessions; whereas pretreatment with 0.5 mg/kg increased cocaine intake during the last three hours of the session. Larger pretreatment dosages, i.e., 1.0, 2.0, and 3.0 mg/kg, produced increases in cocaine intake during only the first three hours of the session. The peak effect with these dosages was seen during the second hour; intake had returned to normal by the fourth hour with all three of these dosages.

Figure 57 illustrates the effect of methylatropine pretreatment on cocaine self-administration. Pretreatment dosages of 0.5-3.0 mg/kg had no effect on cocaine self-administration. The effects of methylatropine pretreatment in M2069 are illustrated in Figure 58. There was no change in cocaine intake seen during any part of the session after pretreatment with methylatropine in dosages of 0.5-3.0 mg/kg.

Figure 55. Mean percentage change in cocaine self-administration as a function of the pretreatment dosage of atropine. Each point represents the mean of four subjects and the vertical lines illustrate the range. The brackets at the left represent the range of change in cocaine self-administration, which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 55

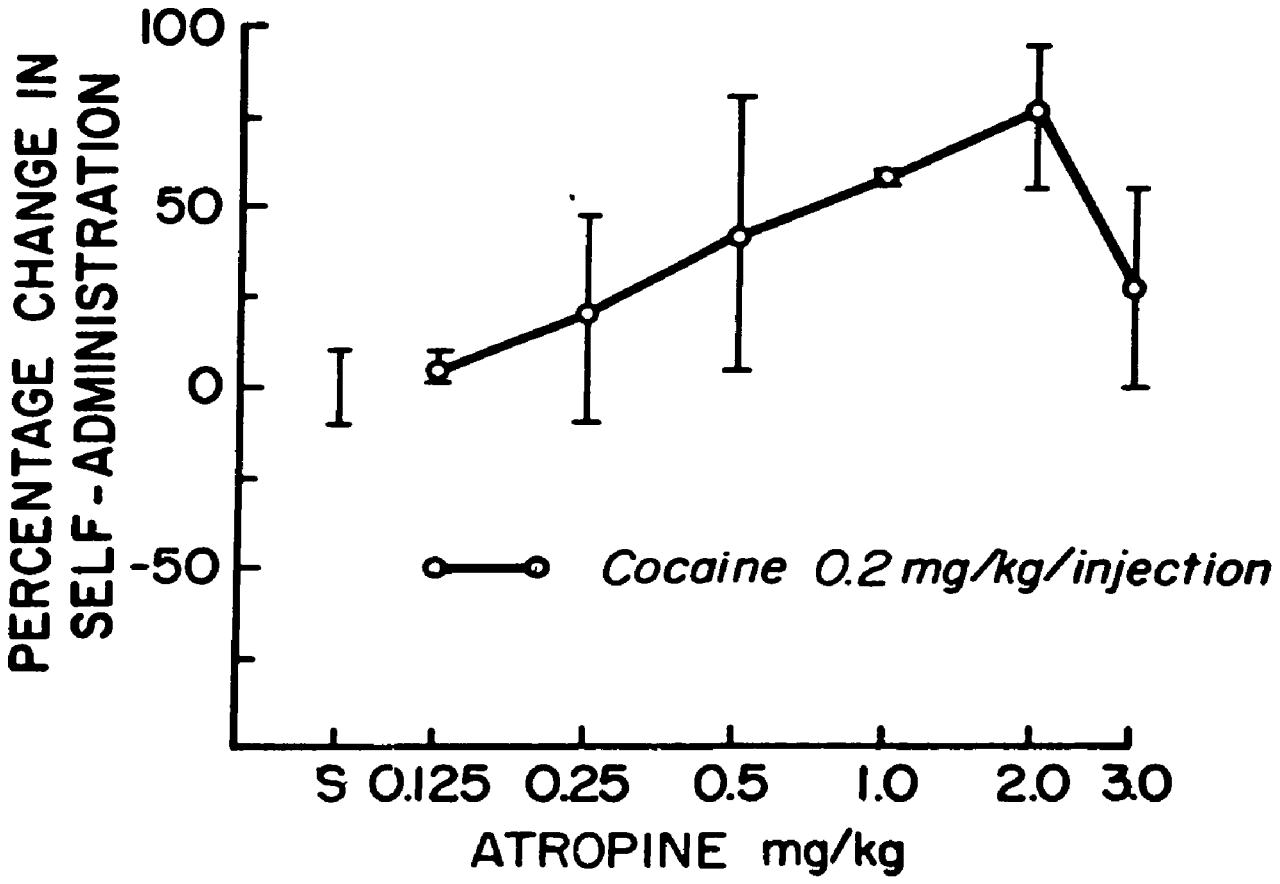

PERCENTAGE CHANGE IN SELF-ADMINISTRATION
100
50
0
-50
Cocaine 0.2 mg/kg/injection
S 0.125 0.25 0.5 1.0 2.0 3.0
ATROPINE mg/kg

Figure 56. Alteration in cocaine intake in M2121 as a function of the pretreatment dosage of atropine. The height of the bars indicates cocaine intake during that period, following pretreatment with a given dosage of atropine. The height of the bars over the letter "S" indicates mean cocaine intake in that period after pretreatment with saline on five different occasions. The vertical lines represent the range of cocaine intake for these five control sessions.

**Figure 56**

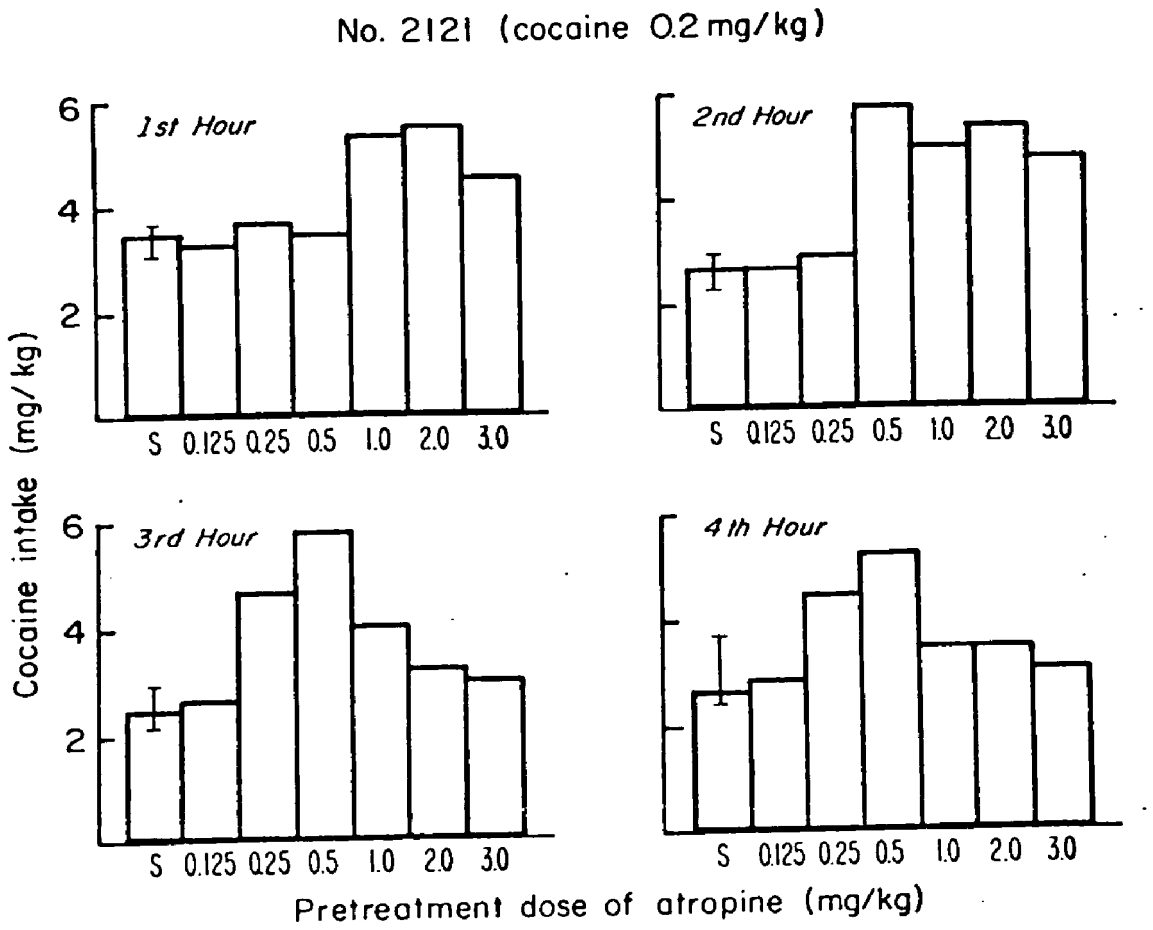

No. 2121 (cocaine 0.2 mg/kg)
1st Hour
2nd Hour
3rd Hour
4th Hour
Cocaine intake (mg/kg)
6
4
2
S 0.125 0.25 0.5 1.0 2.0 3.0
Pretreatment dose of atropine (mg/kg)

Figure 57. Mean percentage change in cocaine self-administration as a function of the pretreatment dosage of methylatropine. Each point represents the mean of four subjects, and the vertical lines illustrate the range. The brackets at the left represent the range of change in cocaine self-administration, which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 57

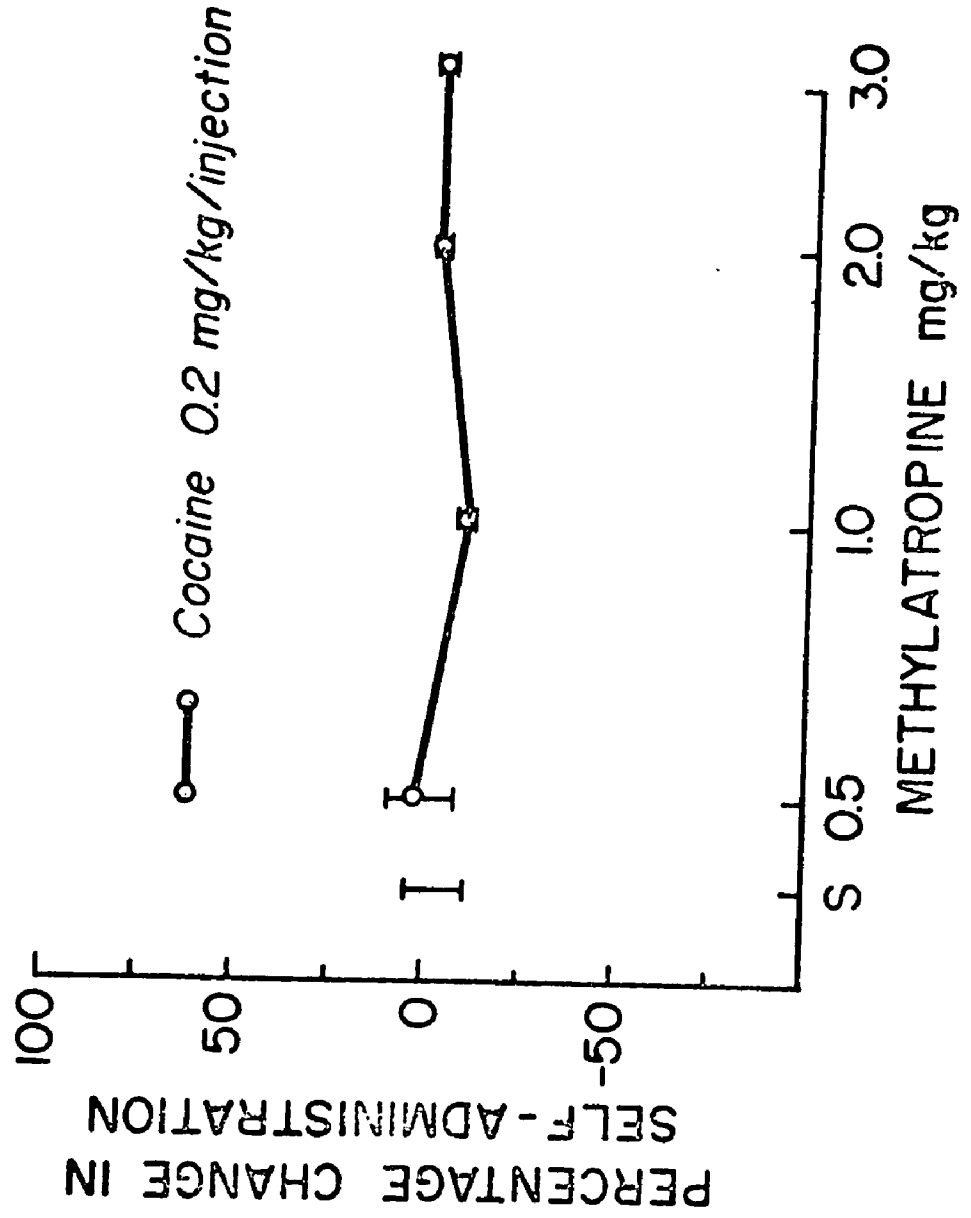
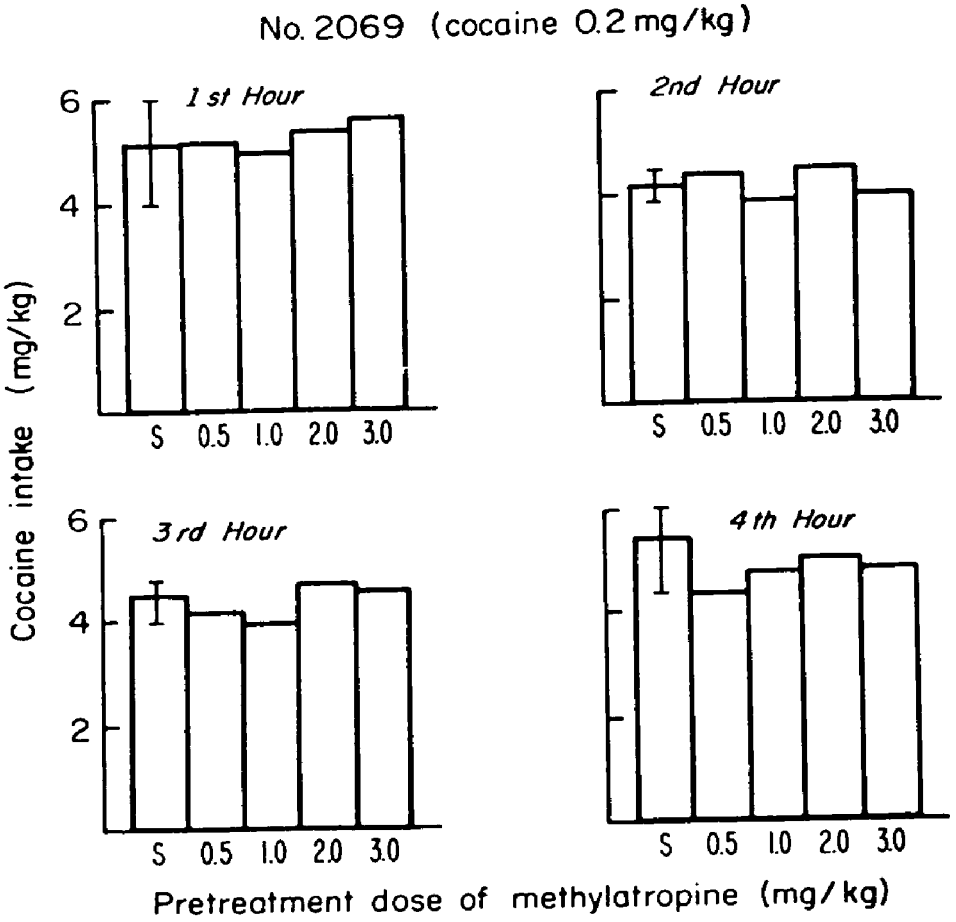

Cocaine 0.2 mg/kg/injection
PERCENTAGE CHANGE IN SELF-ADMINISTRATION
100
50
0
-50
S 0.5
1.0
2.0
3.0
METHYLATROPINE mg/kg

Figure 58. Alteration in cocaine intake in M2069 as a function of the pretreatment dosage of methylatropine. The height of the bars indicates cocaine intake during that period following pretreatment with a given dosage of methylatropine. The height of the bars over the letter "S" indicates mean cocaine intake in that period, after pretreatment with saline on five different occasions. The vertical lines represent the range of cocaine intake for these five control sessions.

**Figure 58**


No. 2069 (cocaine 0.2 mg/kg)
1 st Hour
2nd Hour
3rd Hour
4th Hour
Cocaine intake (mg/kg)
6
4
2
S 0.5 1.0 2.0 3.0
Pretreatment dose of methylatropine (mg/kg)

The effects of physostigmine pretreatment on cocaine self-administration are illustrated in Figure 59. Pretreatment with 0.05 mg/kg produced no change in cocaine intake; however, increases in pretreatment dosage to 0.5 mg/kg produced a dose-related decrease in cocaine administration. Severe nausea, vomiting, diarrhea and lassitude also occurred during those sessions in which cocaine intake was depressed. The effects of physostigmine pretreatment on cocaine intake in M294 are represented on Figure 60. Pretreatment with 0.05 mg/kg of physostigmine produced no change in cocaine intake at any time during the session. Cocaine intake was not affected during the first hour of the session after pretreatment with 0.1 and 0.25 mg/kg. However, dose-related decreases in cocaine intake were observed during the second, third and fourth hours of the session. Pretreatment with 0.5 mg/kg almost completely suppressed cocaine intake during the entire session.

The effects of chronic, i.e., ten day, treatment with reserpine, 0.1 and 0.3 mg/kg, on cocaine self-administration are illustrated in Figure 61. Pretreatment with 0.1 mg/kg of reserpine for ten days produced small increases in cocaine intake on the third day of pretreatment in all subjects. This effect was not seen in any other sessions during treatment, or for seven days after the conclusion of treatment. Cocaine intake remained normal throughout the remainder of the treatment period. Treatment with 0.3 mg/kg of reserpine produced greater increases in cocaine intake than the smaller dosage. This effect was seen in two of the three subjects, and occurred on day one after initiation of treatment in one subject and on days one through four in the other

Figure 59. Mean percentage change in cocaine self-administration as a function of the pretreatment dosage of physostigmine. Each point represents the mean of four subjects, and the vertical lines illustrate the range. The brackets at the left represent the range of change in cocaine self-administration which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 59

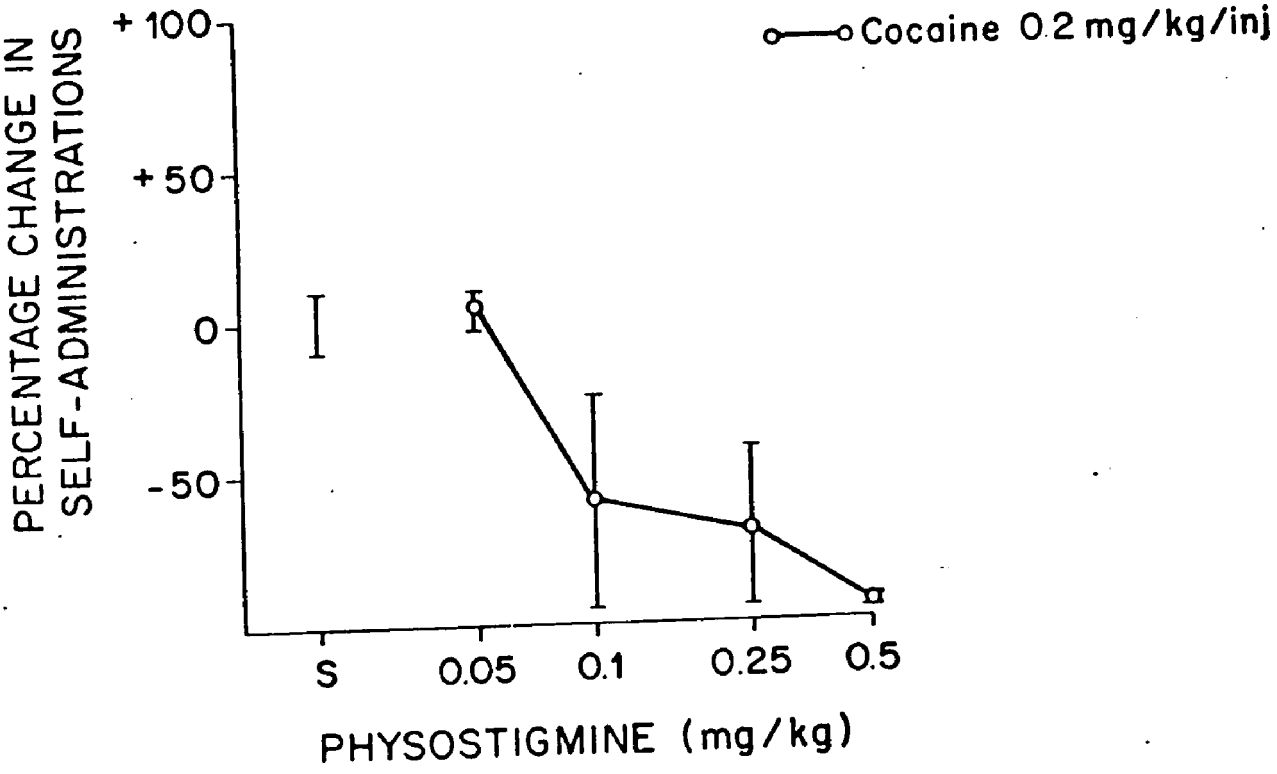

Cocaine 0.2 mg/kg/inj
PERCENTAGE CHANGE IN SELF-ADMINISTRATIONS
+100
+50
0
-50
S
0.05
0.1
0.25
0.5
PHYSOSTIGMINE (mg/kg)

Figure 60. Alteration in cocaine intake in M294 as a function of the pretreatment dosage of physostigmine. The height of the bars indicates cocaine intake during that period, following pretreatment with a given dosage of physostigmine. The height of the bars over the letter "S" indicates mean cocaine intake in that period, after pretreatment with saline on five different occasions. The vertical lines represent the range of cocaine intake for these five control sessions.

Figure 60

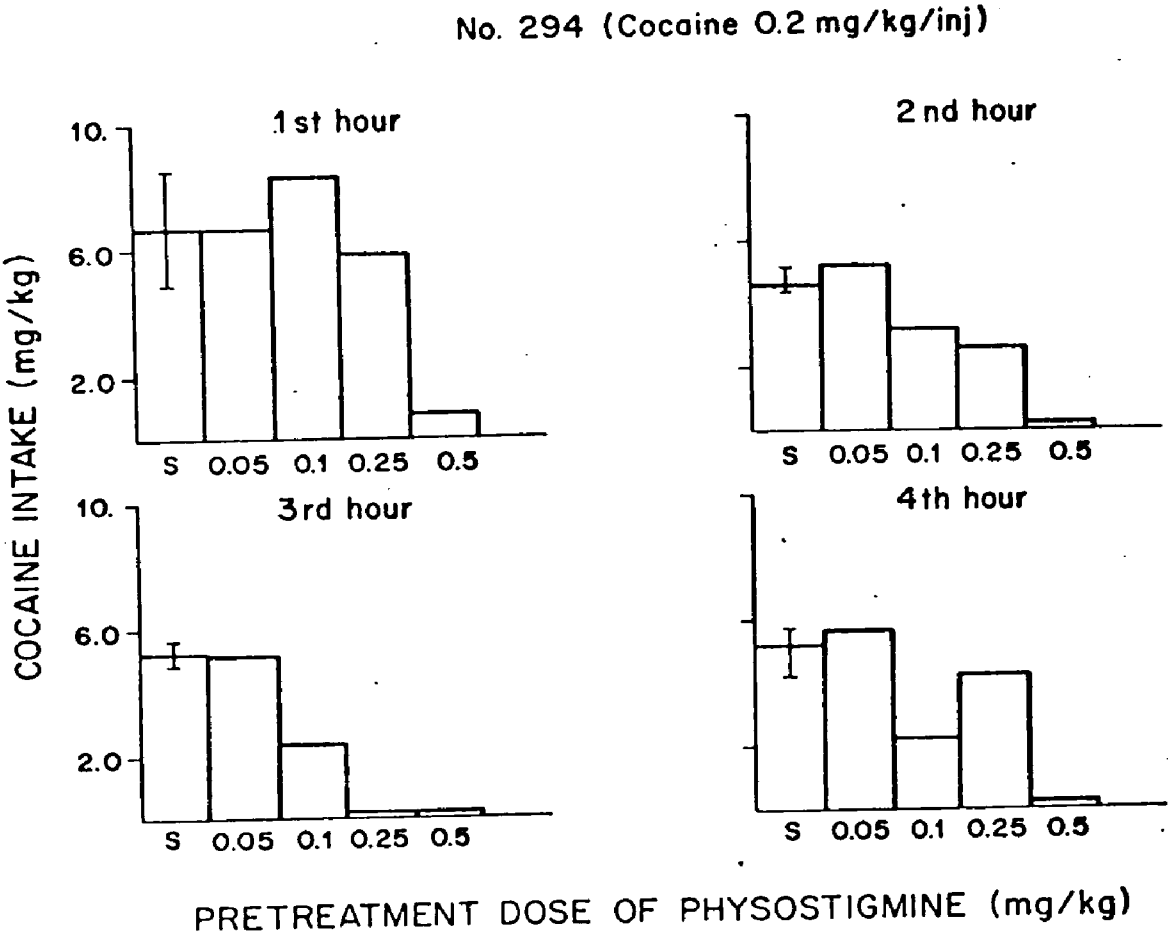
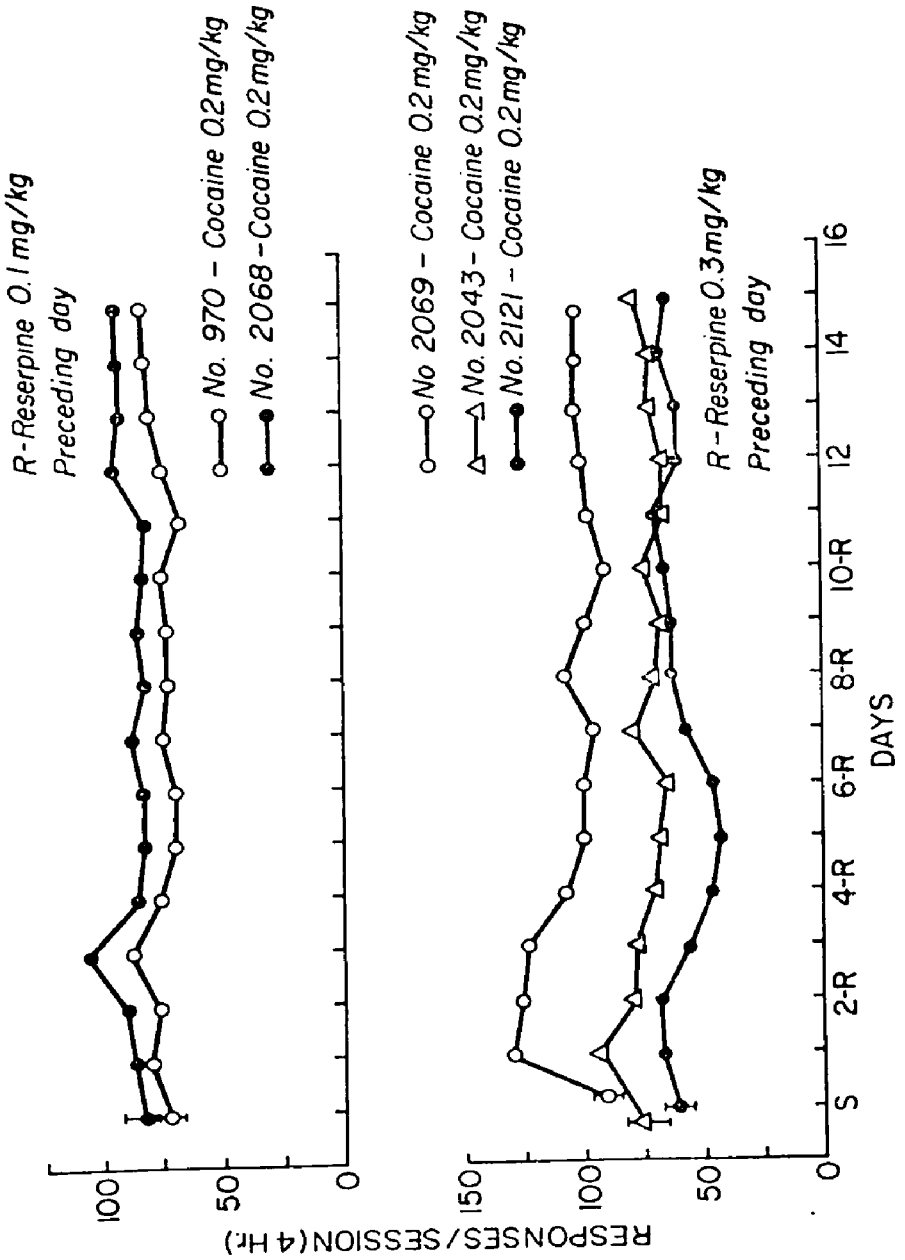

No. 294 (Cocaine 0.2 mg/kg/inj)
1st hour
2nd hour
3rd hour
4th hour
10.
6.0
2.0
S
0.05
0.1
0.25
0.5
COCAINE INTAKE (mg/kg)
PRETREATMENT DOSE OF PHYSOSTIGMINE (mg/kg)

Figure 61. Number of cocaine self-administrations per session during and after chronic treatment with reserpine (0.1 mg/kg, upper graph; 0.3 mg/kg, lower graph). The vertical lines and superimposed symbols at the left represent the range and mean respectively of the number of cocaine self-administrations per session which occurred during the five days prior to the initiation of reserpine treatment.

**Figure 61**


R-Reserpine 0.1 mg/kg
Preceding day
No. 970 – Cocaine 0.2mg/kg
No. 2068 – Cocaine 0.2mg/kg
No 2069 – Cocaine 0.2mg/kg
No. 2043 – Cocaine 0.2mg/kg
No. 2121 – Cocaine 0.2mg/kg
R – Reserpine 0.3mg/kg
Preceding day
RESPONSES/SESSION (4 Hr.)
0
50
100
150
S
2-R
4-R
6-R
8-R
10-R
12
14
16
DAYS

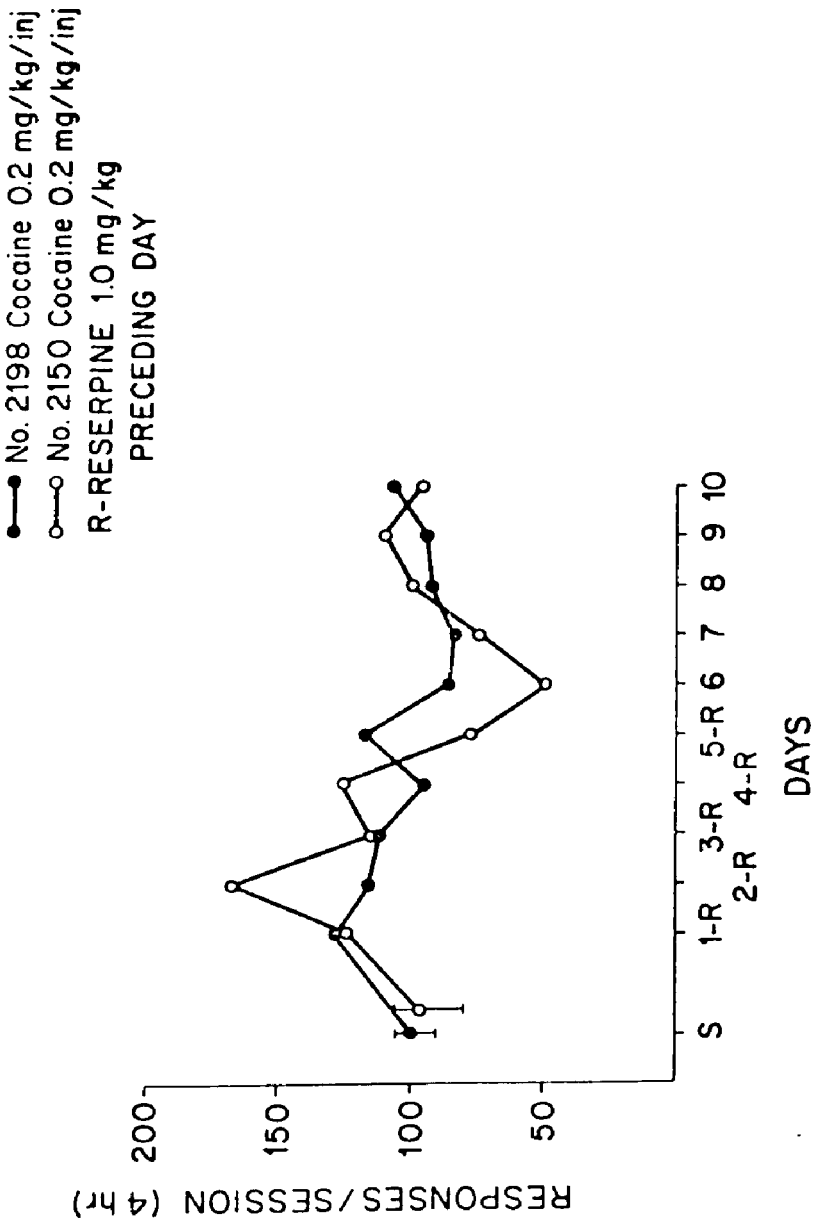
subject. Cocaine intake was within the control range in all other sessions during treatment and for seven days after treatment had concluded. Figure 62 illustrates the effects of five days of treatment with reserpine, 1.0 mg/kg, on cocaine self-administration in two subjects. An increase in cocaine self-administration occurred in both subjects in every session during the period of reserpine treatment. Cocaine intake returned to control levels in one subject, M2198, on the first day after conclusion of the study, and remained within this range for five days. In the other subject, M2150, cocaine intake was depressed in the first session following the termination of reserpine treatment, i.e., forty-four hours following the last injection of reserpine. On the four succeeding days, cocaine intake was within the control range for this subject.

## D. DISCUSSION

The effects of chlorpromazine pretreatment in animals self-administering cocaine is indeed significant. CPZ usually produces a dose-related depression in lever-response frequency for other reinforcers, e.g., food, water[166], intracranial self-stimulation[137], and shock avoidance.[44] Thus, the increased lever-pressing frequency for cocaine following CPZ pretreatment appears to be uniquely related to the nature of this reinforcer. This effect does not appear to be related to the schedule of reinforcement, since similar increases in cocaine intake occurred in subjects on FR-1, FR-10, and FR-25 schedules. The increase in cocaine intake on a given unit dosage may have occurred because CPZ antagonized the reinforcing property of cocaine. Since decreasing the

Figure 62. Number of cocaine self-administrations per session during and after chronic treatment with 1.0 mg/kg of reserpine. The vertical lines and superimposed symbols on the left represent the range and mean respectively of cocaine self-administrations per session which occurred during the five days prior to the initiation of reserpine treatment.

**Figure 62**


No. 2198 Cocaine 0.2 mg/kg/inj
No. 2150 Cocaine 0.2 mg/kg/inj
R-RESERPINE 1.0 mg/kg
PRECEDING DAY
RESPONSES/SESSION (4 hr)
200
150
100
50
S
1-R
2-R
3-R
4-R
5-R
6
7
8
9
10
DAYS

unit dosage of cocaine leads to an increase in the self-administration frequency, an antagonist of cocaine would also initially increase the rate of self-administration.

The work of Stein and Ray[183] provides data which also suggests that CPZ may be acting by blocking the reinforcing effects of cocaine self-administration. These investigators studied the effects of CPZ on intracranial self-stimulation in rats. In these experiments, rats were presented with two levers; the depression of one led to stimulation of a "reward" area. However, the shock intensity decreased progressively with each lever press, but could be reset to its original level by a single response on the other lever. At a dosage level of 1.5 mg/kg of CPZ, the animal pressed the reset lever after fewer consecutive presses of the primary reinforcing lever. Apparently the reward threshold was increased after CPZ treatment, i.e., CPZ antagonized the reinforcing effects of the intracranial self-stimulation. The subjects also pressed the primary reinforcing lever more frequently. These authors postulated that this effect resulted from an action of CPZ in shortening the after effects, i.e., aversiveness or behavioral disruption of the brain shock.

One could also interpret our results as an antagonism of those drug effects, e.g., aversiveness or behavioral disruption, or of central regulatory processes, which limit the self-administration of cocaine. Therefore, cocaine intake increases at a given unit dosage.

The results of pretreatment with pentobarbital and morphine strongly suggest that the CNS depressant action of CPZ was not responsible for its ability to increase cocaine self-administration.

If this had been the case, then similar increases in cocaine self-administration would have been produced with any drug which depressed the central nervous system.

Since similar results were obtained with trifluoperazine pretreatment as were obtained with CPZ, it was concluded that some specific pharmacological action of the phenothiazines is responsible for their ability to increase lever-pressing frequency for cocaine.

The effects of administered sympathomimetic amines and of sympathetic nerve stimulation on many tissues can be blocked by chlorpromazine administration.[16,47,104] In order to determine if it was this property of the phenothiazines which was responsible for the increase in cocaine self-administration, pretreatment with phentolamine and phenoxybenzamine was conducted. These drugs are potent peripheral alpha-adrenergic blocking agents. Since pretreatment with these agents did not increase cocaine self-administration, we can assume that the effect seen with CPZ pretreatment is not due to its peripheral adrenolytic property.

The central effect of chlorpromazine is indeed complex and as yet not understood. Under certain experimental conditions, CPZ appears to be able to decrease the initial uptake and to prolong the disappearance of labeled amine.[80] The extent to which brain slices take up or release norepinephrine when stimulated also is influenced by CPZ.[8] Even though CPZ produces striking behavioral effects, it does not alter the brain levels of norepinephrine or serotonin.[170] However, CPZ does lower striatal dopamine content.[115] The fact that CPZ has been

reported to increase the synthesis rate[45] or turnover[21], and yet not produce elevated norepinephrine levels, might be explained by an antagonistic action on the reuptake process during functional activity. Whether this effect on reuptake is the cause or result of the synthesis increase remains to be determined. Despite the wide variety of biochemical effects attributed to CPZ, many of the behavioral actions of CPZ may result from its actions on the reticular formation where it is known to elevate the threshold for arousal by sensory stimulation.[18] In this system, CPZ blocks neurons excited by norepinephrine and potentiates the inhibitory response of norepinephrine on the other responsive cells possibly by interfering with reuptake. It has also been demonstrated by these authors that neurons which can be excited by norepinephrine in the brain stem can be blocked by CPZ. Therefore, it appears that CPZ can not only potentiate the effect of norepinephrine centrally, but also may block its effect perhaps in a similar manner as occurs peripherally.

Since the psychomotor stimulants are thought to act primarily by interaction with central sympathetic pathways, and also since CPZ interacts centrally with norepinephrine, the effects of other drugs which are known to influence central sympathetic activity were studied on cocaine self-administration behavior.

The results of pretreatment with drugs which facilitate central noradrenergic function, i.e., d-amphetamine, phenmetrazine, and imipramine, were expected. The results of pretreatment with other psychomotor stimulants which are also self-administered, e.g., phenmetrazine and d-amphetamine, suggest that the reinforcing and perhaps also the aversive or behaviorally disrupting effects

of these compounds can substitute for those produced by cocaine. Therefore, the subjects would be getting the effects of a larger unit dosage of cocaine than they were in actuality self-administering. We have shown that increases in unit dosage lead to a decrease in the self-administration frequency. When the pretreatment dosage of d-amphetamine was 4.0 mg/kg, and that of phenmetrazine 12 mg/kg, the subjects self-administered almost no cocaine. These are the same total amounts of these compounds which are normally self-administered by monkeys in a daily four-hour session.

Imipramine is thought to interact with norepinephrine by blocking reuptake of previously released norepinephrine back into the neuron from which it was originally released.(78) Imipramine alters neither the brain concentration of norepinephrine(189) nor the catecholamine fluorescence in central nerve terminals.(9) The ability of peripheral sympathetically innervated tissue to accumulate exogenous norepinephrine is impaired by imipramine and its natural metabolite desmethylimipramine.(96,100) This effect has also been demonstrated in brain slices(55) and in the intact rat brain.(75) It has also been demonstrated that imipramine decreases the rate of disappearance from the brain of accumulated radioactive norepinephrine(76); therefore, it may produce a general decrease in membrane permeability to norepinephrine. Therefore, cocaine and imipramine may produce similar effects on norepinephrine activity in the brain. Furthermore, it has been demonstrated by Angel and Roberts that treatment with imipramine increases cerebrovascular permeability to cocaine in the rat.(3) It would not be

surprising, then, to obtain a decrease in cocaine self-administration following imipramine pretreatment. The effects of imipramine on noradrenergic function may sum with those of cocaine which would be the same as increasing the unit dosage of cocaine, which we have demonstrated leads to a decrease in the frequency of self-administration.

The amount of norepinephrine available for function at synapses may also increase after inhibition of the enzymes that metabolize this biogenic amine in the brain. Monoamine oxidase (MAO) is the enzyme responsible for intraneuronal metabolism of norepinephrine and it has been assumed that MAO inhibitors act in this way. However, the MAO inhibitors may affect norepinephrine metabolism at other sites, and it may be that these are the actions responsible for the antidepressant effect of these compounds. The increased intraneuronal norepinephrine concentration may result in a net increase in the amount of norepinephrine appearing in the synaptic region. This net extraneuronal increase in norepinephrine would help to explain the stimulating effects which result from the administration of MAO inhibitors. MAO inhibitors have been shown to enhance the central stimulation and elevation of catecholamine concentration produced by the administration of precursors of norepinephrine.[30,206] They also reverse the depression and depleting effects on brain amines produced by reserpine[174]; they also enhance the central effects of stimulants like amphetamine, which affect brain norepinephrine metabolism.[32] Pargyline is a MAO inhibitor; therefore, a decrease in cocaine self-administration was expected to be produced by pargyline pretreatment. Pargyline decreased cocaine intake

presumably because the action of cocaine in increasing extraneuronal norepinephrine concentration in the synaptic cleft was potentiated. Therefore, as with imipramine, the effect would be that seen after an increase in unit dosage of cocaine, i.e., a decrease in the number of cocaine self-administrations. This effect of pargyline on cocaine self-administration occurred only when large pretreatment dosages were administered. This was not surprising since Smith demonstrated that treatment with another MAO inhibitor, iproniazid, had no effect on cocaine-induced locomotor activity in mice.(224)

Reserpine lowers brain catecholamine concentration presumably by depletion of intraneuronal norepinephrine. Reserpine exerts similar biochemical effects in the peripheral sympathetic system as in the brain. In the brain, as in peripheral sympathetically innervated tissues, there appears to be a small store of norepinephrine that is not depleted by reserpine.(76,67) The effects of a single dose of reserpine may persist for 48 hours.(46) At the time of functional recovery, central amine concentrations had returned only to a small fraction of normal values. This behavioral recovery paralled the appearance of a small store of brain amines.(90) At the same time, the ability of the brain to accumulate small amounts of exogenous norepinephrine was noted.(79) Similarly the return of sympathetic function after reserpine administration was correlated with the ability of peripheral sympathetically innervated tissue to accumulate small amounts of exogenous norepinephrine.(101)

Reserpine alters the metabolism of brain norepinephrine in a similar manner as in the periphery. There is an increase in

deaminated metabolites[76] which suggests that, after reserpine, more norepinephrine is exposed to intraneuronal MAO. Norepinephrine exists in at least two states in intact neurons; the norepinephrine found in the supernatant subcellular fraction is rapidly depleted by reserpine.[77]

Reserpine also prevents the accumulation of exogenous norepinephrine in the brain as in peripheral tissue, and this is thought to be due to a failure of retention rather than of reuptake.[91,101]

It seems well established, then, that the central catecholamine depleting effect of reserpine involves interference with intraneuronal storage which then allows an increase in the metabolism of norepinephrine by MAO to occur. One might surmise that this decrease in norepinephrine concentration may result in a decrease in norepinephrine which is available for release into the synaptic cleft upon nerve stimulation. If this is indeed the case, then one would expect reserpine to antagonize the action of cocaine if these actions are due to cocaine's effect on reuptake of norepinephrine. The dose-related increase in the frequency of cocaine self-administrations seen with reserpine treatment supports this hypothesis. The antagonism of the effects of cocaine would be similar to decreasing the unit dosage of cocaine, which leads to an increase in the self-administration frequency of cocaine. However, the development of tolerance to this effect of reserpine on cocaine self-administration is difficult to explain. Pirch and Rech have also demonstrated the development of tolerance to the decrease in spontaneous locomotor activity produced by reserpine in the rat.[155]

If one would administer a compound which blocks central neuronal norepinephrine synthesis, one would speculate that the actions of cocaine would be antagonized, if indeed these actions are dependent on the availability of norepinephrine for release into the synaptic cleft. In effect, then, one would be decreasing the unit dosage of cocaine, which we have demonstrated increases the frequency of cocaine self-administration. Alpha-methylparatyrosine (AMPT) is a competitive inhibitor of the enzyme tyrosine hydroxylase, which converts tyrosine to dopa.[175] This is the rate-limiting step in the intraneuronal synthesis of norepinephrine. AMPT produces a rapid and profound decrease in brain norepinephrine.[175] The results seen with AMPT pretreatment in our monkeys which self-administered cocaine, and rats which self-administered methamphetamine[153], indicate that AMPT apparently is antagonizing the actions of cocaine.

Agents which may facilitate central noradrenergic function via prevention of NEPI reuptake, stimulation of NEPI release, or MAO inhibition, tend to cause a decrease in the self-administration frequency of cocaine. This may occur due to a potentiation of cocaine's reinforcing effect, which would be similar to increasing the unit dosage of cocaine, which leads to a reduction in self-administration frequency. Drugs which may interfere with central noradrenergic function via a reduction of NEPI synthesis, postsynaptic receptor blockade, NEPI depletion, etc., cause an increase in the self-administration frequency. Perhaps norepinephrine is a neurotransmitter involved in mediating the reinforcing effects of cocaine and the other psychomotor stimulants.

Drugs which interfere with central noradrenergic function would produce the same effect as decreasing the unit dosage which results in an increase in cocaine self-administration frequency. Drugs which facilitate central noradrenergic function would have the opposite effect.

Another explanation of the results seen with the pretreatment studies which I have discussed up to this point would be the following. Norepinephrine may be the neurotransmitter involved in mediating the action of the psychomotor stimulants, which limits the quantity of their self-administration. Consequently, drugs which facilitate the central actions of NEPI would decrease the frequency of cocaine self-administration. Drugs which interfere with norepinephrine in some manner would have the opposite effect, i.e., an increase in self-administration frequency.

Up to this point, only the results of pretreatment studies with drugs which influence central noradrenergic function in some way have been discussed. The effects seen on cocaine self-administration behavior following pretreatment with agents which affect predominantly the cholinergic system are indeed interesting.

Atropine sulfate has been shown to block the neural transmitting action of acetylcholine at several peripheral neural synaptic sites, and also to have a definite central action.[17] Atropine methylnitrate has a similar peripheral action[66] but does not affect CNS activity as readily as atropine.[144] Therefore, by using these drugs, it is possible to compare the effects of central and peripheral actions of known cholinergic blocking

agents on cocaine self-administration behavior. The increase in cocaine self-administration seen with atropine pretreatment, but not with methylatropine pretreatment, suggests that a central anticholinergic action is responsible for this effect. The increase in cocaine administration may have resulted from atropine antagonizing the reinforcing effects of the cocaine. The subject then would be self-administering a lower unit dosage of cocaine, which leads to an increase in self-administration frequency.

However, this explanation seems less plausible after one reads the literature concerning the interaction of atropine and psychomotor stimulants. Atropine has been shown to potentiate the stimulant effect of cocaine and amphetamine on avoidance responding.(165) Atropine has also been shown to enhance the hypermotility produced either by cocaine or amphetamine.(73) This phenomenon could be explained in the following way: central cholinergic blocking agents, such as atropine, result in an adrenergic predominance and increases the cocaine effect through this mechanism. Carlton and Didamo have demonstrated that atropine, in dosages which are ineffective by themselves, markedly augmented the increases in the rate of lever pressing by rats in a shock avoidance paradigm produced by amphetamine administration.(33) Meannear has also demonstrated that central cholinergic blocking agents potentiate the toxicity of amphetamine in grouped mice.(127) Arnfred and Randrup demonstrated that amphetamine-induced stereotyped hyperactivity of rats was found to be enhanced by anticholinergic drugs and antagonized by cholinergic drugs.(4)

Therefore, since atropine enhanced these effects of cocaine and amphetamine in a number of experimental situations, one would expect to see a decrease in the frequency of cocaine self-administration. This is the effect observed following pretreatment with other drugs which potentiate the action of the psychomotor stimulants.

A possible explanation of the results of atropine pretreatment on cocaine self-administration may be the following: perhaps atropine antagonized the behavioral disrupting or aversive effects of cocaine, thereby permitting an increase in self-administration frequency. Carlton has reviewed experiments in which the results tended to support the hypothesis of a cholinergic inhibitory system which functions to antagonize behavioral activations.(34) Atropine would block such an inhibitory system, thereby permitting behavioral activation or arousal, which, in our example, would be an increase in responding for cocaine.

The results of pretreatment with physostigmine are very difficult to interpret. Decreases in cocaine self-administration were only seen with pretreatment dosages which produced vomiting and diarrhea. However, physostigmine tends to depress conditioned behavior in general. It produces a decrease in active(162) and passive avoidance(24) responding and also food-reinforced responding.(29) These effects were recently confirmed by Vaillant.(201) Therefore, perhaps the decrease in cocaine self-administration was totally unrelated to the gastrointestinal disturbances. Physostigmine, which is a central and

peripheral acting anticholinesterase, would activate the previously postulated cholinergic inhibitory mechanism and thereby decrease ongoing behavior. Perhaps this is the way in which physostigmine depresses operant behavior in general and cocaine self-administration in particular.

## VI. EFFECTS OF CHLORPROMAZINE PRETREATMENT ON THE SELF-ADMINISTRATION OF OTHER PSYCHOMOTOR STIMULANTS (METHYLPHENIDATE, PIPRADROL, D-AMPHETAMINE AND PHENMETRAZINE).

### A. INTRODUCTION

The results of previous experiments dealing with the self-administration of these psychomotor stimulants demonstrated that total drug intake was independent of the magnitude of reinforcement over a wide range of unit dosages. It was also demonstrated that the frequency of self-administration was inversely proportional to the unit dosage over this range of unit dosages. These are the same results which were seen in an identical study in which cocaine self-administration was examined. Therefore, it appeared that a direct effect of these drugs or a central regulatory system was functioning to limit the intake of these compounds. Furthermore, we had demonstrated that pharmacological intervention, i.e., drug pretreatment, could significantly alter the amount of cocaine self-administered at a given unit dosage. It was shown that pretreatment with chlorpromazine increased cocaine intake over a wide range of unit dosages. The present study was designed to determine if pretreatment with chlorpromazine would yield similar results in subjects which were self-administering a wide variety of psychomotor stimulants. If this was the case, then this would provide further evidence in support of the hypothesis that the reinforcing effects of all of the psychomotor stimulants are mediated via a common mechanism or that similar mechanisms control the self-administration behavior of all psychomotor stimulants.

B. METHODS

1. Subjects. The subjects were eight adult Rhesus monkeys, weighing between 3.9 and 5.2 kg. They had been surgically prepared with chronic indwelling jugular catheters. Following surgery, they had been conditioned to self-administer cocaine, 0.2 mg/kg/injection, on a FR-1 schedule of reinforcement. The subjects had access to cocaine for four hours daily, and each subject's total daily cocaine intake varied less than 10% from day to day.

2. Apparatus. The subjects were housed in individual experimental cubicles and were restrained by a stainless steel arm and harness, which were previously described in detail in previous sections of this dissertation. The internal jugular catheter was attached to a connecion on the harness. A second catheter was attached to the other side of the connection and traversed the lumen of the restraining arm, exited the cage through the back wall, and was attached to an injection system which was mounted on the outside of the back wall. A stimulus light and lever were located on the inside of the back wall; when the lever was pressed with at least 100 grams of force during the time in which the stimulus light was illuminated, a microswitch was closed which activated the injector unit. A given amount of drug was injected into the internal jugular vein. The stimulus light was illuminated only during the four-hour drug access period; lever-presses in the absence of the discriminative stimulus were recorded but were without consequence. Cables connected the cubicles to programming and recording equipment which were located in an adjacent

room. Programmed injections were administered to the subjects every six hours to retard clot formation in the catheters.

3. General procedure. Methylphenidate, at a unit dosage of 0.05 mg/kg/injection, was substituted for the cocaine in four of the subjects, and pipradrol, 0.1 mg/kg/injection, was substituted for the cocaine in the other four subjects. Drug solutions were prepared every third day to prevent potency loss due to decomposition. The vehicle for the solutions was sterile physiological saline. Each of the subjects self-administered these compounds for fourteen days. Stable baselines of daily drug intake were attained within this period. Seven pretreatment dosages of chlorpromazine, ranging from 0.125 to 8.0 mg/kg, were administered to each of the eight subjects in a systemmatic order. The pretreatment volume was constant, e.g., 1.0 cc, and pretreatment solutions were prepared on the day in which they were to be used. All pretreatment solutions were prepared using sterile physiological saline. Pretreatment dosages were administered intramuscularly five minutes before the start of the experimental session. At least three days elapsed between drug pretreatment sessions to allow daily drug intake to return to baseline levels and to also provide adequate time for metabolism and excretion of the previously administered pretreatment dosage. Five control pretreatment sessions, i.e., 1.0 cc of sterile physiological saline, were conducted in each subject throughout the course of the study. After the control sessions and CPZ pretreatment sessions had been conducted in these subjects, which were self-administering methylphenidate and pipradrol, the

psychomotor stimulants being self-administered were changed. Phenmetrazine, 0.1 mg/kg/injection, was substituted for the methylphenidate and d-amphetamine, 0.025 mg/kg/injection, was substituted for the pipradrol. The same procedure was then repeated in the eight subjects. Following stabilization of total daily uptake within fourteen days, each subject was pretreated with five dosages of chlorpromazine and five injections of saline.

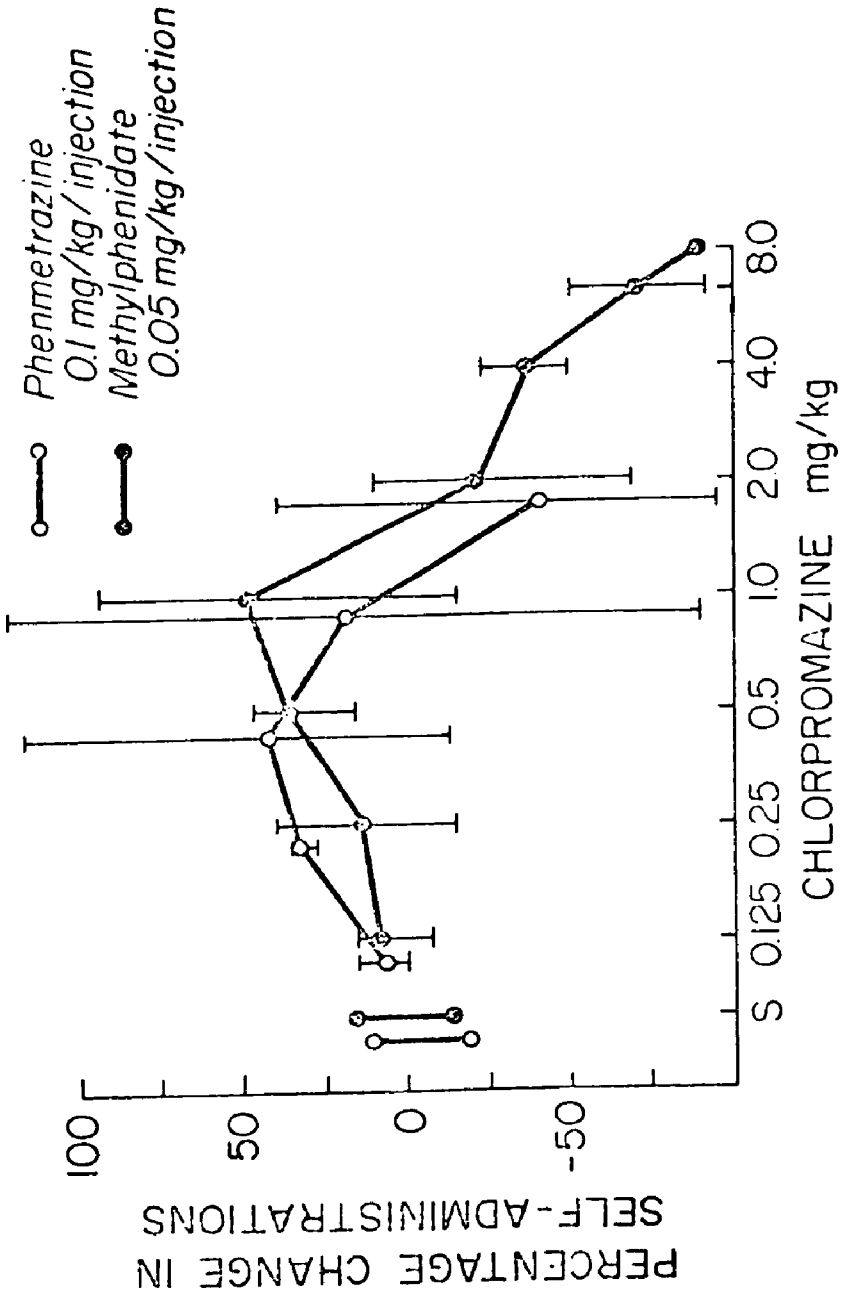
C. RESULTS

Figure 63 demonstrates that chlorpromazine pretreatment increased both phenmetrazine and methylphenidate self-administration behavior. CPZ in dosages of 0.25-1.0 mg/kg increased phenmetrazine intake. Increases were not seen in all subjects with all of these pretreatment dosages, however. As the pretreatment dosage was increased from 0.25-1.0 mg/kg, the variability in effect increased. This was due to intersubject sensitivity to the general CNS depressant effects of CPZ. Increases in the pretreatment dosage of CPZ above 1.0 mg/kg decreased phenmetrazine self-administration. The subjects at these dosages were catatonic and markedly depressed.

Pretreatment with 0.5 and 1.0 mg/kg of CPZ increased methylphenidate self-administration. Lower dosages also increased this behavior in some of the subjects. Pretreatment with 0.125 mg/kg of CPZ had no effect on methylphenidate self-administration in any of the subjects. Pretreatment with 2.0, 4.0, and 8.0 mg/kg of CPZ produced a dose-related depression in methylphenidate self-administration. At these dosages, the subjects exhibited extreme

Figure 63. Mean percentage change in phenmetrazine and methylphenidate self-administration as a function of the pre-treatment dosage of chlorpromazine. Each point represents the mean of four subjects and the vertical lines illustrate the range. The brackets at the left represent the range of change in phenmetrazine and methylphenidate self-administration which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 63


Phenmetrazine
0.1 mg/kg/injection
Methylphenidate
0.05 mg/kg/injection
PERCENTAGE CHANGE IN
SELF-ADMINISTRATIONS
100
50
0
-50
S 0.125 0.25 0.5 1.0 2.0 4.0 8.0
CHLORPROMAZINE mg/kg

motor incapacitation.

The effects of chlorpromazine pretreatment on methylphenidate self-administration in M2150 is illustrated in Figure 64. Pretreatment with 0.125 mg/kg of CPZ increased drug intake in the first and second hours of the session; whereas pretreatment with 0.25 mg/kg increased intake in the first, second, and fourth hours. Methylphenidate intake was increased in all four hours of the session after pretreatment with 0.5, 1.0 and 2.0 mg/kg of CPZ. Pretreatment with 4.0 mg/kg had no effect on drug intake during any part of the session; whereas, pretreatment with 6.0 mg/kg of CPZ completely suppressed self-administration behavior in the last three hours of the session.

The effects of chlorpromazine on phenmetrazine self-administration in M212 is shown in Figure 65. CPZ in dosages of 0.125 and 0.25 mg/kg did not alter phenmetrazine self-administration during any hour of the session. Phenmetrazine intake was increased during every hour of the session following pretreatment with 0.5 and 1.0 mg/kg of CPZ. Pretreatment with 2.0 mg/kg of CPZ decreased drug intake in the first two hours, but increased phenmetrazine intake above control values during the last two hours of the session.

Figure 66 illustrates the mean percentage changes in pipradrol and d-amphetamine self-administration as a function of the pretreatment dosage of chlorpromazine. Pretreatment with 0.125 mg/kg of CPZ had no effect on d-amphetamine self-administration behavior; however, dosages of 0.25 and 0.5 mg/kg increased d-amphetamine intake in some of the subjects. Pretreatment with

Figure 64. Alteration in methylphenidate intake in M2150 as a function of the pretreatment dosage of chlorpromazine. The height of the bars indicates methylphenidate intake during that period following pretreatment with a given dosage of chlorpromazine. The height of the bars over the letter "S" indicates mean methylphenidate intake in that period after pretreatment with saline on five different occasions. The vertical lines represent the range of methylphenidate intake for these five control sessions.

Figure 64

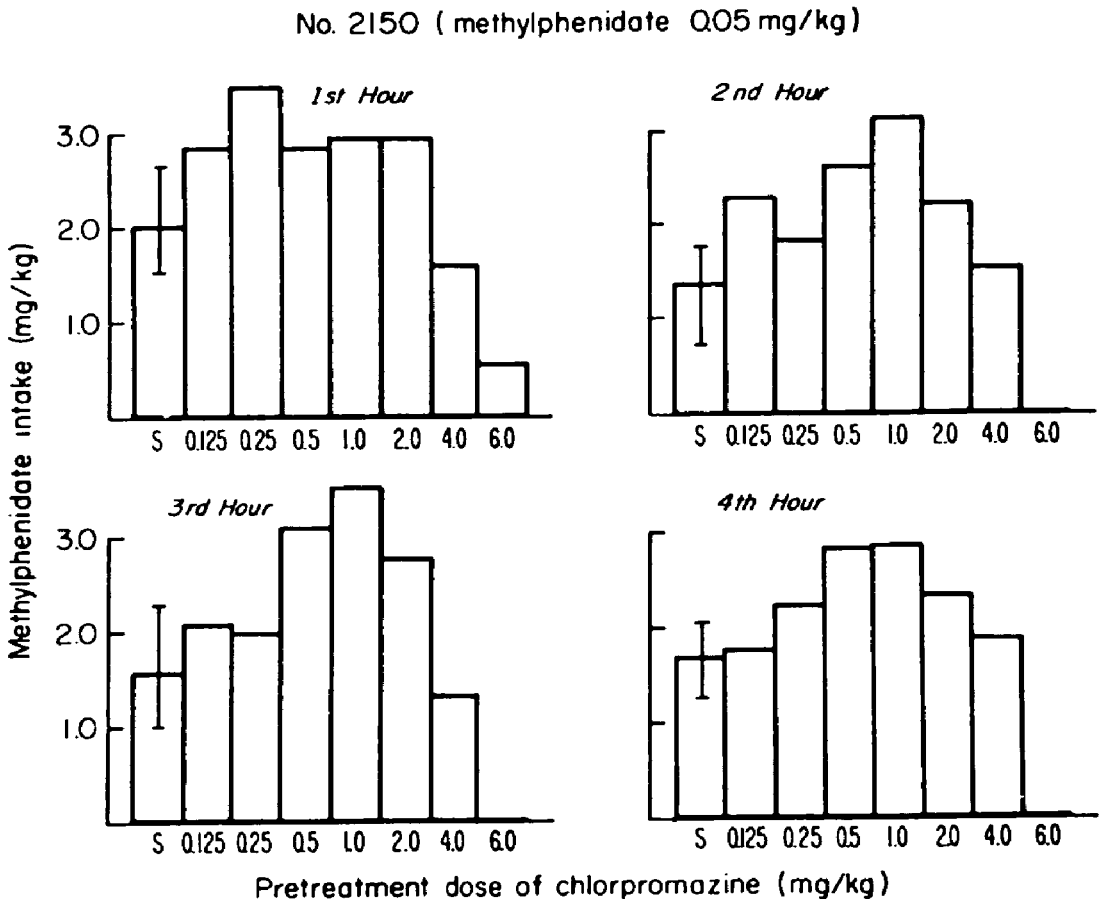

No. 2150 ( methylphenidate 0.05 mg/kg)
1st Hour
2nd Hour
3rd Hour
4th Hour
3.0
2.0
1.0
S 0.125 0.25 0.5 1.0 2.0 4.0 6.0
Methylphenidate intake (mg/kg)
Pretreatment dose of chlorpromazine (mg/kg)

Figure 65. Alteration in phenmetrazine intake in M212 as a function of the pretreatment dosage of chlorpromazine. The height of the bars indicates phenmetrazine intake during that period following pretreatment with a given dosage of chlorpromazine. The height of the bars over the letter "S" indicates mean phenmetrazine intake in that period after pretreatment with saline on five different occasions. The vertical lines represent the range of phenmetrazine intake for these five control sessions.

**Figure 65**

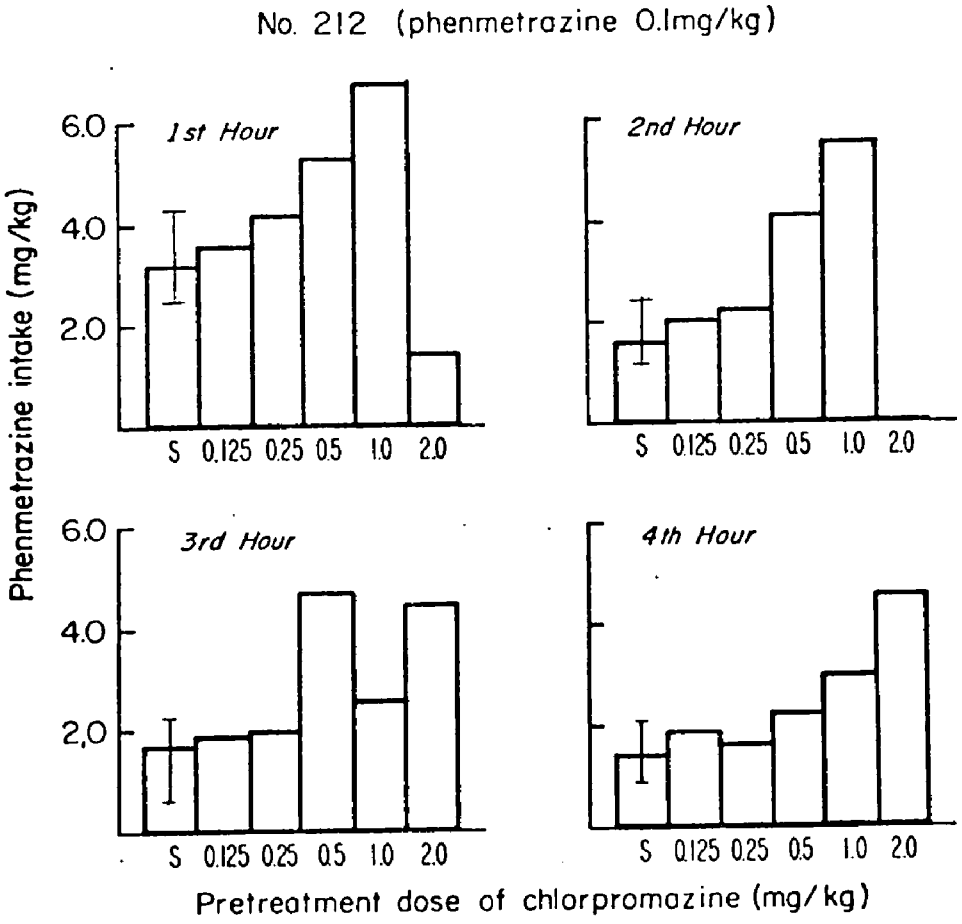
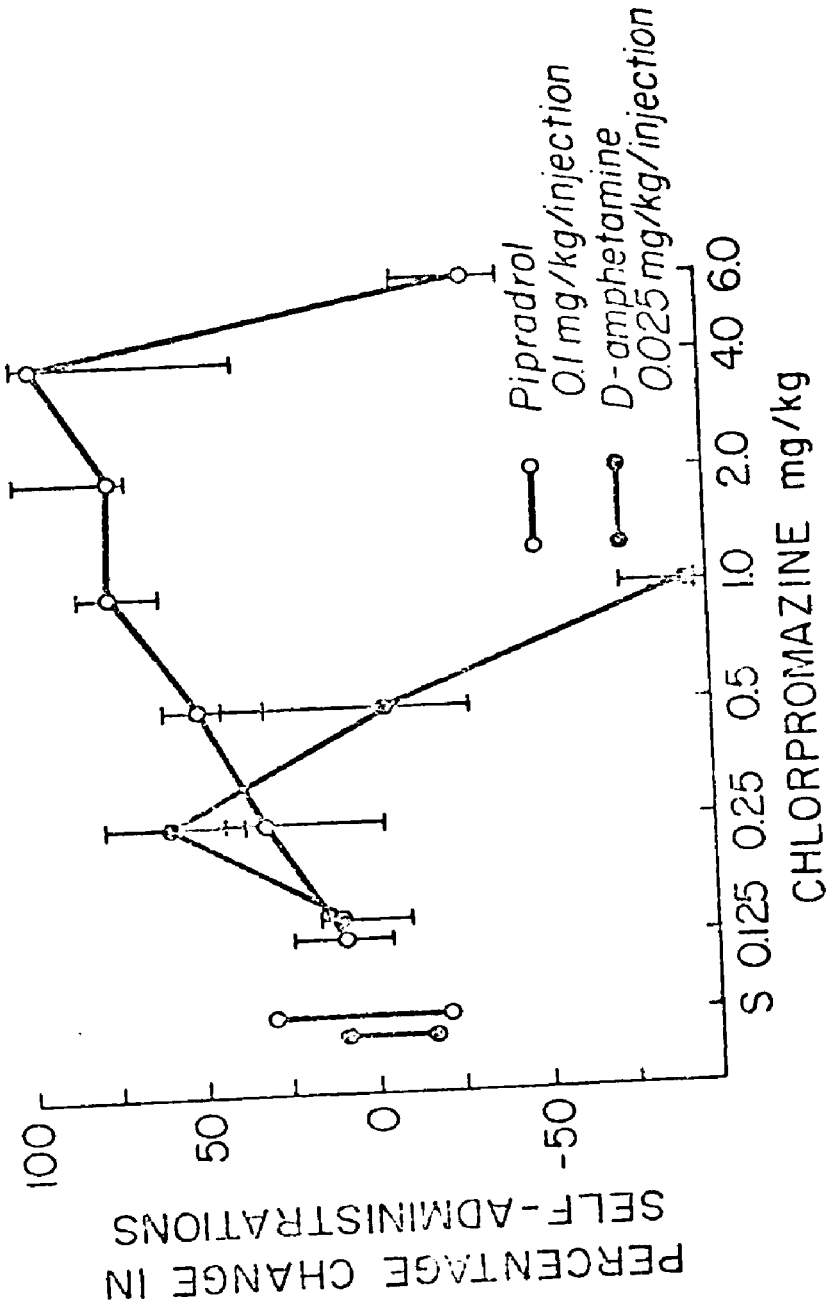

No. 212 (phenmetrazine 0.1mg/kg)
1st Hour
2nd Hour
3rd Hour
4th Hour
6.0
4.0
2.0
S 0.125 0.25 0.5 1.0 2.0
Phenmetrazine intake (mg/kg)
Pretreatment dose of chlorpromazine (mg/kg)

Figure 66. Mean percentage change in pipradrol and d-amphetamine self-administration as a function of the pretreatment dosage of chlorpromazine. Each point represents the mean of four subjects, and the vertical lines illustrate the range. The brackets at the left indicate the range of change in pipradrol and d-amphetamine self-administration which occurred following pretreatment with saline. Five of these control sessions were conducted in each subject.

Figure 66


PERCENTAGE CHANGE IN SELF-ADMINISTRATIONS
100
50
0
-50
S 0.125 0.25 0.5 1.0 2.0 4.0 6.0
CHLORPROMAZINE mg/kg
Pipradrol 0.1 mg/kg/injection
D-amphetamine 0.025 mg/kg/injection

1.0 mg/kg of CPZ severely depressed d-amphetamine self-administration behavior in all of the subjects. The subjects exhibited signs of extreme central depression with this pretreatment dosage.

Pretreatment with 0.125 and 0.25 mg/kg of CPZ had no effect on pipradrol self-administration. However, pretreatment with 0.5, 1.0, 2.0, and 4.0 mg/kg increased pipradrol self-administration in a dose-related manner. Further increases in pretreatment dosage depressed pipradrol intake below control levels.

The effects of CPZ pretreatment on pipradrol intake in M2198 are illustrated in Figure 67. CPZ in dosages of 0.25-4.0 mg/kg produced a dose-related increase in pipradrol intake during the first hour of the session. Pretreatment with 6.0 mg/kg decreased pipradrol intake in the first hour, and completely suppressed intake in the remaining three hours. Pipradrol was increased in the second hour by pretreatment with 1.0, 2.0, and 4.0 mg/kg of CPZ; however, the magnitude of the increase was much less than that seen during the first hour. Only the 4.0 mg/kg pretreatment dose still increased intake during the third hour, and none of the pretreatment dosages increased pipradrol intake in the fourth hour of the session.

The effects of CPZ pretreatment on d-amphetamine self-administration in M2170 are illustrated in Figure 68. Pretreatment with 0.25 mg/kg of CPZ increased drug intake in the last three hours of the session; the magnitude of the increase decreased with time. Pretreatment with 0.5 mg/kg of CPZ decreased d-amphetamine intake in the first hour, but increased intake in the second hour, but not to as great an extent as the 0.25 mg/kg

Figure 67. Alteration in pipradrol intake in M2198 as a function of the pretreatment dosage of chlorpromazine. The height of the bars indicates pipradrol intake during that period, following pretreatment with a given dosage of chlorpromazine. The height of the bars over the letter "S" indicates mean pipradrol intake in that period after pretreatment with saline on five different occasions. The vertical lines represent the range of pipradrol intake for these five control sessions.

Figure 67

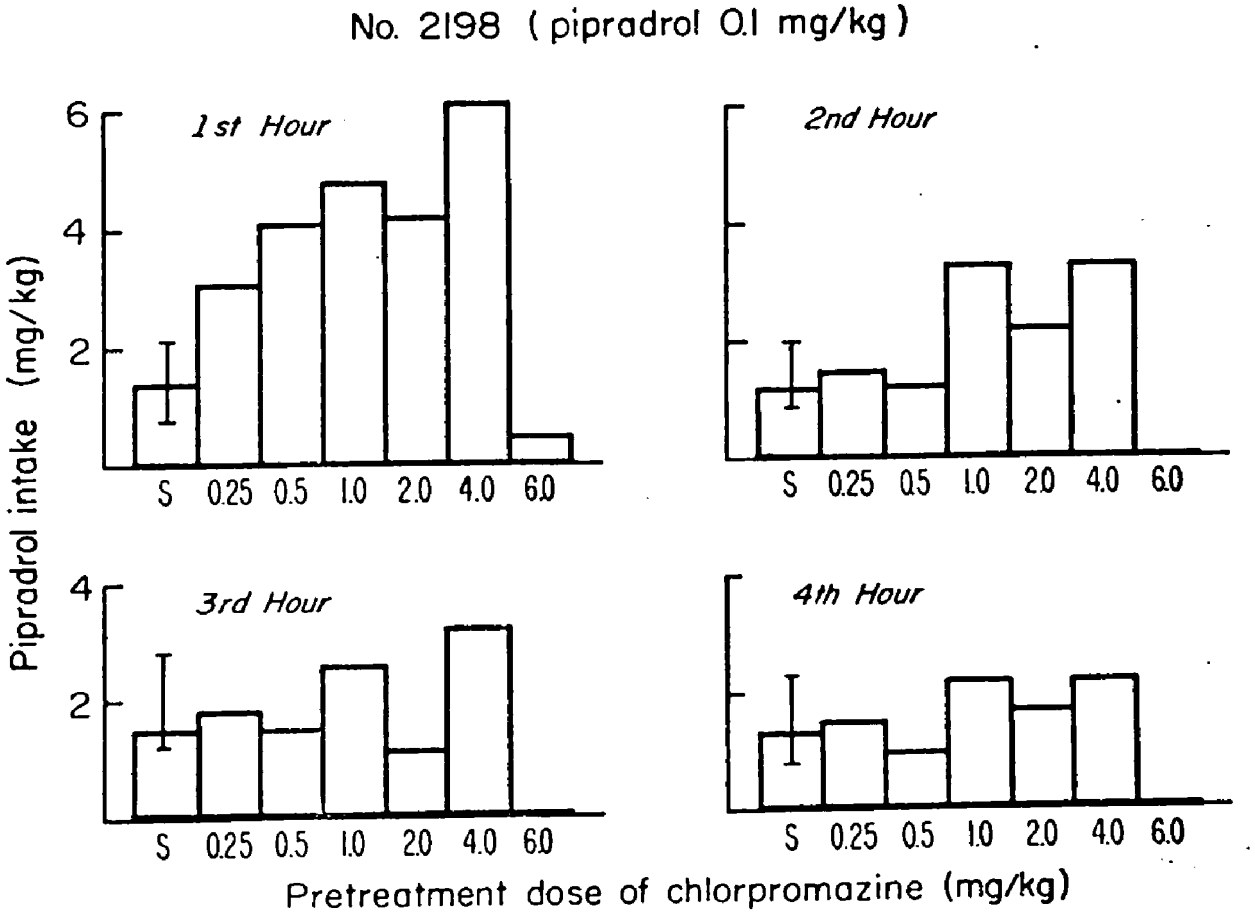
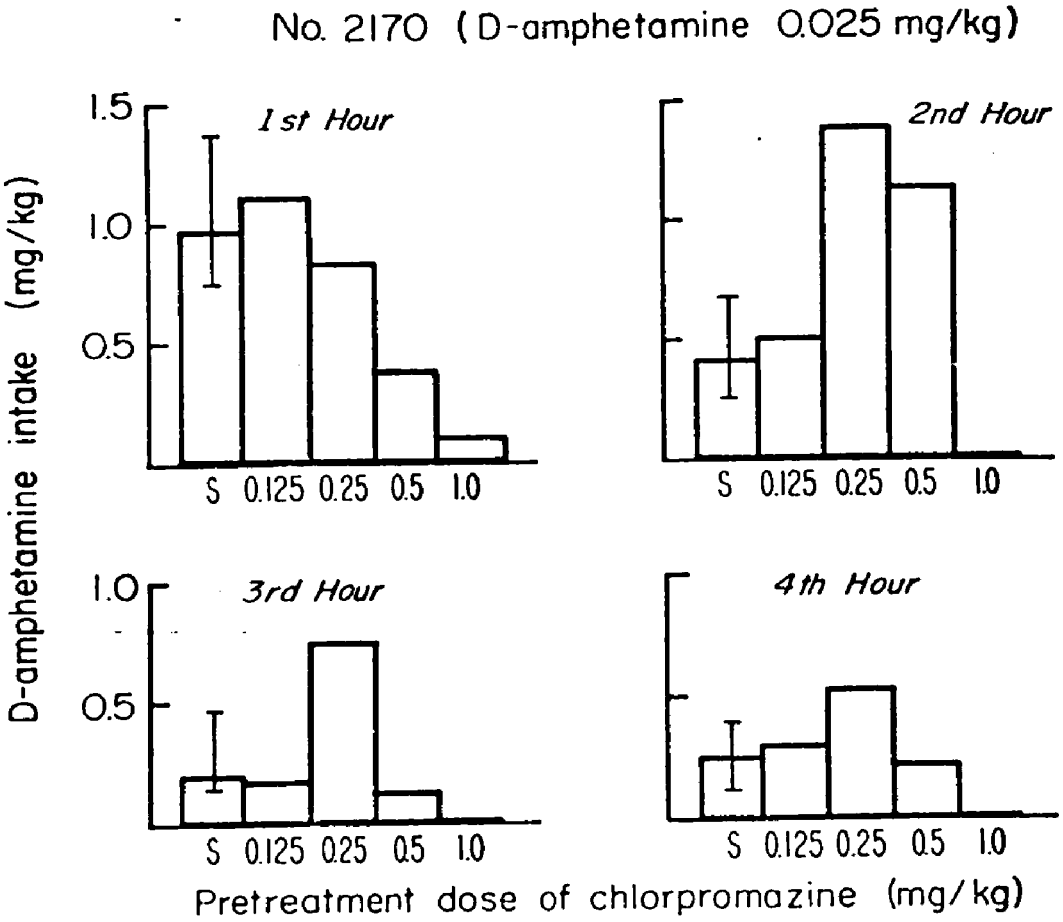

No. 2198 ( pipradrol 0.1 mg/kg )
1st Hour
2nd Hour
3rd Hour
4th Hour
Pipradrol intake (mg/kg)
6
4
2
S 0.25 0.5 1.0 2.0 4.0 6.0
Pretreatment dose of chlorpromazine (mg/kg)

Figure 68. Alteration in d-amphetamine intake in M2170 as a function of the pretreatment dosage of chlorpromazine. The height of the bars indicates d-amphetamine intake during that period following pretreatment with chlorpromazine. The height of the bars over the letter "S" indicates mean d-amphetamine intake in that period after pretreatment with saline on five different occasions. The vertical lines represent the range of d-amphetamine intake for these five control sessions.

**Figure 68**


No. 2170 (D-amphetamine 0.025 mg/kg)
1st Hour
2nd Hour
3rd Hour
4th Hour
D-amphetamine intake (mg/kg)
1.5
1.0
0.5
S 0.125 0.25 0.5 1.0
Pretreatment dose of chlorpromazine (mg/kg)

dosage. Pretreatment with 1.0 mg/kg of CPZ completely suppressed d-amphetamine intake in all four hours of the session. No effect on drug intake was produced by pretreatment with 0.125 mg/kg of CPZ.

## D. DISCUSSION

Pretreatment with chlorpromazine increases the frequency of the self-administration of all of the psychomotor stimulants which are self-administered by the Rhesus monkey. This effect results in an increase in drug intake. As the pretreatment dosage of CPZ is increased, an inverse relationship between pretreatment dosage and self-administration behavior is exhibited. The dosage at which this relationship becomes inverse rather than direct differs with the psychomotor stimulant being self-administered, and also the unit dosage being self-administered. It appears that the inverse relationship is the result of the general central depressant effects of CPZ.

The increase in psychomotor stimulant self-administration behavior produced by pretreatment with chlorpromazine is probably due to an antagonism between the two drugs. CPZ may antagonize the reinforcing effect of these compounds so that the subjects are in effect self-administering a lower unit dosage of these compounds. We have shown that a decrease in unit dosage results in an increase in self-administration frequency. CPZ may also produce this effect by antagonizing an action of the psychomotor stimulants which limits the amount of these compounds which are self-administered, i.e., aversive effect or a behavioral disrupting effect.

There are many references in the literature which demonstrate that CPZ can antagonize the effects of psychomotor stimulants in addition to cocaine. Fann has used methylphenidate clinically to counteract the acute dystonic effects of phenothiazines.[64] Reid has demonstrated that CPZ antagonizes the anorexic action of phenmetrazine in mental patients.[160] It has also been shown that CPZ increases the LD50 of phenmetrazine in mice.[11] Several studies have demonstrated that an antagonism exists between CPZ and amphetamine. Maickel has shown that d-amphetamine can reverse the decrease in gross behavior and motor activity produced by CPZ.[119] Other investigators have demonstrated that CPZ can counteract the hypermotility and hyperthermia produced by amphetamine in rats.[15,188] Proctor et al. have demonstrated that CPZ can reverse the potentiated toxicity of amphetamine in aggregated mice.[159] This antagonism between CPZ and amphetamine has been utilized in the clinic to effectively treat amphetamine poisoning.[61] Therefore, there is ample evidence to suggest that the increase in self-administration of psychomotor stimulants seen after CPZ pretreatment may be due to an antagonistic action between the two compounds. More research must be conducted to determine if this claim can be substantiated.

# VII. INTERACTION OF CHLORPROMAZINE AND COCAINE AND OF ATROPINE AND COCAINE ON FOOD REINFORCED BEHAVIOR.

## A. INTRODUCTION

Pretreatment with either chlorpromazine or atropine produces increases in cocaine self-administration behavior. Increases in the frequency of cocaine self-administration also are produced by decreasing the unit dosage, i.e., dosage per injection. Therefore, we attributed the increase in responding for cocaine to an antagonistic action between cocaine and atropine or chlorpromazine. However, the pharmacology of atropine is much different from that of chlorpromazine; therefore, these agents probably did not produce the increase in cocaine self-administration via the same mechanism. Perhaps CPZ was antagonizing the reinforcing property of cocaine; whereas atropine may have been antagonizing the drug effect or central mechanism which functions in limiting the intake of the psychomotor stimulants. Therefore, a study was designed to demonstrate whether a common mechanism was functioning to mediate the antagonism between atropine or chlorpromazine and cocaine. The effect of atropine, chlorpromazine, and cocaine individually on food-seeking behavior was determined; then the affects of a combination of cocaine with atropine and of cocaine with chlorpromazine on this same behavior were analyzed. The results of this study would demonstrate whether a general antagonism was exhibited between atropine or chlorpromazine and cocaine, or whether a specific action of cocaine, i.e., reinforcing effect, was antagonized by CPZ and atropine.

B. METHODS

1. Subjects. The subjects for this study were three adult Rhesus monkeys, weighing between 4.0 and 4.6 kg. A chronic indwelling jugular catheter was implanted in each subject.

2. Apparatus. The subjects were housed in individual experimental cubicles. The cubicles were completely closed and were ventilated by exhaust fans. The top and sides were made of nontransparent white plastic; the floor of the cage was one inch galvanized wire mesh. Beneath the floor was a stainless steel pan; these pans were automatically washed every four hours. An aluminum door served as the front of the cage. A Foringer food pellet dispensor was mounted on the outside of the door. Metal tubing connected the feeder to a food cup which was mounted on the inside of the door. A one-inch hole was made in the door and the tubing passed through this hole. The top half of the back of the cubicle was also made from nontransparent plastic; however, the bottom half was made of stainless steel. A stainless steel panel was in turn mounted on the stainless steel back of the cubicle. A red stimulus light (4 watts), pressure-sensitive water spout, and a lever were mounted on this panel. The water spout provided constant access to water. A food pan was also located in one of the back corners of the cubicle. An exhaust fan, which ran constantly, was mounted on the top of the cubicle. Since the subjects were completely enclosed in the cubicle, they were unaffected by movements of laboratory personnel and of other subjects. Although the cubicles were not sound-proofed, the noise of the exhaust fan masked much of the laboratory noise.

The subjects were restrained by a stainless steel arm and harness. The restraining arm was attached to the back of the cubicle. This method of restraint allowed relatively free movement of the subject within the cubicle. The jugular catheter was attached to a connection on the back of the harness. A second catheter was also attached to this connection; it traversed the lumen of the restraining arm and passed out of the cubicle and was attached to a Harvard infusion pump. The pump was placed on a stainless steel shelf which was attached to the outside of the rear wall of the cubicle. Cables connected the infusion pump and cubicle to programming and recording equipment, i.e., Gerbrands Cumulative Recorders, which were located in an adjacent room.

Depression of the lever with at least 100 grams of force during the presence of the discriminative stimulus, i.e., illumination of the stimulus light, resulted in the intravenous administration of sterile physiological saline (0.2 cc/kg of body weight), and also in the presentation of a 0.7 gram Dietrich and Gambrell monkey food pellet.

3. General procedure. All laboratory animals were usually given 15 Purina Monkey Chows twice a day, at 8:30 a.m. and 4:30 p.m. The subjects normally consumed all of this food within a relatively short time. The subjects in this study were fed only at 4:30 p.m. Under these conditions of food deprivation, the subjects were conditioned to lever press for food pellets on a FR-10 schedule of reinforcement. The subjects had access to the food pellets for two hours a day, i.e., 11:00 a.m. to 1:00 p.m. The onset of this

period was signaled by the illumination of the stimulus light. After the subject pressed the lever ten times, a food pellet would be delivered by the pellet dispensor to the food cup on the inside of the cage door. Following the completion of each ratio, i.e., pellet presentation, a one-minute time-out period ensued. During this time-out period, the stimulus light was no longer illuminated and lever presses had no consequence. The cumulative recorder was stopped during the time-out period; however, the timer which terminated the session did not stop. Stable baseline performance on this schedule of food reinforcement was established within two weeks in each subject. At this time a jugular catheter was implanted in each subject. Following catheter implantation, completion of the FR-10 ratio resulted not only in the presentation of a food pellet, but also in the intravenous administration of sterile physiological saline (0.2 cc/kg of body weight). The average pellet consumption per session initially decreased under this contingency, but returned to normal baseline levels within one week.

The effects of pretreatment with atropine and chlorpromazine on this baseline behavior were determined. Pretreatment dosages of 0.25, 0.5, 1.0 and 2.0 mg/kg of atropine, and of 0.125, 0.25, 0.5, 1.0, 2.0 and 4.0 mg/kg of chlorpromazine, were administered to each subject intramuscularly five minutes before the start of the two-hour session. The drugs were dissolved in sterile physiological saline and all solutions were prepared on the day in which they were to be used. The injection volume was held constant throughout the study, i.e., 1.0 cc. At least three days elapsed between drug pretreatment sessions to allow for food intake to

return to baseline levels and to also allow time for the drug administered previously to be metabolized. Five control sessions, i.e., pretreatment with 1.0 cc of saline, were conducted in each subject during the course of the study.

The effects of cocaine on this baseline of food seeking behavior was also determined. Cocaine in dosages of 0.5, 1.25, 2.5, 5.0, and 10 mg/kg were administered to each subject. These dosages were administered via slow intravenous infusion through the catheter. The infusion lasted for fifteen minutes and the volume of the infusion was kept constant, e.g., 20 cc. The infusions were started after fifteen minutes of the session had elapsed. This time was chosen to approximate the time of onset of drug action following IM pretreatment with CPZ and atropine. The cocaine was dissolved in sterile physiological saline and solutions were prepared on the day in which they were to be used. Three days elapsed between drug treatment sessions to allow time for food intake to return to baseline levels. Five control sessions, i.e., fifteen minute IV infusions with 20 cc of saline, were conducted in each subject. During this infusion period, completion of the FR-10 ratio resulted only in pellet presentation.

Following the determination of the effect of each of these dosages of cocaine, atropine, and CPZ individually on food-seeking behavior in each subject, the effects of administering combinations of CPZ and cocaine and of atropine and cocaine were determined. The subjects were pretreated with a given dosage of atropine or CPZ five minutes before the start of the session, and a fifteen minute infusion of cocaine was started after fifteen minutes of the session had elapsed.

C. RESULTS

The effects of CPZ pretreatment on food reinforced behavior is illustrated in Figure 69. Pretreatment with 0.125 mg/kg of CPZ did not alter the frequency of food-seeking behavior. However, further increases in pretreatment dosage from 0.25 to 4.0mg/kg produced a dose-related decrease in lever-pressing frequency for food pellets. There appeared to be a dose-related general CNS depression associated with these pretreatment dosages. Pretreatment dosages of 0.5 mg/kg and above produced evidence of catatonia and marked motor incapacitation.

Figure 70 illustrates the cumulative recorder records of CPZ pretreatment sessions in one subject. This figure demonstrates the dose-related depression of food reinforced responsing seen with CPZ pretreatment. The duration of the depression of this behavior was also dose-related. The onset of this depressent effect occurred after fifteen minutes of the session had elapsed and this effect lasted for the remainder of the session when the subject was pretreated with either 2.0 or 4.0 mg/kg of CPZ.

The effect of atropine pretreatment on food reinforced behavior is demonstrated in Figure 71. Atropine in dosages of 0.25-2.0 mg/kg also produced a dose-related depression in lever-pressing behavior for food pellets. However, no evidence of a general CNS depression was seen with these dosages in contrast to the effects seen with CPZ pretreatment.

Figure 72 shows the cumulative recorder records of atropine pretreatment sessions in M338. These records readily demonstrate that the decrease in food reinforced behavior is dose-related and

Figure 69. Mean percentage change in food reinforcements as a function of the pretreatment dosage of chlorpromazine. Each point represents the mean of three subjects and the vertical lines indicate the range of effect. The brackets at the left represent the range of effects produced by saline pretreatment in fifteen sessions, five conducted in each subject.

Figure 69

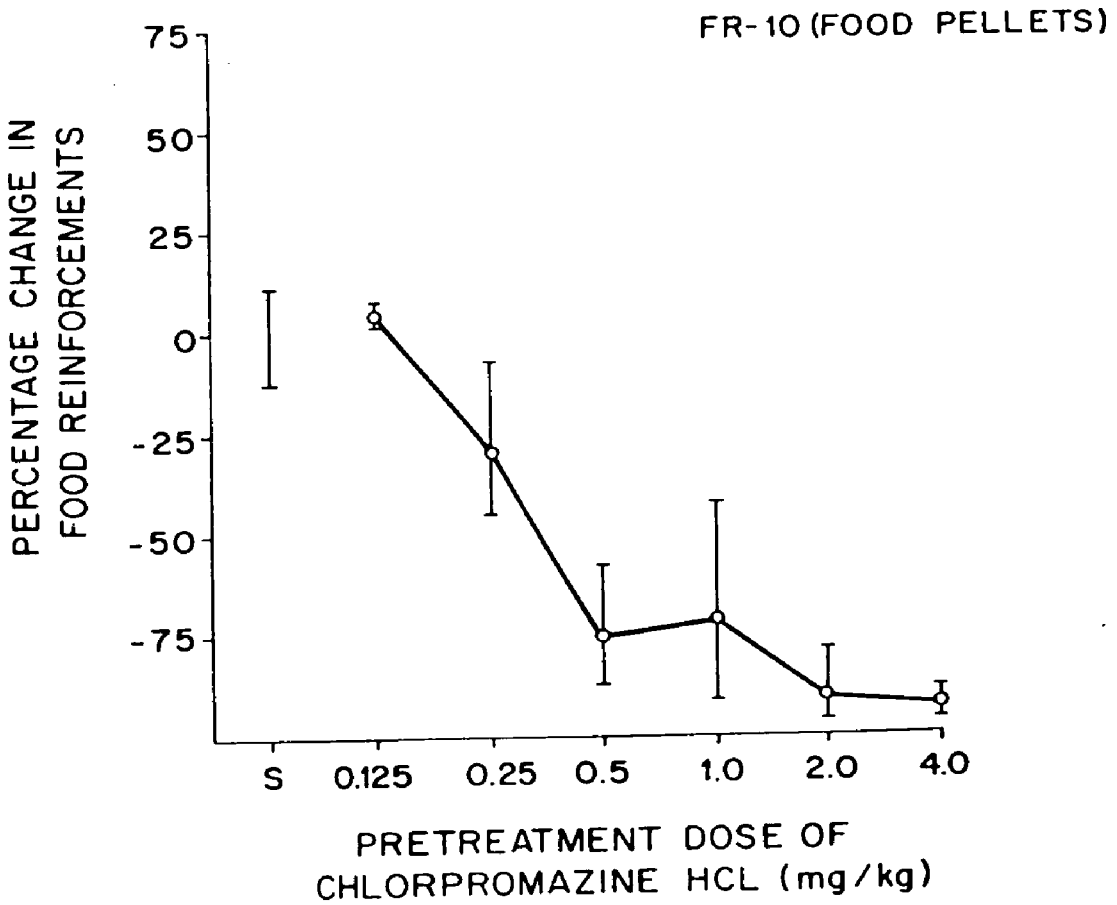

FR-10 (FOOD PELLETS)
PERCENTAGE CHANGE IN FOOD REINFORCEMENTS
75
50
25
0
-25
-50
-75
S
0.125
0.25
0.5
1.0
2.0
4.0
PRETREATMENT DOSE OF CHLORPROMAZINE HCL (mg/kg)

Figure 70. Cumulative response records which illustrate the effect of CPZ pretreatment on food reinforced behavior in M2161. Each vertical mark on the horizontal line represents presentation of one food pellet, i.e., reinforcement. The end of the sessions are indicated by the change in character of the horizontal line from a solid to a broken form. The response pen reset after every 400 responses or 40 reinforcements. The recorder was stopped during the one-minute time-out following each reinforcement, but the session timer continued to operate. Therefore, the length of the solid horizontal line was inversely proportional to the number of reinforcements received.

# Figure 70

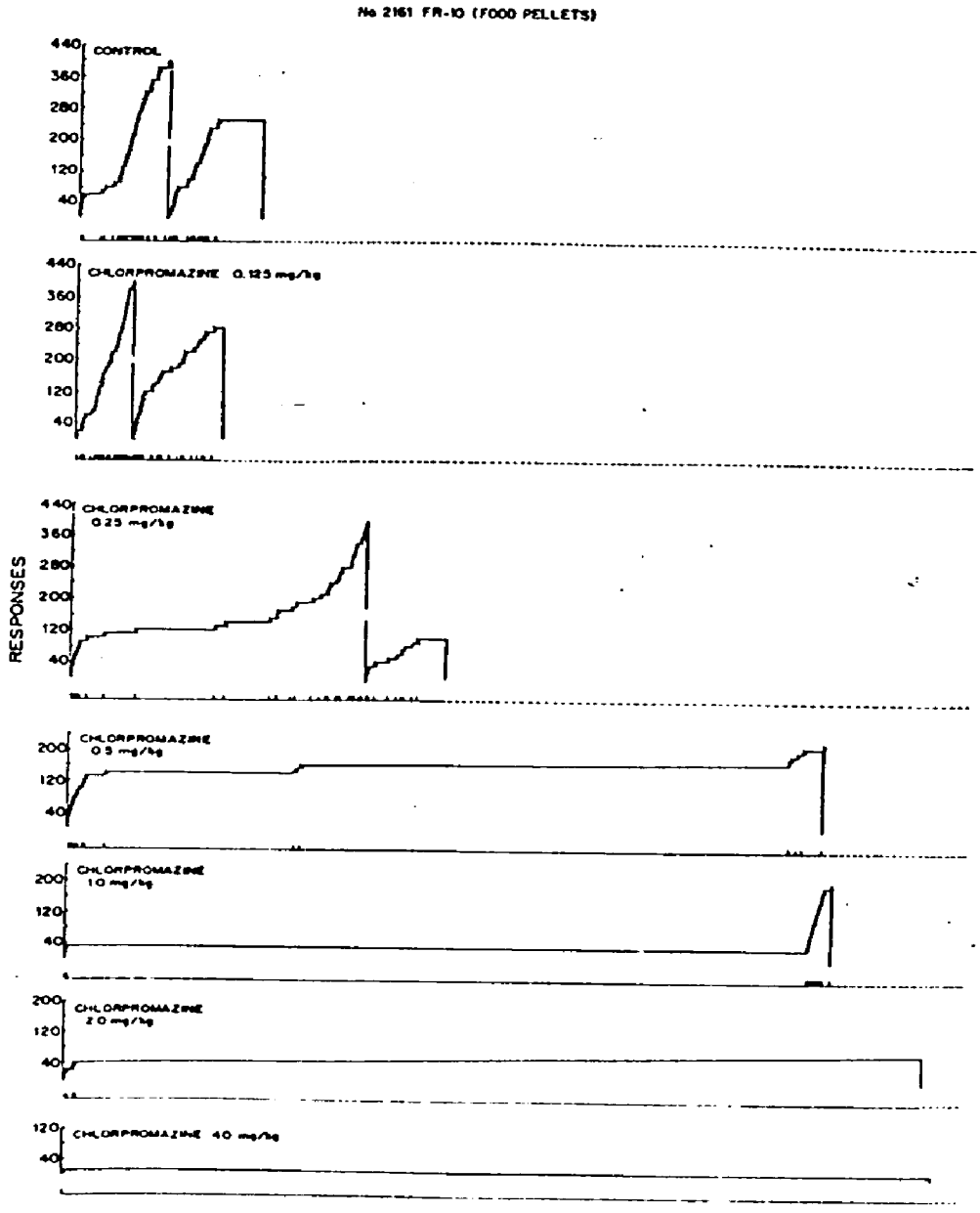

No 2161 FR-10 (FOOD PELLETS)
CONTROL
CHLORPROMAZINE 0.125 mg/kg
CHLORPROMAZINE 0.25 mg/kg
CHLORPROMAZINE 0.5 mg/kg
CHLORPROMAZINE 1.0 mg/kg
CHLORPROMAZINE 2.0 mg/kg
CHLORPROMAZINE 4.0 mg/kg
RESPONSES
440
360
280
200
120
40

Figure 71. Mean percentage change in food reinforcements as a function of the pretreatment dosage of atropine. Each point represents the mean of three subjects, and the vertical lines indicate the range of effect. The brackets at the left represent the range of effects produced by saline pretreatment in fifteen sessions, five conducted in each subject.

Figure 71

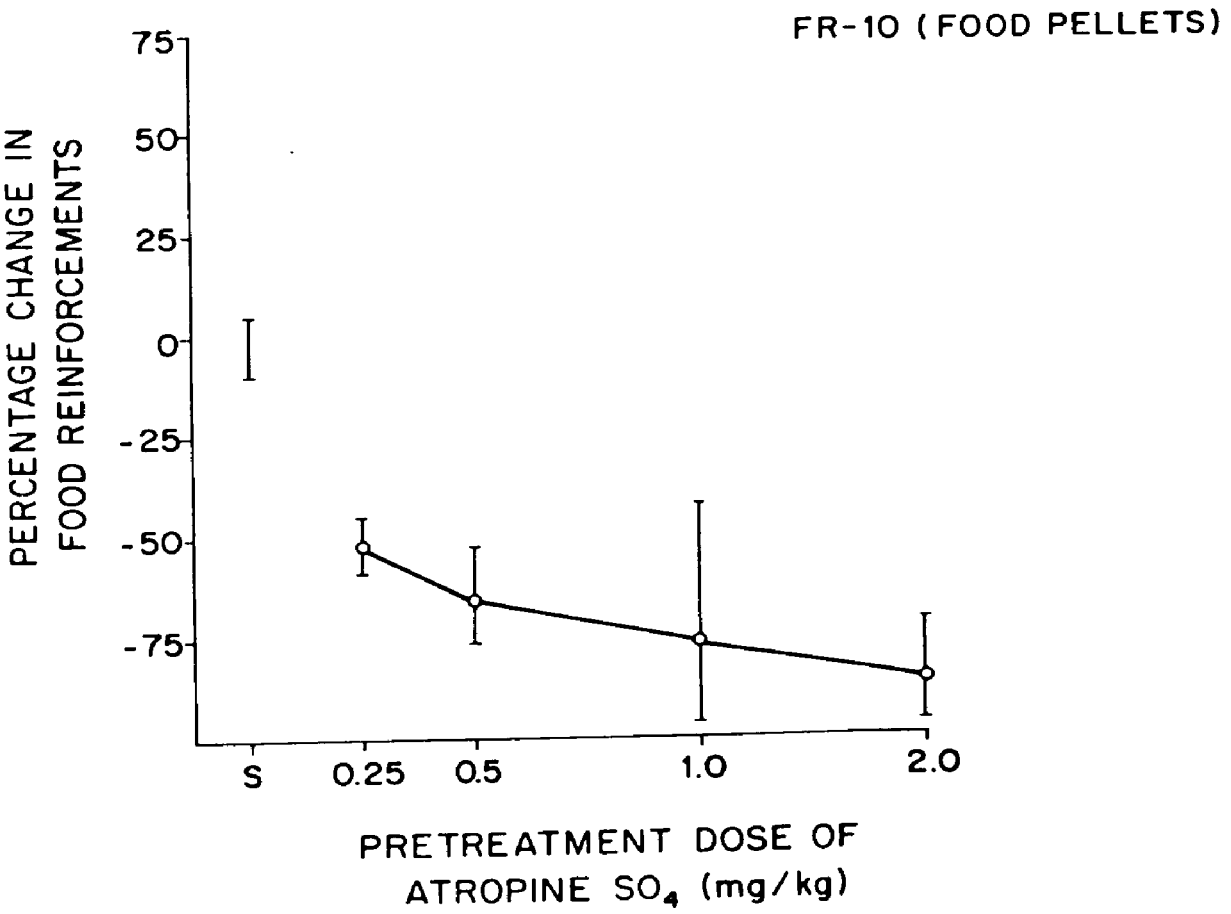
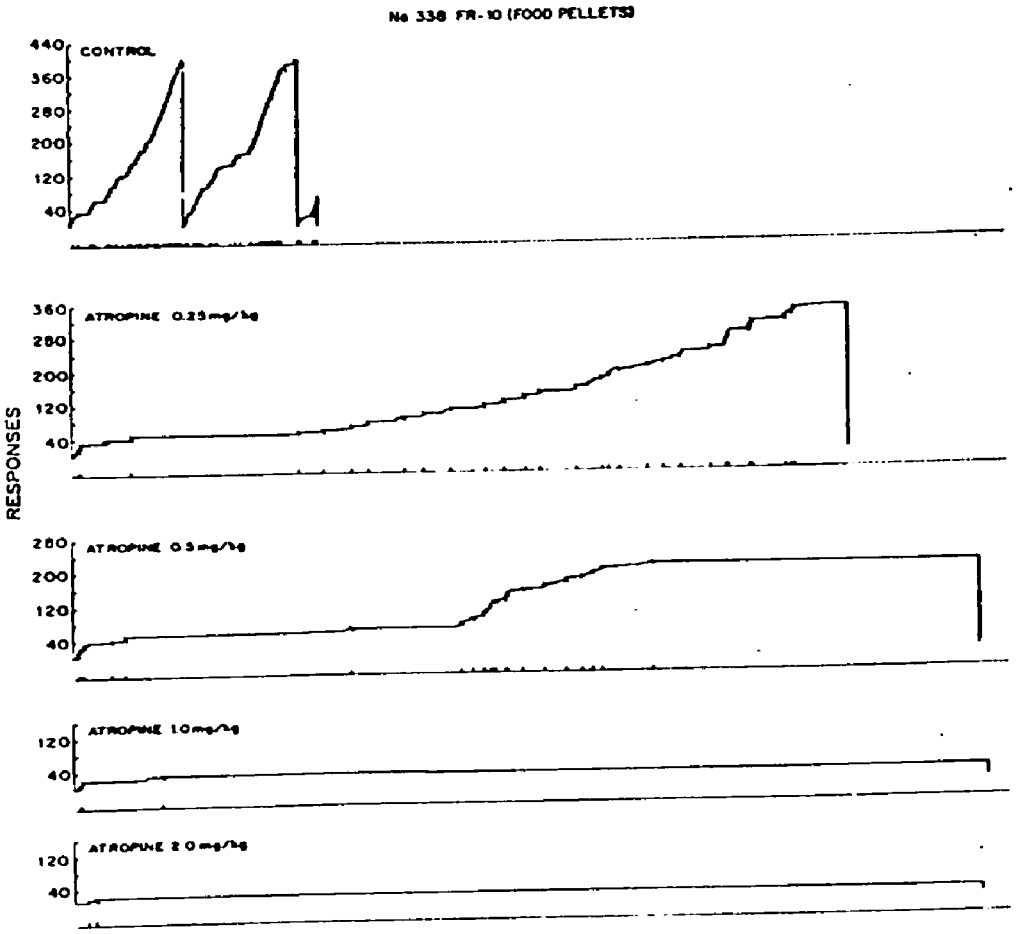

FR-10 (FOOD PELLETS)
PERCENTAGE CHANGE IN FOOD REINFORCEMENTS
75
50
25
0
-25
-50
-75
S
0.25
0.5
1.0
2.0
PRETREATMENT DOSE OF ATROPINE SO4 (mg/kg)

Figure 72. Cumulative response records which illustrate the effect of atropine pretreatment on food reinforced behavior in M338. Each vertical mark on the horizontal line represents presentation of one food pellet, i.e., reinforcement. The end of the sessions are indicated by the change in character of the horizontal line from a solid to a broken form. The response pen reset after every 400 responses or 40 reinforcements. The recorder was stopped during the one-minute time-out following each reinforcement, but the session timer continued to operate. Therefore, the length of the solid horizontal line was inversely proportional to the number of reinforcements received.

Figure 72


No 338 FR-10 (FOOD PELLETS)
CONTROL
440
360
280
200
120
40
ATROPINE 0.25 mg/kg
ATROPINE 0.5 mg/kg
ATROPINE 1.0 mg/kg
ATROPINE 2.0 mg/kg
RESPONSES

that the duration of this effect is also related directly to pretreatment dosage. The onset of this effect occurred after fifteen minutes of the session had elapsed.

The effect of cocaine administration on food reinforced behavior is illustrated in Figure 73. Increases in infusion dosage of cocaine from 0.5 to 10.0 mg/kg produced a dose-related depression in food reinforced behavior. The cumulative recorder records of these cocaine treatment sessions conducted in M2161 are illustrated in Figure 74. Food-reinforced behavior was disrupted immediately after the onset of the cocaine infusion. The duration of this behavioral disruption was directly related to the treatment dosage of cocaine.

Therefore, atropine pretreatment, cocaine administration, and CPZ pretreatment all produce a dose-related depression in food-reinforced behavior. The effects of a combination of CPZ pretreatment and cocaine administration on this behavior are illustrated in Figure 75. This figure illustrates the number of food reinforcements obtained in the last 90 minutes of the session, i.e., period of session following cocaine administration, as a function of the infusion dose of cocaine and pretreatment dosage of chlorpromazine in M335, left graph, and in M338, right graph. The depression in food reinforced behavior produced by pretreatment with 0.25 and 0.5 mg/kg of CPZ was antagonized by the administration of 0.25 and 0.5 mg/kg of cocaine in both subjects. Furthermore, the depression in food reinforced behavior produced by 0.25 and 0.5 mg/kg of cocaine was antagonized by pretreatment with 0.25 and 0.5 mg/kg of CPZ in one of the subjects. This was surprising since all four of these dosages depress food reinforced behavior when administered

Figure 73. Mean percentage change in food reinforcements as a function of the infusion dosage of cocaine. Each point represents the mean of three subjects, and the vertical lines indicate the range of effect. The brackets at the left represent the range of effects produced by saline infusions in fifteen sessions, five conducted in each subject.

Figure 73

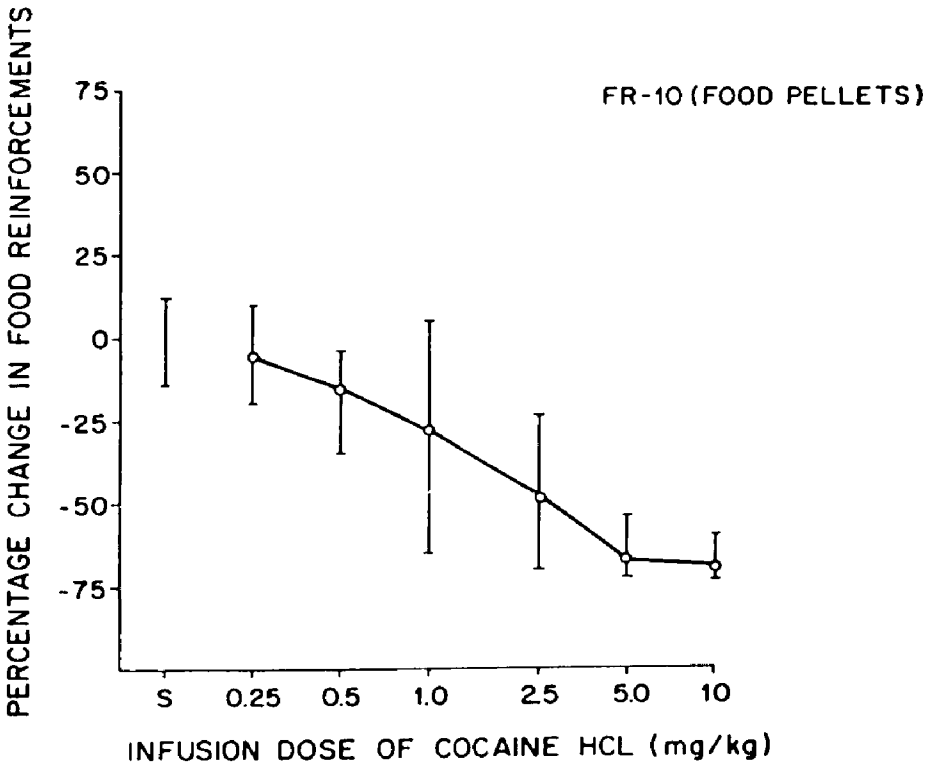

FR-10 (FOOD PELLETS)
PERCENTAGE CHANGE IN FOOD REINFORCEMENTS
75
50
25
0
-25
-50
-75
S
0.25
0.5
1.0
2.5
5.0
10
INFUSION DOSE OF COCAINE HCL (mg/kg)

Figure 74. Cumulative response records which illustrate the effect of cocaine on food reinforced behavior in M2161. Each vertical mark on the horizontal line represents presentation of one food pellet, i.e., reinforcement. The downward displacement of the solid horizontal line indicates the start of cocaine administration. The length of the cocaine infusion is indicated by the length of this negative deflection. Return of the horizontal line to the normal position indicates termination of the cocaine infusion. The end of the sessions are indicated by the change in character of the horizontal line from a solid to a broken form. The response pen reset after every 400 responses or 40 reinforcements. The recorder was stopped during the one-minute time-out following each reinforcement, but the session timer continued to operate. Therefore, the length of the solid horizontal line was inversely proportional to the number of reinforcements received.

# Figure 74

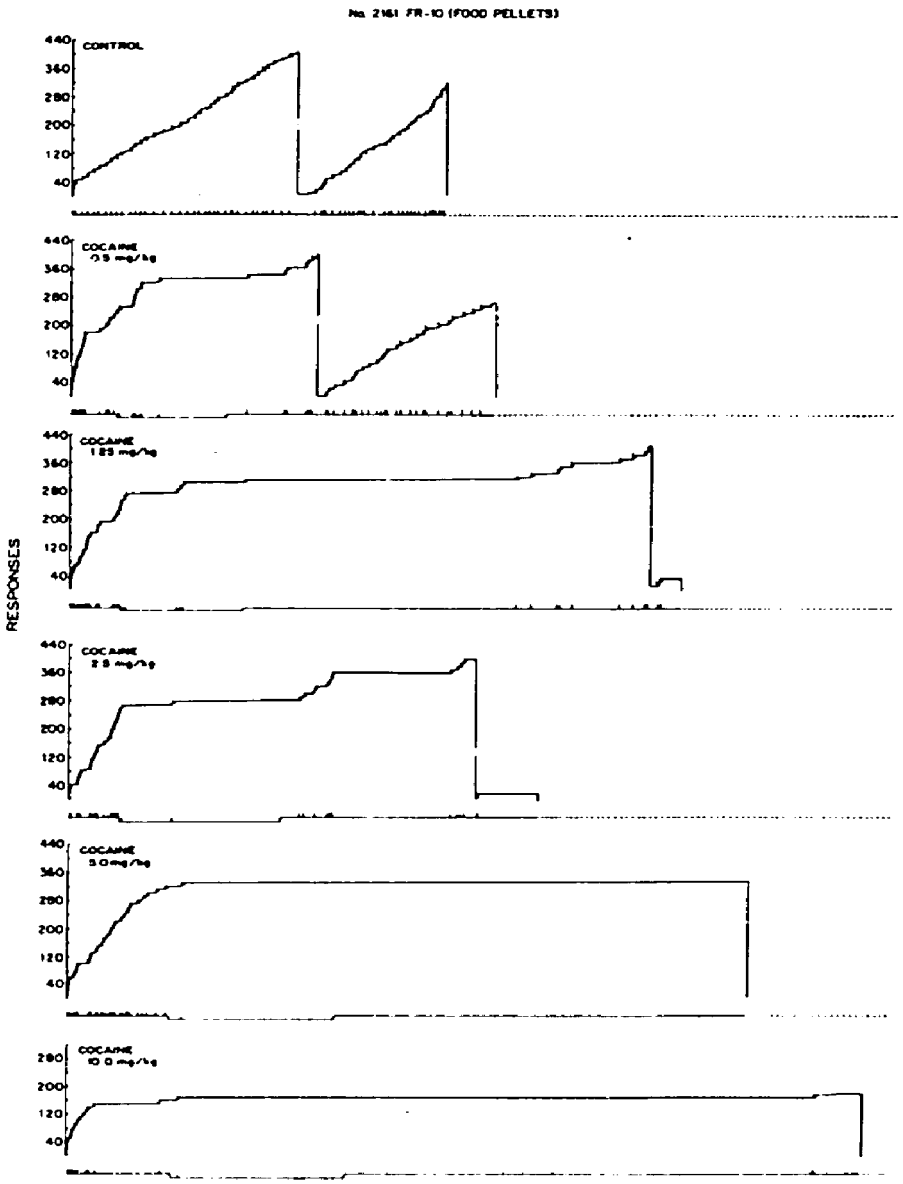
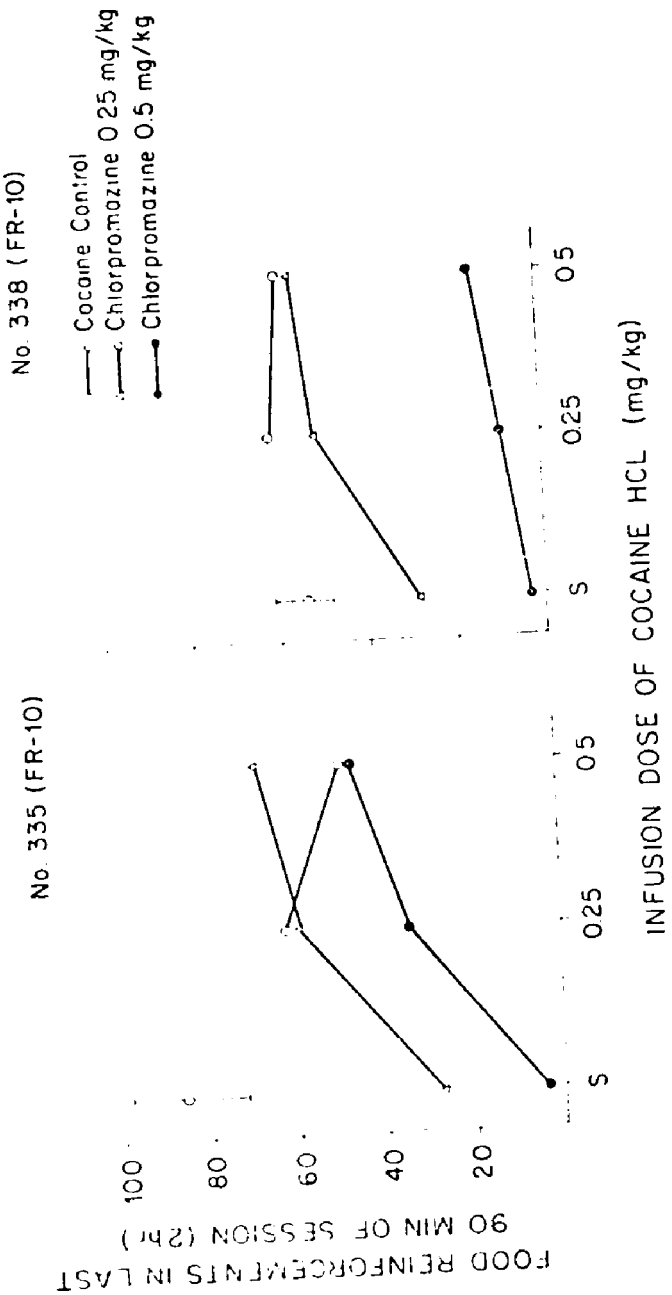

No. 2161 FR-10 (FOOD PELLETS)
CONTROL
COCAINE
COCAINE
COCAINE
COCAINE
COCAINE
RESPONSES
440
360
280
200
120
40

Figure 75. Food reinforcement obtained during last 90 minutes of a two-hour session as a function of the pretreatment dosages of CPZ and infusion dosage of cocaine, individually and in combination. The graph on the left indicates results obtained from M335; that on the right, from M338. The brackets and superimposed symbol indicate the range and mean obtained from ten control sessions, i.e., five with saline pretreatment and five with saline infusion. The symbols above the letter "S" indicate the effect seen with CPZ pretreatment alone.

Figure 75


No. 338 (FR-10)
Cocaine Control
Chlorpromazine 0.25 mg/kg
Chlorpromazine 0.5 mg/kg
No. 335 (FR-10)
FOOD REINFORCEMENTS IN LAST
90 MIN OF SESSION (2hr)
100
80
60
40
20
S
0.25
0.5
INFUSION DOSE OF COCAINE HCL (mg/kg)

individually. The degree of antagonism of a given dosage of CPZ was directly proportional to the infusion dosage of cocaine and vice versa. Cumulative recorder records of sessions in which this antagonism was exhibited are illustrated in Figure 76.

Figure 77 demonstrates the effects of atropine pretreatment and cocaine administration both individually and in combination on food reinforced behavior. Cocaine potentiated the depression of food reinforced behavior produced by atropine. The magnitude of this potentiation was dose-related. Likewise, atropine increased the depression in food reinforced behavior produced by cocaine administration; this effect was also dose-related. Figure 78 illustrates cumulative recorder records which demonstrate these results.

## D. DISCUSSION

The decrease in food reinforced behavior produced by the administration of cocaine was not at all surprising. The anorexic effects of the psychomotor stimulants have been known for some time. Evidence indicates that these agents act on the hypothalamic "feeding center". Stark and Totty have demonstrated that the i.p. administration of several psychomotor stimulants increases the current intensity required to elicit eating in food satiated rats by lateral hypothalamic stimulation.[178] However, the norepinephrine potentiating action of these compounds makes it extremely difficult to interpret the results of the numerous studies which have demonstrated that norepinephrine administered intraventricularly and intracerebrally increases food intake.[85]

Figure 76. Cumulative response records which illustrate the effects of CPZ and cocaine individually and in combination on food reinforced behavior in M335. Each vertical mark on the horizontal line represents presentation of one food pellet. The downward displacement of the solid horizontal line indicates the start of cocaine administration. The length of the cocaine infusion is indicated by the length of this negative deflection. Return of the horizontal line to the normal position indicates termination of the cocaine infusion. The ends of the sessions are indicated by the change in character of the horizontal line from a solid to a broken form. The response pen reset after every 400 responses or 40 reinforcements. The recorder was stopped during the one-minute time-out following each reinforcement, but the session timer continued to operate. Therefore, the length of the solid horizontal line was inversely proportional to the number of reinforcements received.

Figure 76

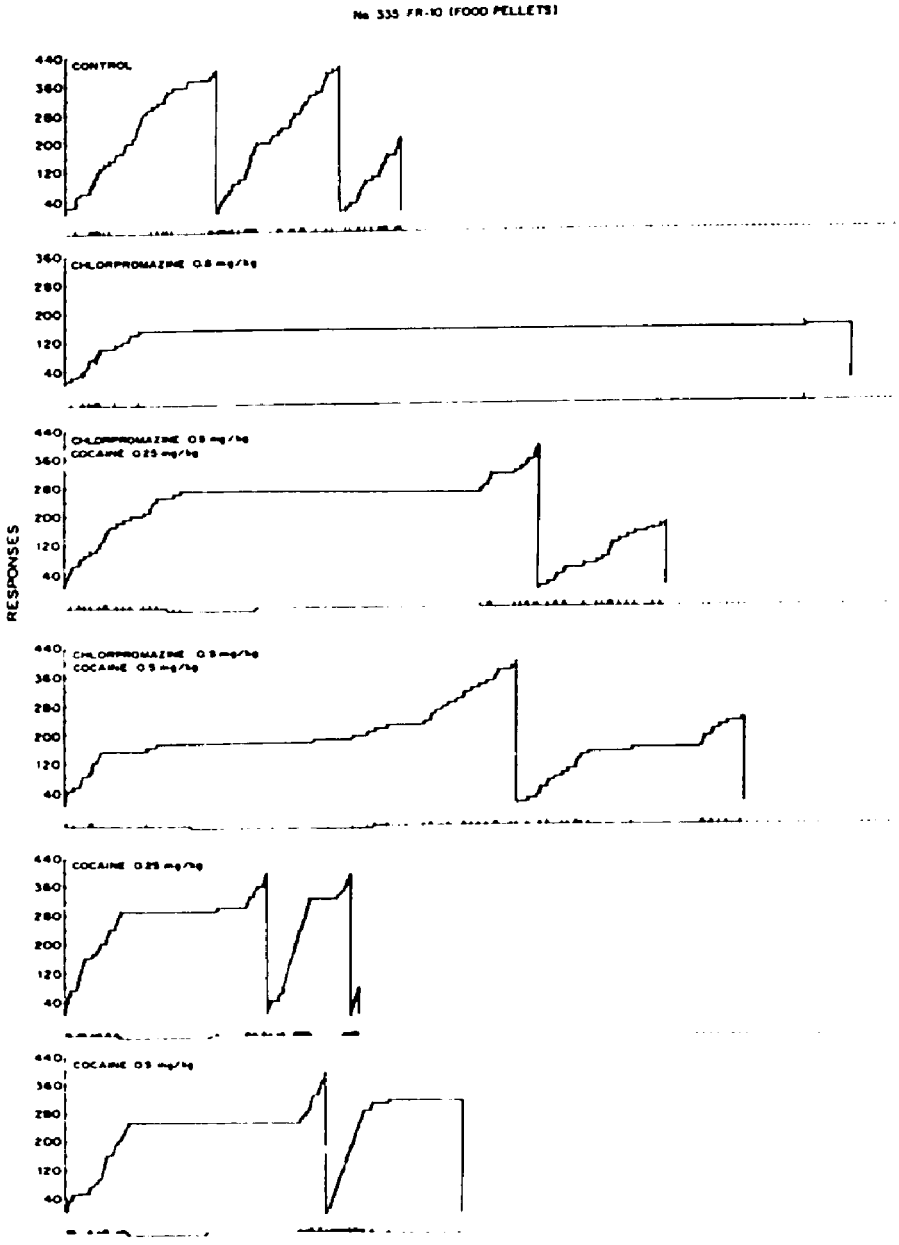

No 335 FR-10 (FOOD PELLETS)
CONTROL
CHLORPROMAZINE 0.8 mg/kg
COCAINE 0.25 mg/kg
COCAINE 0.5 mg/kg
RESPONSES
440
360
280
200
120
40

Figure 77. Food reinforcements obtained in last 90 minutes of a two-hour session as a function of the pretreatment dosage of atropine and infusion dosage of cocaine, individually and in combination. The graph on the left represents results obtained from M338 and that on the right from M335. The brackets and superimposed symbol indicate the range and mean obtained from ten control sessions, i.e., five with saline pretreatment and five with saline infusion. The symbols above the letter "S" indicate the effect seen with atropine pretreatment alone.

Figure 77

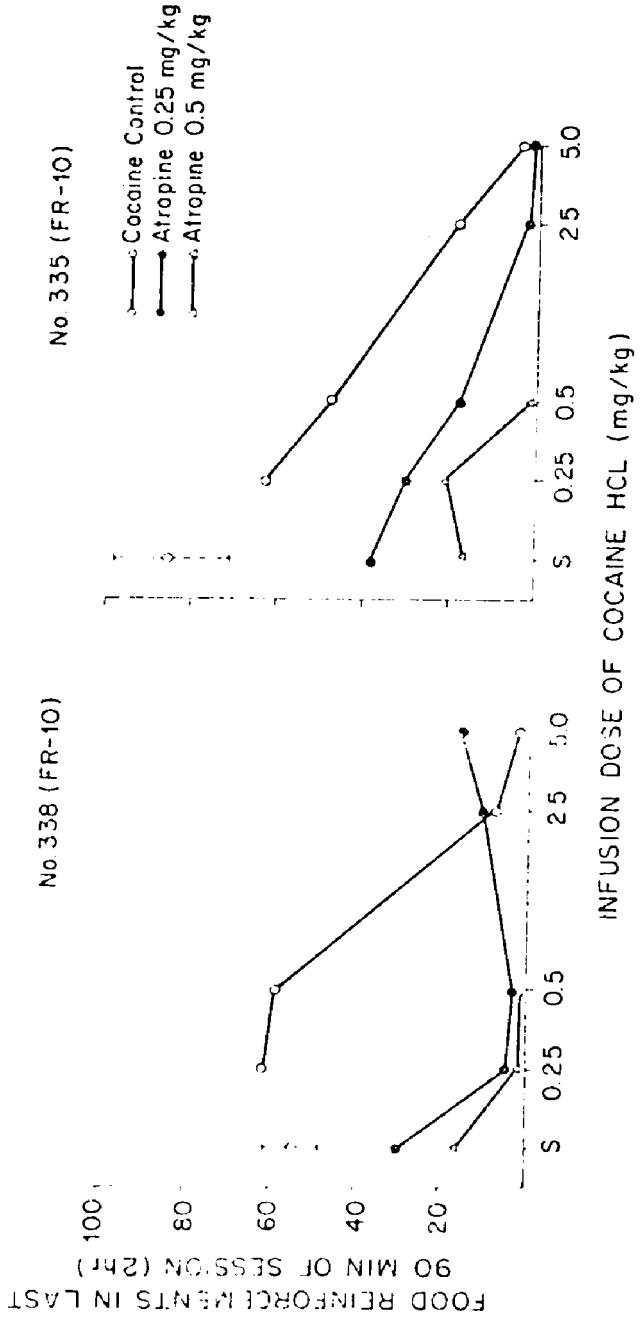
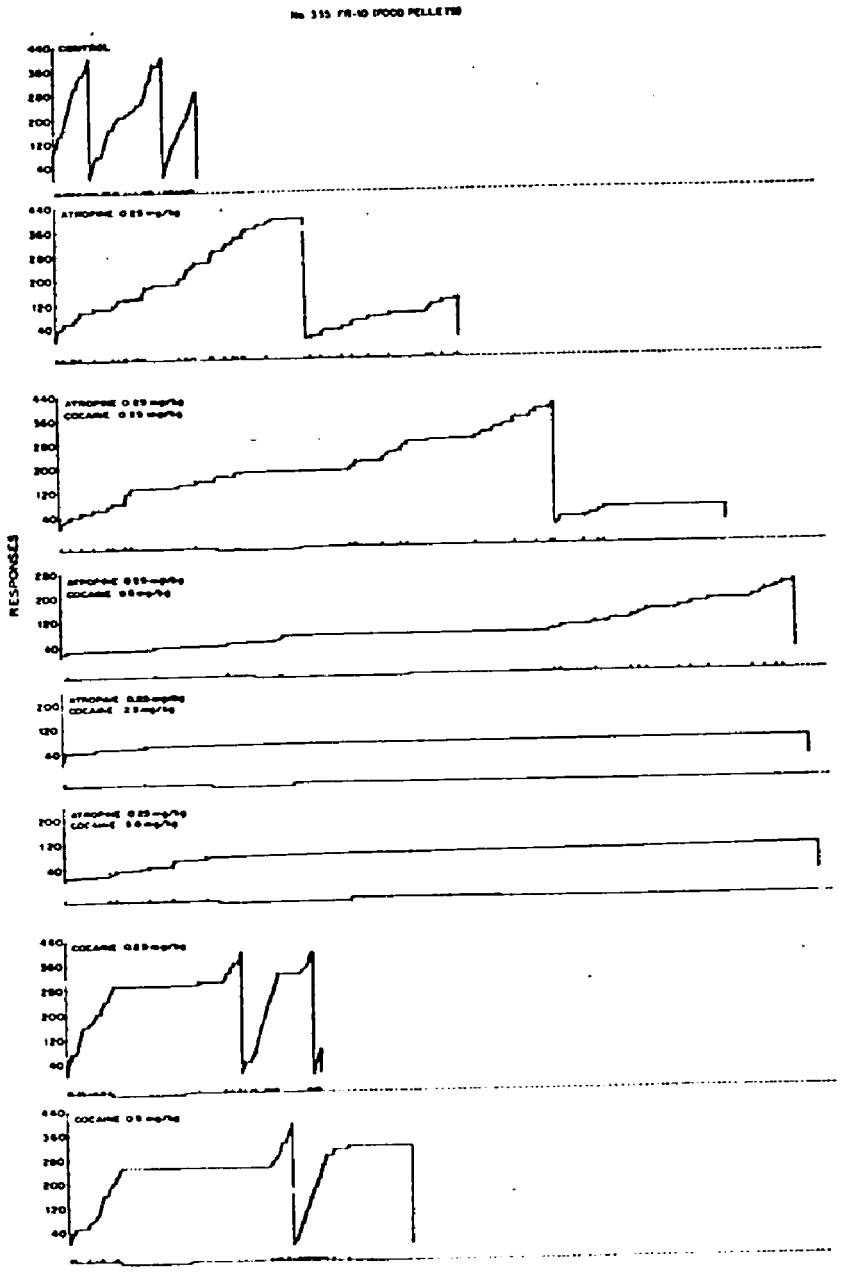

No 335 (FR-10)
Cocaine Control
Atropine 0.25 mg/kg
Atropine 0.5 mg/kg
No 338 (FR-10)
S 0.25 0.5 2.5 5.0
INFUSION DOSE OF COCAINE HCL (mg/kg)
FOOD REINFORCEMENTS IN LAST 90 MIN OF SESSION (24hr)
100
80
60
40
20

Figure 78. Cumulative response records which illustrate the effects of atropine and cocaine individually and in combination on food reinforced behavior in M335. Each vertical mark on the horizontal line indicates presentation of one food pellet. The downward displacement of the solid horizontal line indicates the start of cocaine administration. The length of the cocaine infusion is indicated by the length of this negative deflection. Return of the horizontal line to normal position indicates termination of the cocaine infusion. The ends of the sessions are denoted by a change in character of the horizontal line from a solid to a broken form. The response pen reset after every 400 responses or 40 reinforcements. The recorder was stopped during the one-minute time-out following each reinforcement, but the session timer continued to operate. Therefore, the length of the solid horizontal line was inversely proportional to the number of reinforcements received.

Figure 78



Pickens and Thompson[154] demonstrated that cocaine administered intravenously to an animal responding on an FR-10 schedule of food reinforcement produced a complete disruption of performance. The length of this disruption was dose-dependent. The results of this study are in complete agreement with results which we have obtained. The pausing produced in food reinforced behavior by cocaine administration is similar to the post-reinforcement pause seen with cocaine self-administration. This suggests that perhaps a direct effect of cocaine, i.e., behavioral disruption, rather than cocaine satiation, is responsible for the regulation seen in cocaine self-administration behavior.

The effects of CPZ on food reinforced behavior are very difficult to interpret. It is indeed difficult to determine whether the decrease in food reinforced behavior seen after CPZ administration is the result of general CNS depression or of a specific anorexic effect. Fogle has demonstrated that CPZ in dosages of 0.5-1.5 mg/kg depresses food-reinforced behavior in rats which were run on a multiple FIFR schedule of reinforcement. Responding was decreased in each component of the schedule and the magnitude of the effect was directly related to dosage.[68]

Soulairac and Soulairac demonstrated that CPZ, in dosages which significantly decreased the spontaneous activity of rats in a running cage, produced only a very slight decrease in food intake.[173] This indicates that the depression in food intake seen after CPZ treatment in our study and that of Fogle's is the result of drug-induced general CNS depression, rather than of a specific action of the drug on hunger.

The results seen with combinations of CPZ and cocaine could then be explained in the following manner. The central stimulant effect of cocaine antagonized the CNS depressant action of CPZ, which then permitted food intake to return toward normal levels. Perhaps a central adrenergic blocking of CPZ is responsible for antagonizing the anorexic effects of cocaine.

Brown has also demonstrated an antagonism between CPZ and a psychomotor stimulant, in this case, d-amphetamine, on a food reinforced operant.[23] Treatment with CPZ, at a dosage which produced no general depression or change in the frequency of the food reinforced behavior, antagonized the d-amphetamine-induced decrease in this behavior. This finding may indicate that the antagonism between CPZ and cocaine, which we have observed in cocaine self-administration behavior, is independent of the depressant effects of CPZ. Further evidence to support this conclusion was provided by the results of pretreatment with other classes of CNS depressants on cocaine self-administration.

Decreases in food reinforced behavior following treatment with atropine have also been demonstrated by other investigators.[214,173] The decrease in food intake was interpreted as being a function of the antisecretory effect of atropine, since the type of food employed was of a dry consistency, as was the case in our study. These investigators obtained similar results after treatment with methylatropine, which does not enter the brain to any appreciable extent since it is a quaternary ammonium compound. This result also supported their conclusion. However, if this is the only reason for the decrease in food intake, the effect should be antagonized by agents which increase salivation, e.g., cocaine. Since

we saw a potentiation rather than an antagonism of the effects of atropine on food seeking behavior after treatment with cocaine, the action of atropine on this behavior is probably more complex. It appears, then, that cocaine and atropine probably act by central mechanisms to decrease the desire for food. These mechanisms may or may not be different. What is apparent is that there is no generalized antagonism of the affects of cocaine by atropine, as is the case with CPZ. Chlorpromazine has been shown to antagonize the effects of the psychomotor stimulants on a number of different behaviors, e.g., aggregate toxicity[114], forced drinking behavior maintained by shock avoidance[193] and conditioned avoidance[103].

# VIII. DISCUSSION

The demonstration that Rhesus monkeys self-administer the same psychomotor stimulants which man abuses provides further support for the concept of using primates to study the physiological and behavioral aspects of drug dependence. Even more significant is the fact that their drug self-administration patterns closely resemble those seen in humans.

These studies have demonstrated that psychomotor stimulant administration can serve as a primary reinforcer in all subjects given the opportunity to engage in drug self-administration behavior. The same behavioral variables which influence the rate of responding for other primary reinforcers, e.g., food, water, also influence drug self-administration behavior. The magnitude of reinforcement and the schedule of reinforcement are two important determinants of the rate of responding for cocaine self-administration. As we have demonstrated, the frequency of lever-pressing for cocaine is inversely related to the magnitude of reinforcement and directly related to the value of a FR schedule of reinforcement. One of the most significant results of these studies is that when subjects have limited daily access to compounds, such as cocaine, the total amount which they self-administer per day appears to be independent of the magnitude of reinforcement and of the value of the FR schedule of reinforcement. Each subject tends to self-administer the same amount of these compounds daily. These effects were seen with all the psychomotor stimulants which we have studied. This lends further support to the hypothesis

that the reinforcing properties, like other actions of these compounds, are mediated by a common mechanism and pathway. As I have indicated earlier, all of these agents facilitate the actions of norepinephrine peripherally and centrally, and it is indeed tempting to attribute their reinforcing property to this effect. Some investigators have implicated norepinephrine as functioning as the neurotransmitter in a common central reward system. A decrease in the amount of functioning norepinephrine in such a system is thought to be the basis of mental depression by some scientists and clinicians.[179,181] However, this is only speculation and not fact.

Olds and Milner, in 1954, demonstrated that electrical stimulation to certain parts of the brain could serve as a reward or reinforcement.[139] Since that time, a number of investigators, principally Olds, have provided data which implicate the hypothalamic medial forebrain bundle and its connections in mediating reward or reinforcement.[138] Cats and rats will emit a response which results in intracranial self-stimulation if a stimulating electrode is located in this area of the brain. The frequency of this behavior appears to be inversely related to the magnitude of reinforcement which is identical to the relationship which we have demonstrated with psychomotor stimulant self-administration behavior.[135]

Drugs can markedly alter this self-stimulation behavior. Stein and Horovitz have demonstrated that pretreatment with methamphetamine increases this behavior, and imipramine administration potentiates this action of methamphetamine. Both of these agents enhance the actions of norepinephrine. Compounds which deplete or block

norepinephrine, or interfere with its synthesis, antagonize the effects of methamphetamine on this behavior.[99,182] Stein and Ray have also demonstrated that amphetamine decreases and CPZ increases the threshold for rewarding brain stimulation at a given electrode placement. The agents antagonize each other when administered in combination.[183] Cholinergic agents, such as physostigmine, depress this behavior and this effect can be blocked by atropine.[177,105] This suggests that there is a cholinergic system capable of inhibiting self-stimulation behavior.

The results of the self-stimulation experiments lead one to speculate even more strongly that the effects of the psychomotor stimulants on central noradrenergic function are responsible for their reinforcing effects. Norepinephrine has been shown to possess both facilitory and inhibitory effects on central neurons. Perhaps it is this inhibitory effect which acts to limit the self-administration of the psychomotor stimulants and the facilitory effects which are reinforcing or vice versa. All available evidence leads one to believe that it is a direct behavioral effect of these compounds which limits their self-administration.

The pretreatment experiments also provided evidence which suggested that it is the interaction of the psychomotor stimulants with central noradrenergic systems which makes them reinforcing. Compounds which interfere with norepinephrine in some manner, i.e., blockade of receptors, interference with synthesis, depletion of stores, increase self-administration frequency, which we interpreted as an antagonism of the reinforcing property of these compounds. Agents which may facilitate central noradrenergic function decrease

this behavior, which we interpreted as a potentiation of the reinforcing effect. The effects of CPZ and amphetamine of the self-stimulation reward threshold serve to substantiate this interpretation. A general cholinergic inhibitory system also may function in mediating the frequency of this self-administration behavior. Blockade of this system with atropine increased the frequency of this behavior as it did with self-stimulation behavior. Perhaps, then, atropine is not antagonizing a drug effect, but is only disinhibiting drug-seeking behavior. It is very possible that the stimulants facilitate this inhibitory mechanism when a certain dosage level is reached, and this limits the intake of these agents. Therefore, maybe atropine is antagonizing cocaine in this manner.

Therefore, in conclusion, it appears that the reinforcing efficacy of a psychomotor stimulant can be influenced by environmental and pharmacological variables. Those compounds which antagonize the reinforcing effects of these compounds, e.g., CPZ, may possibly serve as methods of treating psychomotor stimulant dependence. If these compounds were no longer reinforcing, they would no longer be abused. However, the problem is in providing a compound which specifically blocks only the reinforcing effect and has little overt effect of its own. This would indeed be very difficult if norepinephrine is the mediator of this reinforcement. It is hard to visualize a compound antagonizing only one of the myriad of actions of norepinephrine in the nervous system.

# IX. SUMMARY

The results of these studies indicate that the administration of psychomotor stimulants is a primary reinforcement, such as food and water presentation, in Rhesus monkeys. These subjects will self-administer those drugs which are abused by man, e.g., cocaine, phenmetrazine, methylphenidate, and d-amphetamine. Many of the same variables which influence the frequency of the emission of a given response for other reinforcers also determine the frequency of psychomotor stimulant self-administration. The magnitude of reinforcement, i.e., dosage per administration, and the schedule of reinforcement are powerful determinants of the frequency of lever-pressing behavior when the reinforcement is the administration of psychomotor stimulants. The frequency of the self-administration behavior is inversely proportional to the magnitude of reinforcement and directly proportional to the value of a fixed ratio schedule of reinforcement within the values of one to fifty. These results were the same regardless of whether the psychomotor stimulant was cocaine, pipradrol, phenmetrazine or methylphenidate; this leads one to speculate that the reinforcement produced by the administration of these agents is mediated by a common effect or pathway. It has been demonstrated that all of these agents have one effect in common: facilitation of central noradrenergic function.

Deprivation or satiation with food had no direct effect on the frequency of this self-administration behavior. This indicates that the anorexic effects of these compounds are not

involved in their capacity to provide reinforcement. It also indicates that deprivation of one type of reinforcement does not cause a second type of reinforcer to be more reinforcing.

Although the frequency of drug self-administration behavior was influenced by the schedule and magnitude of reinforcement, daily drug intake during a limited access period was independent of these two variables. These variables could be altered by a factor of fifty and daily drug intake only changed slightly. This indicated that something was occurring to limit the total amount of the psychomotor stimulants which would be self-administered.

One possibility is that some central control system is monitoring the intake of these compounds and that, after a certain amount is self-administered, a system is activated which results in the inhibition of self-administration behavior. This might be analogous to the hypothalamic system which supposedly functions to regulate food intake. A second possibility is that a direct behavioral effect of the drug limits the amount of that drug which is self-administered. Perhaps the onset of such an action decreases the reinforcing efficacy of the drug. Perhaps when a certain blood level of these compounds is achieved, the drug becomes aversive or disrupts any ongoing behavior. Experiments which have studied the effects of these drugs on the frequency of a given behavior, which results in the presentation of other reinforcers, e.g., food, have produced results which favor the latter hypothesis. However, these results have been distorted by the fact that these compounds are also anorexic agents.

The pausing which occurs after each self-administration may indicate that ongoing behavior is disrupted by the drug; the behavior is not initiated again until a sufficient quantity of the drug has been inactivated by some mechanism.

Regardless of the mechanism involved, treatment with other drugs should be able to change daily drug intake by interfering with the system or drug effect which produces this regulation. Drugs which may facilitate the central actions of norepinephrine, e.g., phenmetrazine, d-amphetamine, imipramine, and pargyline, produce a decrease in cocaine self-administration; whereas, drugs which may interfere with central noradrenergic function, e.g., alphamethylparatyrosine, chlorpromazine, and trifluoperazine, increase cocaine self-administration. Drugs such as phentolamine, phenoxybenzamine, and methylatropine, which have little if any central effect when administered parenterally, produce no change in cocaine self-administration. Pretreatment with morphine and pentobarbital produced no change in self-administration behavior until dosages were administered which produced marked general CNS depression. The anticholinergic agent, atropine, produces an increase in this behavior; whereas the cholinergic agent physostigmine produces a decrease in cocaine self-administration. Increases in cocaine self-administration were interpreted as either resulting from an antagonism of the reinforcing effect of cocaine, since decreases in unit dosage also result in an increase in the frequency of self-administration behavior, or from an antagonism of the effect of the drug or of the general behavioral inhibitory system which may limit cocaine self-administration. Decreases

in cocaine self-administration were interpreted as either a potentiation of the reinforcing property of cocaine, since increases in unit dosage result in a decrease in the frequency of cocaine self-administration, or as a potentiation of the effect of cocaine which limits its self-administration, or of a central behavioral inhibitory mechanism. Similar effects of drug pretreatment occurred with the self-administration of other psychomotor stimulants.

The apparent antagonisms between cocaine and chlorpromazine and between cocaine and atropine which existed in the self-administration procedure were investigated in subjects which were working for food rather than cocaine administration. Cocaine, atropine, and chlorpromazine individually depressed food reinforced behavior. Treatment with a combination of cocaine and atropine resulted in a potentiation of the depressant action on food reinforced behavior which occurred following administrations of either of these agents. However, when chlorpromazine administration was combined with cocaine treatment, an increase in food-seeking behavior occurred over that seen when either of these agents was administered independently. These results indicated that atropine was not a general antagonist of cocaine, but that chlorpromazine may antagonize many of the effects produced by cocaine. The exact mechanism of this antagonism may differ with the effect in question. Whereas the antagonism may be of a specific effect of cocaine, i.e., reinforcing action, in the self-administration study, the antagonism of food-seeking behavior may be of a nonspecific nature, i.e., between the CNS depressant action of CPZ and the CNS stimulant action of cocaine.

Atropine and cocaine may decrease food-seeking behavior by two different mechanisms; therefore, one would expect to see an additive effect when a combination of these two drugs was administered. In the self-administration study, atropine may have increased cocaine self-administration due to a blockade of a central cholinergic behavioral inhibitory system, rather than of a direct action of cocaine.

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