COCAINE DISCRIMINATION IN A CHOICE SELF-ADMINISTRATION PROCEDURE IN RHESUS MONKEYS

A Dissertation

Presented to

the Faculty of the Department of Psychology

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

By

David Mark McLendon

May, 1974

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ABSTRACT

The discrimination of cocaine in a choice intravenous self-administration procedure in six rhesus monkeys was investigated using several techniques.

The first technique allowed the monkey a choice of saline and cocaine simultaneously. The only cue available to differentiate one solution from the other was the introceptive stimuli provided by cocaine. In this preparation, no monkeys discriminated one solution from the other.

The second technique allowed six monkeys access to both solutions successively in 15 minute alternating periods both with and without secondary light cues. One of the monkeys could make a weak discrimination without light cues, but the other two in this condition did not develop a discrimination. The three monkeys with light cues all developed and maintained a strong discrimination and chose cocaine over saline.

All monkeys were then returned to the simultaneous availability of both solutions with each group retaining their discriminative cue conditions. Monkeys without light cues could not develop or maintain discrimination. Monkeys with secondary light cues maintained and improved their discrimination. When the light cues were removed from the schedule, discrimination was disrupted and not regained

indicating the monkeys were largely if not completely dependent upon the light for developing the discrimination.

The cocaine infusion dosage was doubled for one group of animals to determine the effect of cocaine dosage on discrimination. This group had cocaine and saline available simultaneously without secondary discriminative cues. This manipulation did not aid in discrimination but rather resulted in approximately a 50% drop in infusions for both solutions.

Finally, three monkeys were exposed to a simultaneous presentation of both drugs with intermittent light cues. This was an attempt to sensitize the monkey to the discriminable properties of the cocaine by gradually decreasing the duration of the light interval. This manipulation did not aid in discrimination. When the three animals were retested in the original condition of simultaneous availability without light cues, discrimination did not develop.

These results indicate that rhesus monkeys can and will discriminate between two solutions simultaneously available for self-administration if the animal has external cues to aid in discrimination. This technique offers new advantages to self-administration investigation. This procedure represents a model which more closely approximates human drug abuse.

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CHAPTER I

INTRODUCTION

Drugs have been sought after and used beneficially since ancient times. The consumption of these drugs for non-medical reasons, however, has become an individual and social problem during the last few hundred years. The twentieth century and especially recent years has seen a proliferation in drug abuse as well as the number of abuseable drugs. Society has consequently sought to gain insight into this problem which is, at least to some extent, a product of new achievements in technology and communications.

Investigators have recently used experimental animals to study human drug abuse. It has been shown that lower animals will self-administer drugs if given the opportunity. Headlee, Coppock, and Nichols (1955) first demonstrated this in rats. Weeks (1962) found that rats addicted to morphine would maintain their dependence by continued self-administration. Drugs function by reinforcing the animals' bar pressing behavior. The animal either seeks the positive reinforcing effects of the drug or avoids the negative reinforcement effect of abstinence or withdrawal from drugs with addicting properties.

Based on Weeks' techniques, extensive experiments with monkeys began at several laboratories. Rhesus monkeys have

been found to be more appropriate to these types of investigations and most studies have subsequently used these animals. These studies have established that rhesus monkeys self-administer certain drugs and they do so without other incentives. Once started, they self-administer many drugs indefinitely. Rhesus monkeys have been found to reliably self-administer a number of different drugs of the stimulant and depressant classes as well as the opiods (Deneau, Yanagita, and Seevers, 1969). They do not, however, self-administer marihuana (THC) (Harris, Waters, and McLendon, 1974) or the psychedelics (Deneau, Yanagita, and Seevers, 1969). Additionally, it has been found that there is reliable predictability as to the pharmacological classes of drugs monkeys will self-administer. Reasonable reliability also exists across animals in their response to different classes of drugs.

Most investigations in drug self-administration have allowed the animals access to only one drug at a time. To date, a wide variety of drugs have been screened through this procedure for their reinforcing efficacy. A close parallel between animal and human self-administration of drugs has been shown to exist. An exception has been found with drugs which are only occasionally or sporadically used by humans.

The expansion of this model from a single available drug to a choice of drugs opens new areas of consideration for self-administration research. The opportunity for

monkeys to choose between drugs or to mix drugs can possibly lead to a better animal model that offers more information and more closely approximates human drug use and abuse. Patterns of human drug abuse indicate a great deal of individual differences among individual drug users. Many, for instance, prefer stimulants or depressants or narcotics and, once settling upon one if available, may exclude the others. This reflects the fact that most human drug abusers are, in reality, multiple drug users, sometimes remaining so and sometimes having a preferred drug. It is possible that, given the opportunity, rhesus monkeys will exhibit similar tendencies.

In an effort to expand the self-administration model from one of single opportunity to one of choice, this investigator conducted a pilot study to assess the feasibility of such a procedure. Data gathered from this initial investigation (Figure 1) indicated that if a rhesus monkey was given access to two solutions simultaneously, one of cocaine and one of saline, he could not or would not select one solution over the other. Even though the animal was being reinforced by his self-administration of cocaine, he maintained high levels of saline self-administration.

The animal's failure to make a discrimination under these circumstances may have been a behavioral phenomena rather than a reflection of the introceptive effects of the drug solutions. Since the animal received an infusion

Spontaneous Self-Administration of Cocaine and Saline in a Simultaneous Two Lever Presentation

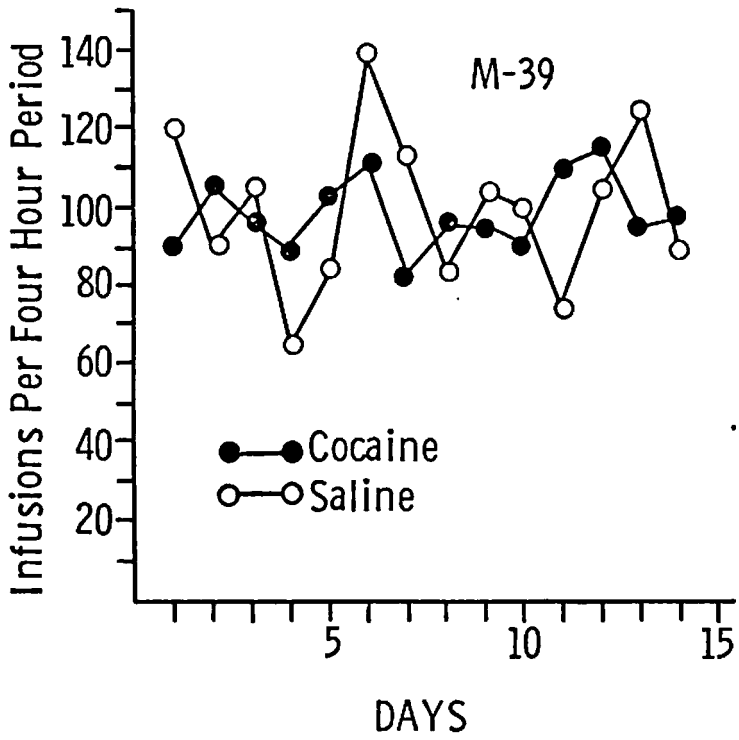


Figure 1a

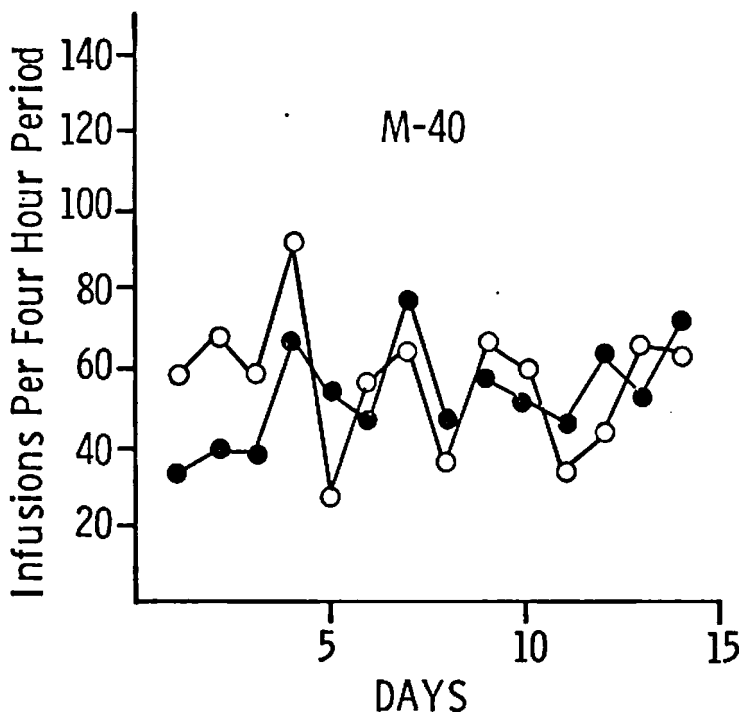


Figure 1b

with each bar press and was being reinforced by the cocaine for his bar pressing behavior, he may have not been motivated to make a choice. If this is not the case, it is probable that his alternative choices were not discriminable because of the physiologically continuous reinforcement. Since the reinforcement effect of cocaine was slightly delayed, his failure to discriminate may be due to this physiological confounding.

The present study was an attempt to determine the extent or limit of cocaine discrimination in a choice self-administration procedure. A variety of experimental conditions were employed attempting to separate the physiological and behavioral variables which influence choice behavior.

CHAPTER II

REVIEW OF THE LITERATURE

This investigation is concerned with the degree of discriminability of cocaine and saline as presented to rhesus monkeys in a choice self-administration procedure. This is a relatively unresearched area and no investigations have been undertaken to thoroughly examine the problems or advantages inherent in such a paradigm. The conceptualization of such a design is a function of the consideration of drugs as discriminable stimuli operating within the framework of the self-administration model expanded to a choice presentation. Each of these areas must be considered individually in order to clarify their relationship to the present investigation.

Self-administration of Drugs

Self-administration research is generally considered to have begun with the investigations of Headlee, Coppock, and Nichols (1955) who first demonstrated that experimental animals (rats) would administer drugs to themselves. Weeks (1964) introduced a technique that provided a chronic preparation that would enable rats to self-administer drugs in solutions via chronic indwelling venous catheters. Using this technique, Weeks found that rats would maintain morphine dependence by bar-pressing for morphine injections (1962).

In 1963, techniques were introduced to study intravenous self-administration in rhesus monkeys (Yanagita, Deneau, and Seevers, 1963; Schuster and Thompson, 1963). Rhesus monkeys have been found to be particularly well-suited for these types of investigations, and most studies have consequently used this species. This model has been subsequently employed in various technical modifications which have established its reliability and usefulness as a means to investigate the parameters involved in the self-administration of various drugs.

Self-administration studies with rhesus monkeys have established that a variety of drugs act as adequately discriminable reinforcers to promote continued self-administration behavior. Given the opportunity, rhesus monkeys will bar press to receive intravenous infusions of stimulants such as cocaine (Yanagita, Deneau, and Seevers, 1963), d-amphetamine (Deneau, 1968), methamphetamine (Harrigan, personal communication, 1972), nicotine (Deneau and Inoki, 1967), SPA (1-2 diphenyl 1-dimethyl-amino ethane hydrochloride) (Estrada, Villareal, and Schuster, 1967), caffeine (Deneau, Yanagita, and Seevers, 1969), and depressants such as pentobarbital and phenobarbital (Deneau, 1968), amobarbital in rats (Davis and Miller, 1963), and ethyl alcohol (Yanagita, Deneau, and Seevers, 1963). In addition, rhesus monkeys will self-administer opiods such as morphine and codeine (Deneau,

Yanagita, and Seevers, 1969) and methadone (Deneau, 1968). Given the same opportunity, monkeys will not self-administer nalorphine, chlorpromazine, mescaline (Deneau, Yanagita, and Seevers, 1965) or marihuana (delta-9-tetrahydrocannabinol) (Harris, Waters, and McLendon, 1974) although they will take the psychotominetic phencyclidine (Balster, Johanson, Harris, and Schuster, 1973).

A wide variety of drugs, therefore, act as powerful reinforcers to initiate and maintain self-administration behavior. Those drugs that are reliably self-administered are, for the most part, the same drugs that are chronically used and abused by humans. As Schuster and Thompson (1969) point out, however, the extent to which any drug is or is not self-administered is influenced additionally by variables other than the drug itself. Self-administration behavior is undoubtedly the result of an interaction of several biological and environmental variables, both in humans and experimental infra-humans. The contribution of these variables is, of course, fundamentally relevant to the question of when and why humans and non-human primates self-administer drugs. For the purpose of this investigation, however, it is important to recognize that rhesus monkeys, when given the opportunity, will self-administer any of a wide variety of drugs reliably and chronically with no incentives other than the drug itself.

Drugs as Discriminable Stimuli

It has been thoroughly established that experimental animals can utilize introceptive stimuli as discriminative cues and consequently develop conditioned responses. Bykov (1957) investigated a number of reflexively conditioned responses that could be elicited by an introceptive stimulus. Delov and Petrova, for instance, used drugs to condition a cardiovascular reflex by pairing it with intravenous morphine injections (Bykov, 1957). A large number of investigations have subsequently established that animals can be trained to respond differentially in a variety of situations contingent upon the administration of a previously associated drug or placebo (Overton, 1971; Schuster and Balster, 1974).

For a drug to act as a reinforcer in self-administration behavior, it must be discriminable. It has been adequately established that all drugs that have been utilized in self-administration studies, whether self-administered or not, are discriminable. A simple saline substitution for a reinforcing drug that is being self-administered, for example, will terminate self-administration behavior. Saline is non-reinforcing, is not self-administered, and the absence of any reinforcing effect when self-administered is immediately discriminable to rhesus monkeys. Likewise, a drug previously determined to be non-reinforcing will terminate self-administration behavior when substituted

for a reinforcing drug that is being self-administered. Reintroduction of the reinforcing agent will reinstate self-administration behavior. These manipulations demonstrate that in the standard single solution self-administration paradigm, rhesus monkeys can discriminate if a drug is or is not reinforcing and will bar press accordingly. This does not, however, elucidate the extent to which the drug is discriminable, the ability of the animal to use this discrimination to direct choice behavior, or the animal's ability to separate this relevant discrimination from other irrelevant secondary reinforcers (such as the infusion itself) that inappropriately reinforce the subject's adventitious behavior.

Self-administration animals respond not merely to the presence or absence of the reinforcing agent, but also to the magnitude of the drug effect. Pickens and Thompson (1968a), by manipulating the magnitude of the drug reinforcement, found an inverse relationship between rate of self-administration and the dosage of the infusion. Woods and Schuster (1968) demonstrated this effect over a wide range of dosages of cocaine with animals, in effect, monitoring the amount of drug self-administered and maintaining a relatively stable intake over a wide range of dosages. Similar relationships have been demonstrated with d-amphetamine (Pickens and Harris, 1968) and methamphetamine (Pickens, Meisch, and McGuire, 1967). Rate of

self-administration has been found to be relatively unaffected, on the other hand, by manipulation of infusion time or infusion volume (Pickens and Thompson, 1968b).

Studies concerning response patterning for different drugs indicate that monkeys emit characteristic patterns of self-administration for some particular drugs. Cocaine self-administration, for example, is characterized by extremely regular spacing of infusions over the standard limited daily four hour access period (Woods and Schuster, 1968). An increase in dosage results in an increase in the inter-infusion response time although the pattern still retains its characteristic spacing pattern. Pentobarbital, on the other hand, results in a pattern of response bursts where the animal loads up on the drug and then abstains for a period of time. Higher unit dosages result in a smaller number of infusions during the loading period, but the same characteristic non-response period is retained (Woods and Schuster, 1970).

The data is consistent, then, that animals respond differentially to the self-administration of various drugs. Since they emit different response patterns for different drugs, the reinforcing property of the drug is a determinate of behavior. Rate of infusion is controlled by infusion dosage. In the self-administration situation, discrimination is a continuous rather than a discreet event. The animal responds continuously to his changing drug state and

modifies his behavior in response to it, rather than simply emitting one response or a series of learned responses to the acute administration of a particular previously conditioned drug.

The Drug Choice

In an effort to establish oral self-administration in the rat, a number of studies have utilized a preference procedure whereby the subject is presented with two or more solutions in drinking bottles, one containing a drug such as alcohol, and another containing water, sucrose, or quinine. The confounding variables in these types of investigations are several including palatability of the solutions, position preference, level of water and food deprivation, and, particularly, latency of onset of the drug effect (Schuster and Thompson, 1969). Moreover, chronic alcohol ingestion leads to addiction and, in addition, the food value of alcohol is a relevant variable in food restricted animals (Richter, 1926; Westerfeld and Lawrow, 1953). Nevertheless, rats will drink solutions containing alcohol in free choice and forced choice conditions (Mendelson and Mello, 1964) although their preference and consumption increases with increased exposure to the drug (Vaele and Myers, 1969). These investigations were largely attempts to develop a model for oral self-administration.

The self-administration technique for monkeys circumvents most of the confounding variables present in the rat preference studies. The most obvious advantages of the monkey model is that since the route of administration is intravenous as opposed to oral, the major variables of palatability and latency of onset are eliminated. Since the drug in this method is introduced directly into the bloodstream, it is not necessary to conduct these investigations in the framework of a preference, since the drug seeking behavior required of the organism (bar-pressing) is not a natural and innate behavior possessing high survival value (drinking). Since the monkey will self-administer cocaine, for instance, but not saline, it is clear that he is seeking a drug effect and not simply engaging in a natural behavior that secondarily leads to a drug effect.

A few investigations have, however, presented the animal with an opportunity to express a choice between two intravenously administered solutions. Deneau, Yanagita, and Seevers (1969) provided four monkeys an opportunity to self-administer morphine (2.5 mg./kg.) and cocaine (1.0 mg./kg.). They could self-administer either or both drugs by the appropriate bar press. Deneau et al. found that all subjects self-administered both drugs but tended to take more cocaine during the day and more morphine during the night. The authors report, however, that within a week to 10 days, all Ss became disoriented and no pattern was

discriminable. This experiment terminated in death for all Ss within two to four weeks. Findley and Robinson (1971) addicted two monkeys to Librium and made available to them a forced choice self-administration situation where a drug infusion was contingent upon the completion of an FR-50 for shock avoidance. Two different colored lights were associated with the two drugs and levers, both levers leading to successful avoidance but the infusion of different drugs. Findley and Robinson reported a greater mg./day intake of Seconal over Librium although they received both. In an extension of this work, Findley, Robinson, and Peregrino (1972), following the same techniques, found monkeys preferred secobarbital and chlordiazepoxide to saline. All infusions were consequent to successful shock avoidance. Monkeys will not freely self-administer these drugs, however.

Other studies have been done, however, that utilize free choice procedures and non-addicting drugs. Johanson (1971) utilized sampling trials and choice trials to provide rhesus monkeys with a choice between two concentrations of cocaine, 0.1 mg./kg. and 0.5 mg./kg. Each concentration had a colored light associated with it functioning as a discriminable stimulus. Using light associated cues, Johanson found his subjects to prefer either dose of cocaine over saline and the higher dose of cocaine over the lower. In a similar study, Balster,

Johanson, and Schuster (1972) drew the same conclusions using sampling and choice trials and discriminative light cues.

Statement of the Problem

Traditional drug self-administration has been a relatively straight-forward proposition whereby the animal either self-administers the available solution or does not. Under these conditions, the animal either may or may not make the appropriate response leading to drug intake, and his tendency to self-administer is reflected in the degree to which he engages in bar pressing behavior and the amount of drug he infuses. In a two lever preparation where two solutions are available, the possibilities and consequent complications are greater. As the pilot work for this investigation suggested, rhesus monkeys can not or do not discriminate and choose between cocaine and saline when presented with the two solutions simultaneously. This finding raises several questions and suggests several possibilities. The first consideration concerns the ability of the animal to discriminate the two solutions. In order to examine this, the present investigation attempted several techniques to allow the animal a clearer chance to improve the possibilities for discrimination. In the pilot work, the monkeys had only the drug effect itself as a discriminable cue. By providing secondary visual discriminative cues, it could be determined if the animal can and

will utilize these additional cues to aid discrimination. Also, the animals were presented with the two solutions on a successive basis so that the animal's experience with each solution was more isolated. This procedure amounts to sampling trials and allowed the animal to experience one solution without it being confounded by the other solution or lever. Successive and simultaneous presentations were considered both with and without secondary light cues.

Additionally, some consideration was given to the effects of cocaine dosage. By increasing the cocaine dosage from 200 μg./kg./infusion to 400 μg./kg./infusion, it could be determined if a greater infusion concentration of cocaine would make the cocaine infusion more discriminable and thereby differentiate it from the saline infusion. Finally, an attempt was made to sensitize the animal to the discriminable effects of the cocaine infusion by pairing the cocaine infusion with secondary light cues that function on an intermittent basis. These light cues could then be faded out so that the animal might become less dependent on these cues and more dependent on the drug cues.

The methods involved in this investigation are basic to the development of procedures to conduct choice drug self-administration in rhesus monkeys. It is important to know if and to what extent the two solutions are discriminable and the extent to which the animal is motivated to express a choice. For this technique to be successful, not

only must the animal be able to discriminate the two solutions, but he must also be willing and motivated to choose one solution over the other. Since the animal was reinforced by the consequent cocaine intake for his bar pressing behavior, it was not at all clear that the animal would attempt to self-administer one solution and not the other.

CHAPTER III

METHOD

Subjects

Six male rhesus monkeys (Macaca mulatta) obtained from Primate Imports were used in this study. Each monkey weighed approximately 3-3.5 kg. at the beginning of the study and all were experimentally naive. Throughout the investigation, all monkeys had water available at all times and were fed once daily in the afternoon, approximately one hour after the completion of the daily session. All were housed in their experimental room throughout the study and were subject to a 12-hour light-dark cycle.

Upon receipt, all animals were placed in individual Shore-line stainless steel cages measuring 22 inches wide by 28 inches high by 30 inches deep. Each was housed individually. Each animal was fitted with a tubular stainless steel harness (Deneau, Yanagita, and Seevers, 1964). The harness was padded with Reston 3-M foam padding to protect the animal against skin lesions. The animal was partially restrained to the cage by the attachment of a 22 inch stainless steel reinforced hydraulic tubing (Aeroquip #2651-6) which attached to a swivel on the back of the harness by a connector (Aeroquip #4412-6) and a 1/2 inch threaded brass pipe. This

connection swiveled vertically and horizontally. The distal end of the restraining arm was attached by a connector (Aeroquip #4411-6) to a machined swivel that bolted to the back of the cage. The bore of the swivel was continuous with the bore of the tubing. The swivel, originally constructed for a full 360° turn was modified for approximately a 300° turn to prevent fouling of the catheters. This restraining device allowed the subject relatively free movement about the cage. All Ss were allowed a period of 7-10 days in which to adapt to the harness and restraining arm.

Apparatus

Each monkey was tested daily in his home cage. The sliding front cage door was displaced to admit an intelligence panel each day. The panel measured 9 inches by 11 inches and was equipped with two levers and two lights. The microswitch levers were 5 inches apart and 6 inches above the floor of the cage. A lamp was located 3-1/2 inches above each lever and would accept interchangeable jeweled lenses.

Each panel connected to an interface and was programmed with electromechanical equipment housed in a separate room. Drug infusions were delivered via Cole Parmer peristaltic pumps through Tygon tubing to the back of the cage where connections were made with the individual catheters. One bar press (when active) resulted in the

administration of .5 ml. of solution delivered over a 10 second infusion period. All infusions and lever presses were recorded on counters and cumulative records during the access period.

Catheter Preparation

Each monkey was prepared with a double lumen Silastic catheter. A 15 inch length of double catheter was prepared by soaking a 15 inch length of Silastic medical grade tubing (.062" i.d. x .095" o.d.) in Toluene for about 30 minutes. Toluene expanded the tubing thereby allowing the passage of two smaller lengths of Silastic tubing (.025" i.d. x .047" o.d.) through the inside. After alignment of the two small catheters to correct for twisting, the larger outer tubing was allowed to contract around the smaller tubes. One end of this double catheter was beveled to facilitate introduction into the vein. The unit was thoroughly cleaned and autoclaved.

Surgical Implantation

Each monkey was pretreated with Ketamine hydrochloride (5 mg./kg.) and removed from his cage and harness. He was then treated with Atropine and administered Sodium pentobarbital in a dilute concentration of 30-40 mg./kg. via the saphenous vein. The animal was then shaved, cleaned, and prepared for surgery. Sterile procedures were followed throughout.

All animals were initially prepared with a chronic indwelling double lumen catheter surgically implanted into the right internal jugular vein. The catheter was passed intravenously toward the heart but did not enter the heart. The vein was ligated around the catheter for security and tied into the muscle tissue. The catheters were then passed subcutaneously over the shoulder and down the animal's back where they exited through an interscapular stab wound. The catheter was then terminated three inches from its exit site and spliced into two lengths of a thicker walled Silastic tubing (.030" i.d. x .065" o.d.) for greater security, and the splice reinforced with Silastic medical grade adhesive. The animal was then placed back in his harness and the catheter passed out the back of the harness and through the restraining arm. The catheters terminated at two stopcocks that attached directly to the tygon tubing of the corresponding peristaltic pumps.

Some monkeys required re-catheterization during the course of the investigation because of faulty catheter performance or removal of the catheter by the animal itself. When this occurred, the other jugular vein was catheterized and then the two femoral veins if necessary.

Drug Solutions

Saline solutions were Baxter/Travenal 0.9% sodium chloride injection. Solutions for cocaine self-administration were prepared by dissolving cocaine hydrochloride crystals (Mallinckrodt) in 0.9% sodium chloride injection (physiological saline). Solutions were prepared in 500 ml. bottles (Baxter/Travenol) and were connected directly to the peristaltic pumps by Plexitron (Travenol) solution administration sets. Cocaine solutions were discarded and replaced if they were more than 7 days old.

CHAPTER IV

PROCEDURE AND RESULTS

Preliminary Training

All animals ran simultaneously for 4 hours each day, 7 days a week. This procedure has been found to maintain regular daily responding without interruption but does not produce toxicity (Woods and Schuster, 1968). Cocaine was chosen as the reinforcing drug since it is easily administered, fast acting, and rapidly metabolized. Furthermore, cocaine does not result in physical dependence although it is often considered to result in psychological dependence (Goodman and Gilman, 1970). In addition, cocaine is used often in self-administration studies to quickly initiate self-administration behavior. A standard dosage of 200 μg./kg./infusion was selected since this results in reliable and consistent responding of about 75-125 infusions per 4 hour access period (Woods and Schuster, 1968). The amount taken each day varies from monkey to monkey but is relatively stable for each individual animal.

Initially, all animals were given training to establish self-administration behavior and to orient the animal to a two-lever manipulanda. During the training period, only one lever was active, and one bar press resulted in one infusion of 200 μg./kg. of cocaine. The other lever was

inactive. The active lever alternated each day. Within 2 weeks, incorrect lever responding was minimal for all animals, and each animal achieved a stable daily drug intake.

Simultaneous Choice Self-Administration without External Cues

The six monkeys (M-43, M-44, M-45, M-46, M-47, and M-48) were presented simultaneously with two active levers, one delivering an infusion of saline with each bar press, the other an infusion of cocaine. The drug positions were reversed each day, and all animals remained in this condition for 2 weeks. This procedure was undertaken to re-examine the lack of discrimination found in the pilot study under the same conditions. Figure 2 shows that all six animals failed to choose between the two solutions during this period and all took approximately equal amounts of both solutions. This result replicates the failure to discriminate under the same conditions with two monkeys (M-39 and M-40) in the pilot study completed prior to this investigation (Figure 1, p.4).

Successive Choice Self-Administration with and without External Light Cues

In order to examine the effect of separate experience with each solution on discrimination, a successive presentation was utilized. Under these conditions, each animal had available only one solution at a time for 15 minutes. When

Replication of Spontaneous Self-Administration of Cocaine and Saline in a Simultaneous Two Lever Presentation

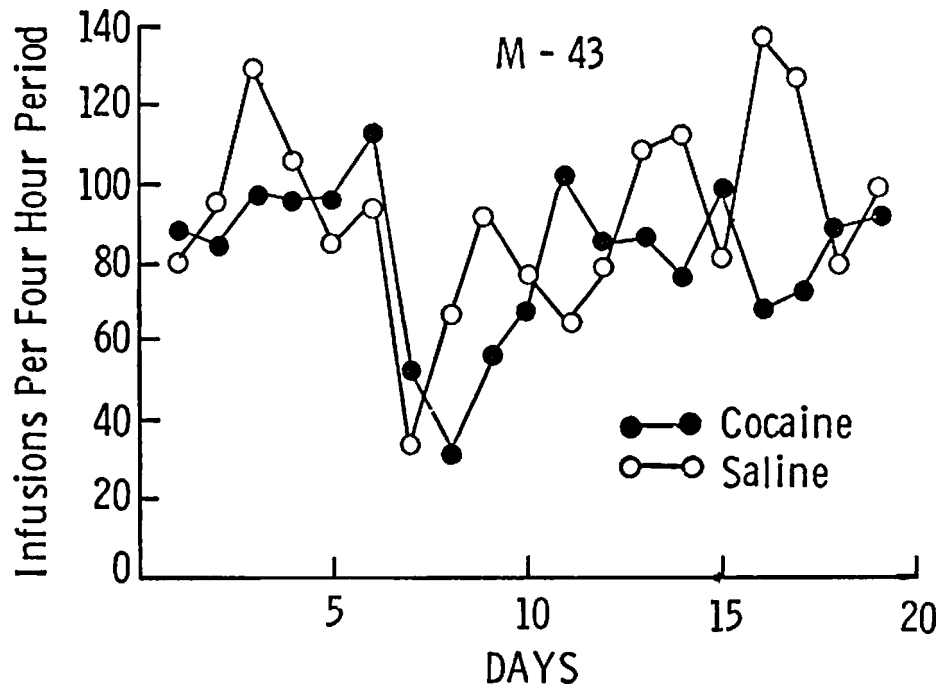
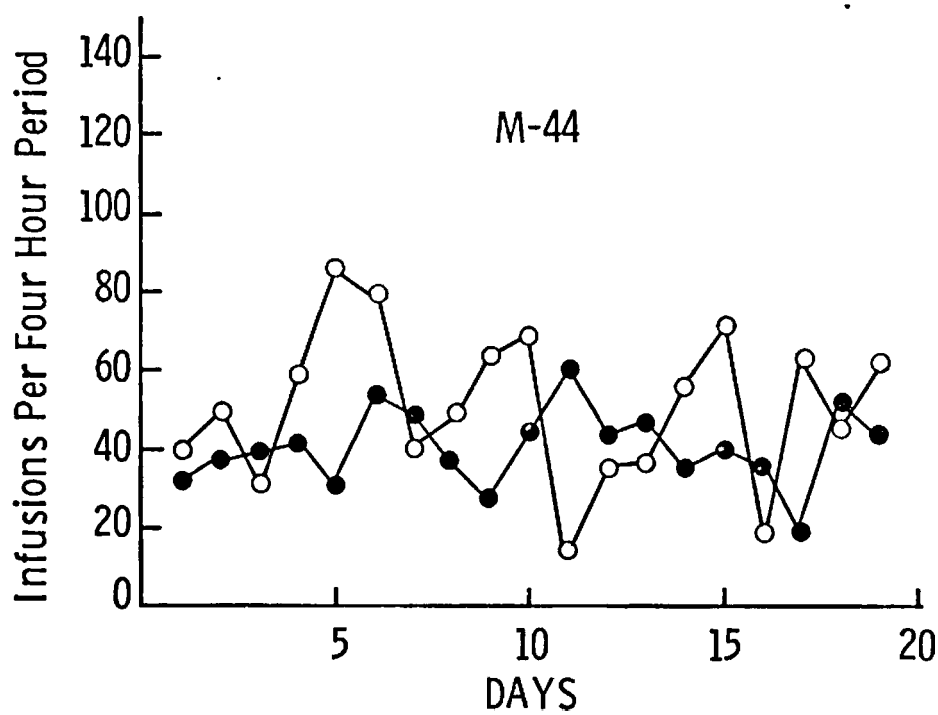


Figure 2a



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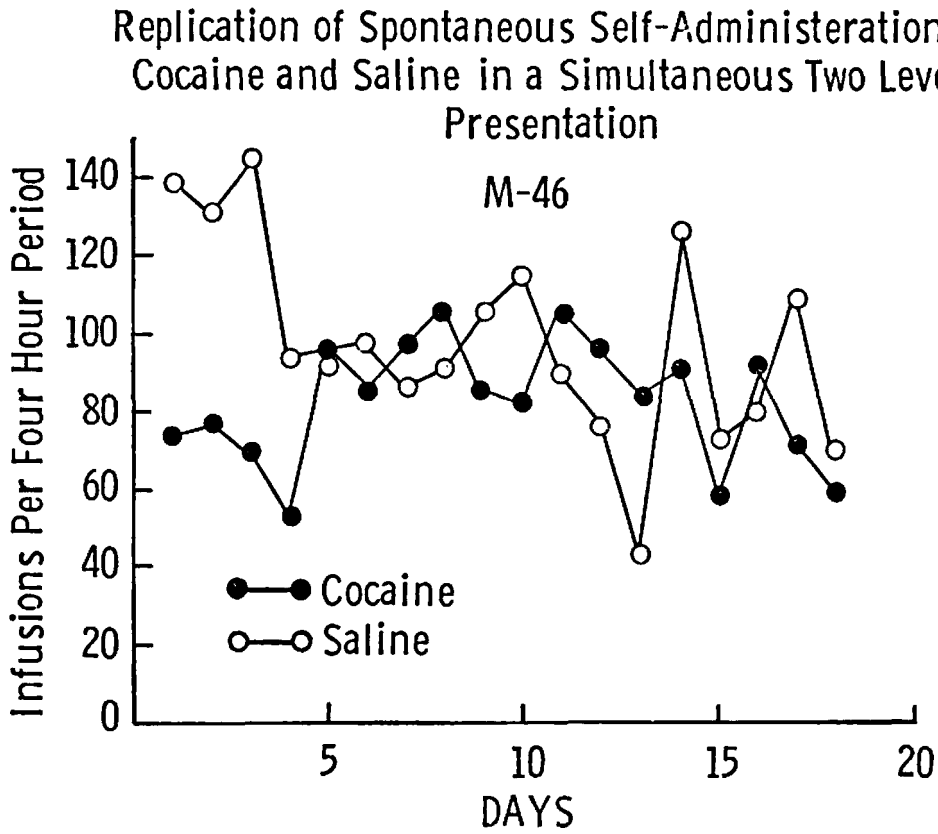

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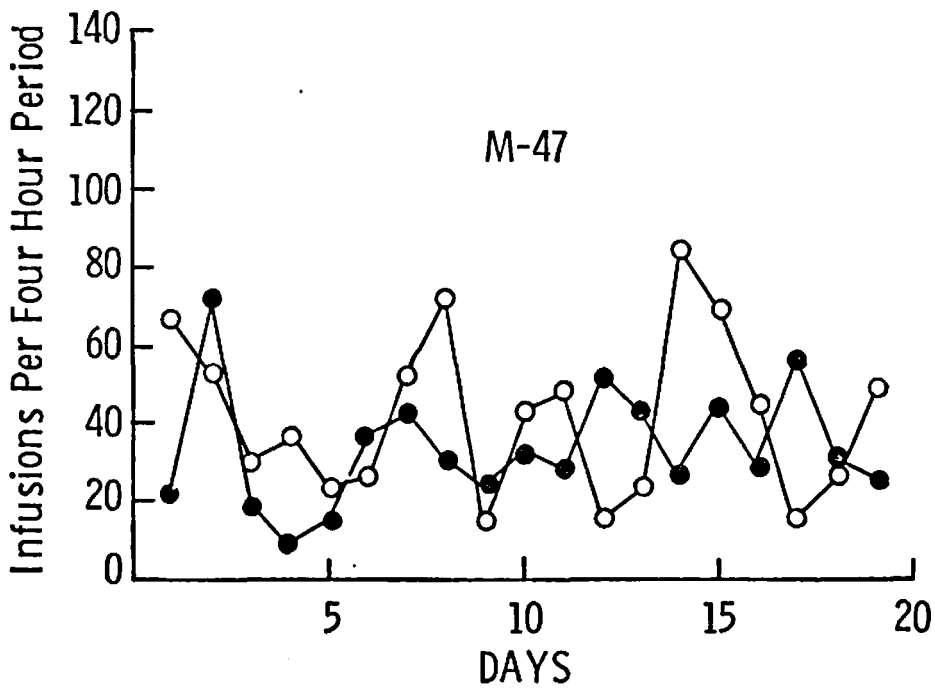


Figure 2d

Replication of Spontaneous Self-Administration of Cocaine and Saline in a Simultaneous Two Lever Presentation

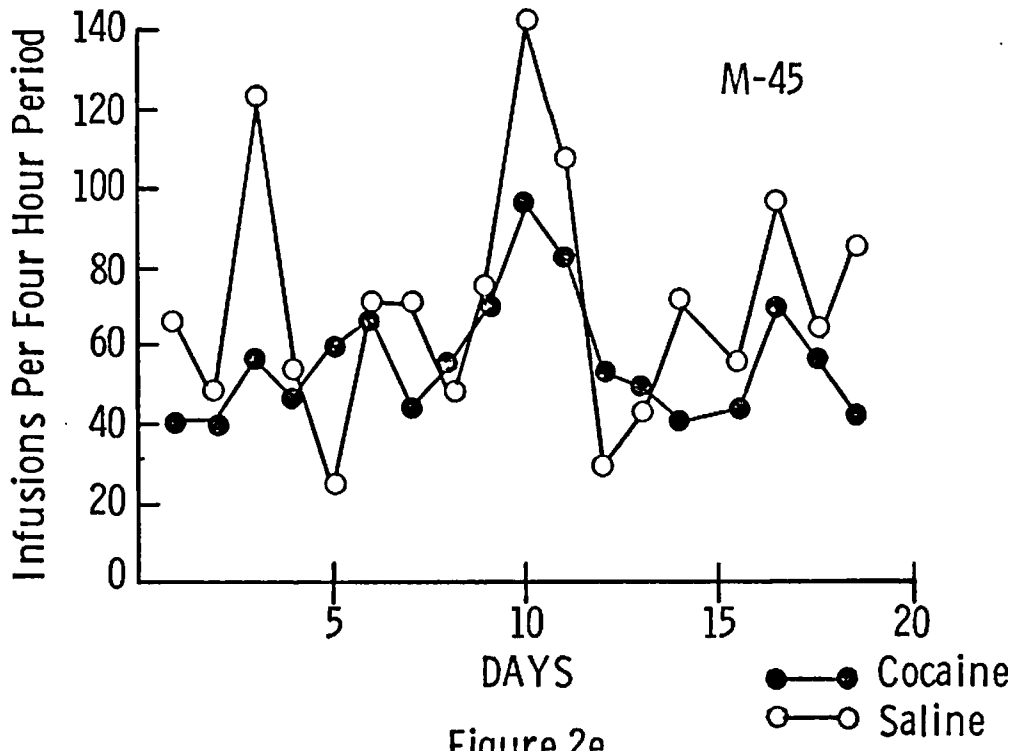


Figure 2e

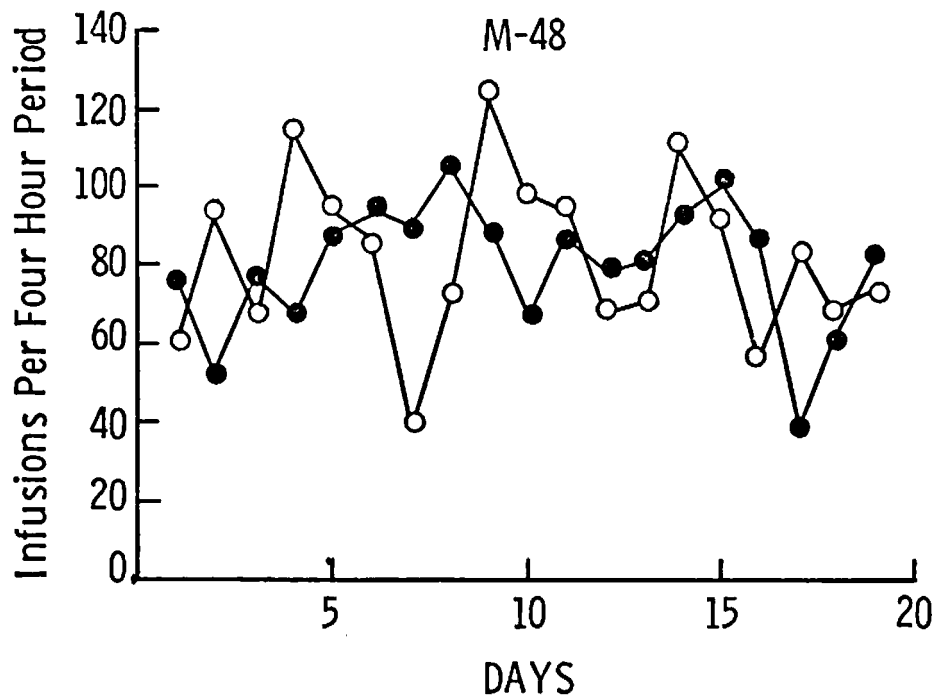


Figure 2f

one lever was active the other was not, and the available solution alternated each 15 minutes. The positions of the cocaine and saline reversed on a daily basis.

Imposed upon this procedure was an assessment of the effect of external visual cues on discrimination and, consequently, choice behavior. Three of the animals had no visual cues. These monkeys (M-43, M-44, and M-45) had a white light cue over the active lever. This light cued the animal to which lever would produce an infusion. There was no light on above the inactive lever. This light, therefore, did not provide a cue to enable the animal to discriminate one solution from the other. Under these conditions (Figure 3) monkeys M-43 and M-45 failed to discriminate between the two solutions. In order to determine the relative infusion rates for the two solutions after experience with the schedule, the mean infusion rates for the last 10 days of each condition was calculated. During the last 10 days of this condition, animal M-43 self-administered a mean of 84 infusions/day of cocaine and 79 infusions/day of saline during the access period. Monkey M-45 took a mean of 101 infusions of cocaine and 107 infusions of saline during the same period. One animal (M-44) did discriminate between the two solutions by responding predominantly for cocaine. During the last 10 days for this animal, he self-administered a mean of 51 infusions/day of cocaine and 20 infusions/day of saline, suggesting a weak although relatively stable discrimination.

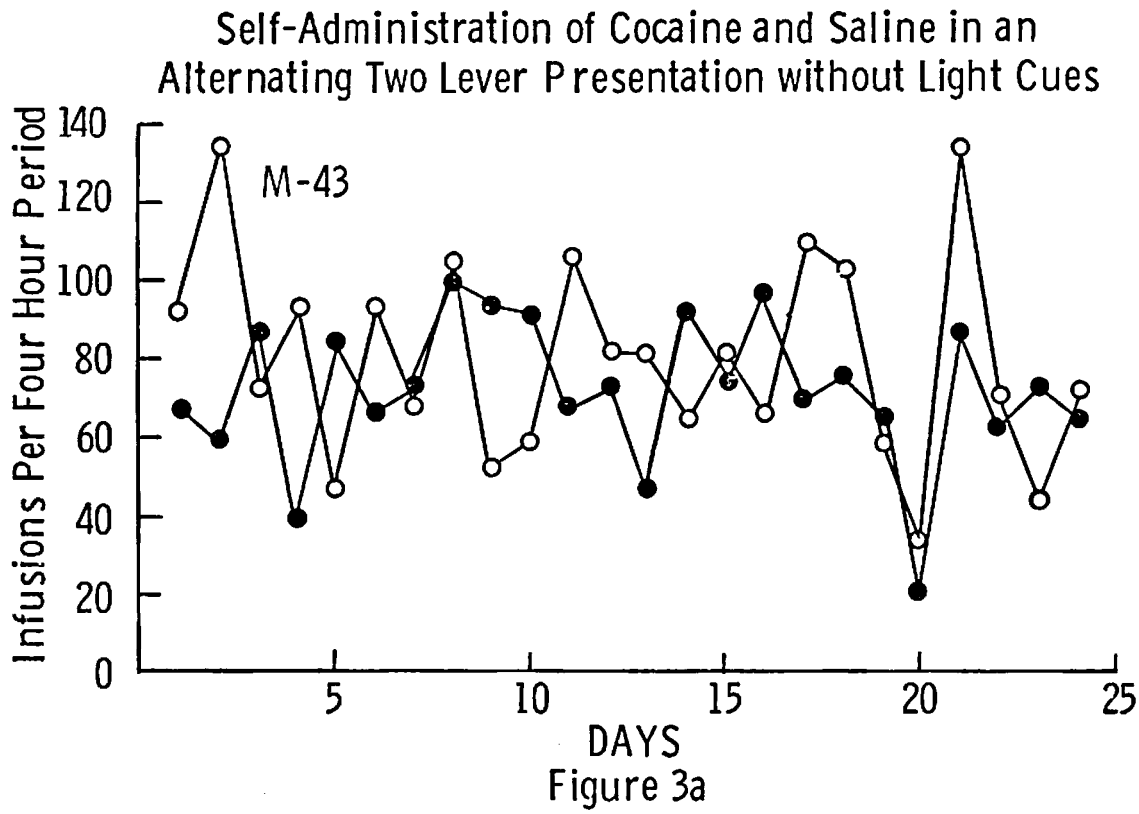


Figure 3a

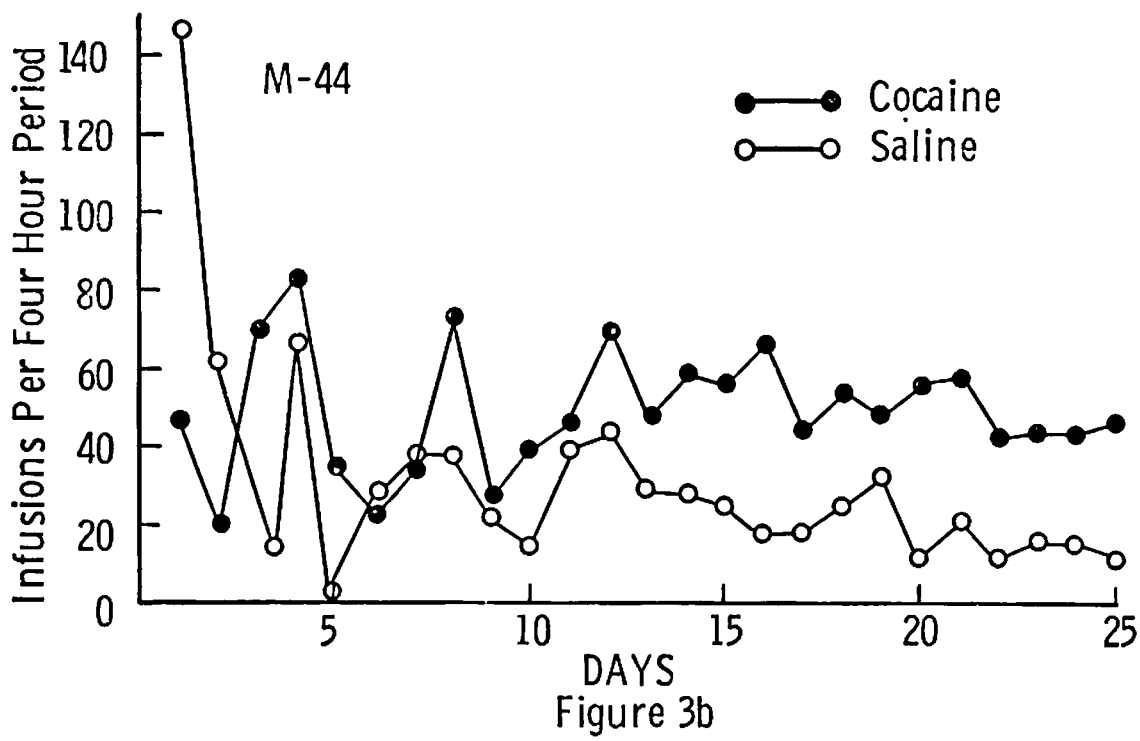


Figure 3b

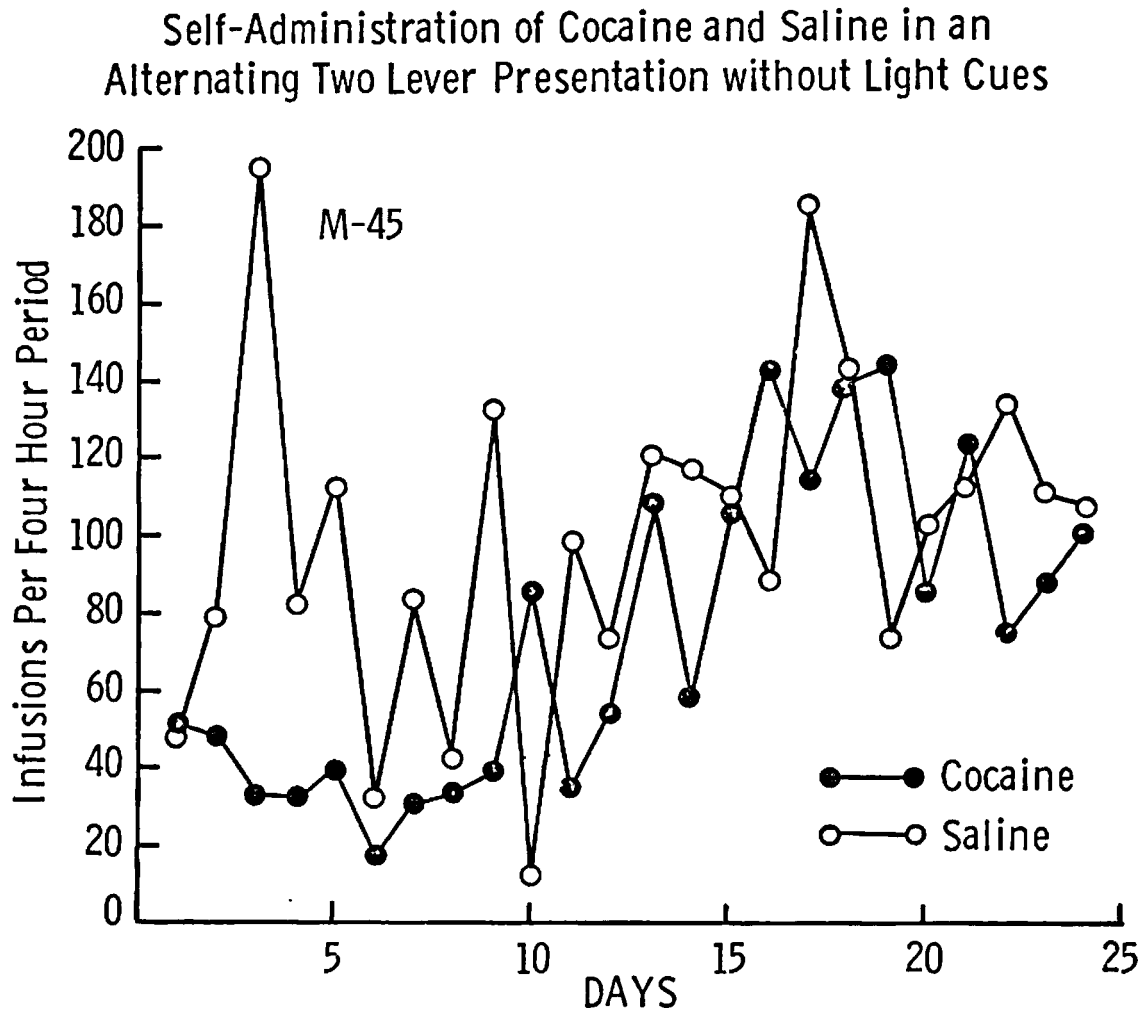

Self-Administration of Cocaine and Saline in an
Alternating Two Lever Presentation without Light Cues
M-45
Infusions Per Four Hour Period
200
180
160
140
120
100
80
60
40
20
0
5
10
15
20
25
DAYS
Cocaine
Saline

Figure 3c

The other three animals in the successive presentation (M-46, M-47, and M-48) had drug-associated light cues available to assess their effect in aiding discrimination. These animals had a white light associated with the cocaine lever and an amber light associated with the saline lever. Figure 4 shows that all three animals discriminated between the two solutions and chose cocaine over saline within 11 days of exposure to this condition. All animals, having made the discrimination, improved and maintained the discrimination throughout their exposure to this condition. During the last 10 days of their 28 day access to this condition, animal M-46 self-administered a mean of 105 infusions/day of cocaine and 12 infusions/day of saline. During the same period of time, M-47 took 38 infusions/day of cocaine and 9 infusions/day of saline while M-48 self-administered a mean of 91 infusions/day of cocaine and 16 infusions/day of saline.

Transfer from Successive to Simultaneous Availability without Light Cues

In order to determine the effects on discrimination of the animal's experience with the individual solutions in the successive condition, all six monkeys were returned to the simultaneous availability. The three animals (M-43, M-44, and M-45) who had only lever appropriate cues, retained this condition by having a white light on above each lever indicating both were active. Lever-solution

Self-Administration of Cocaine and Saline in an Alternating Two Lever Presentation with Light Cues

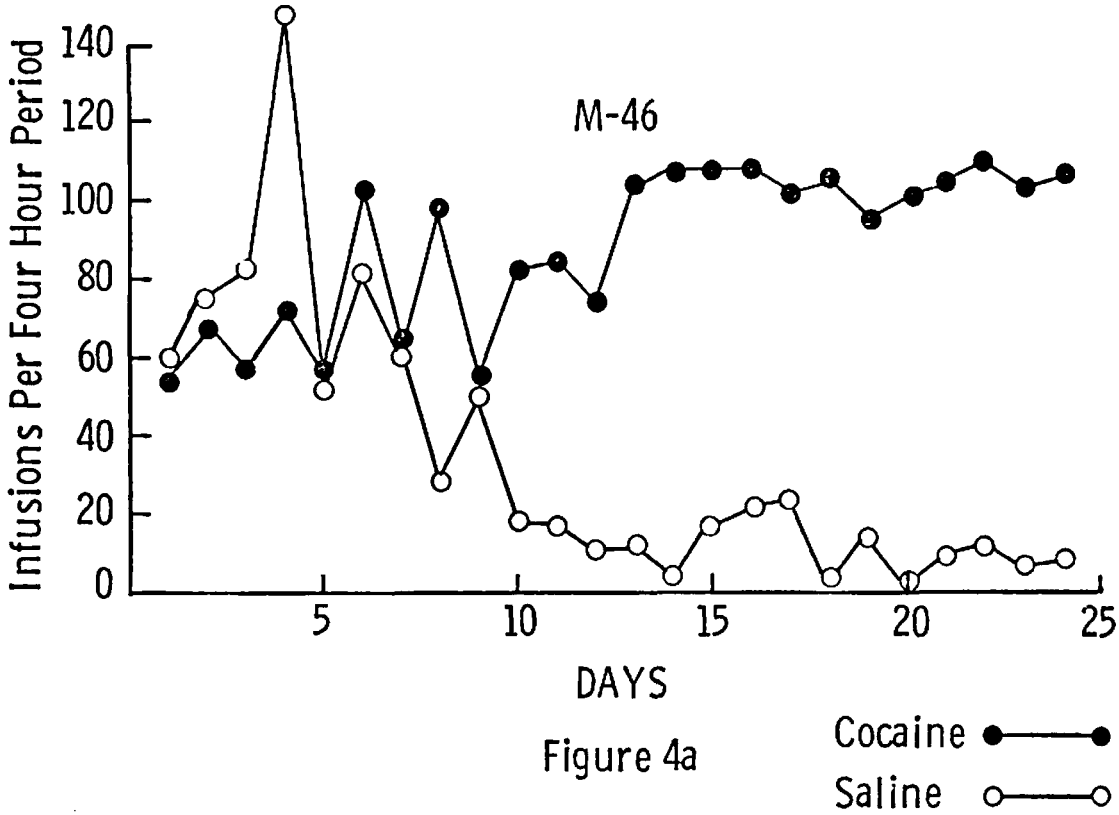


Figure 4a

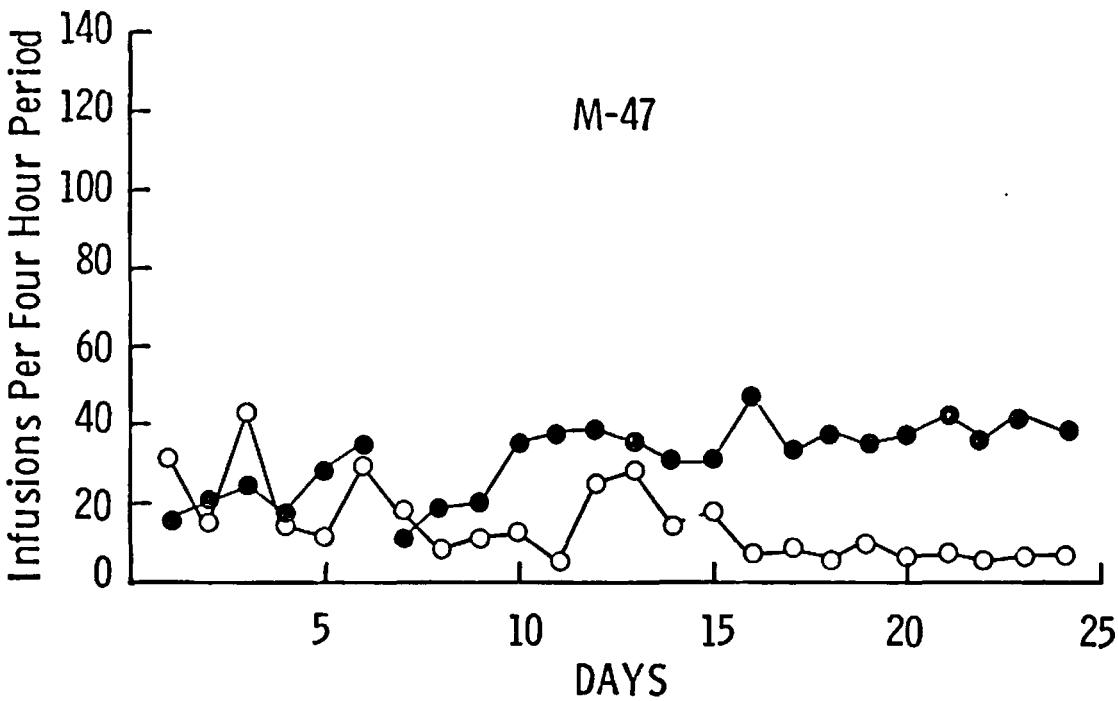


Figure 4b

Self-Administration of Cocaine and Saline in an Alternating Two Lever Presentation with Light Cues

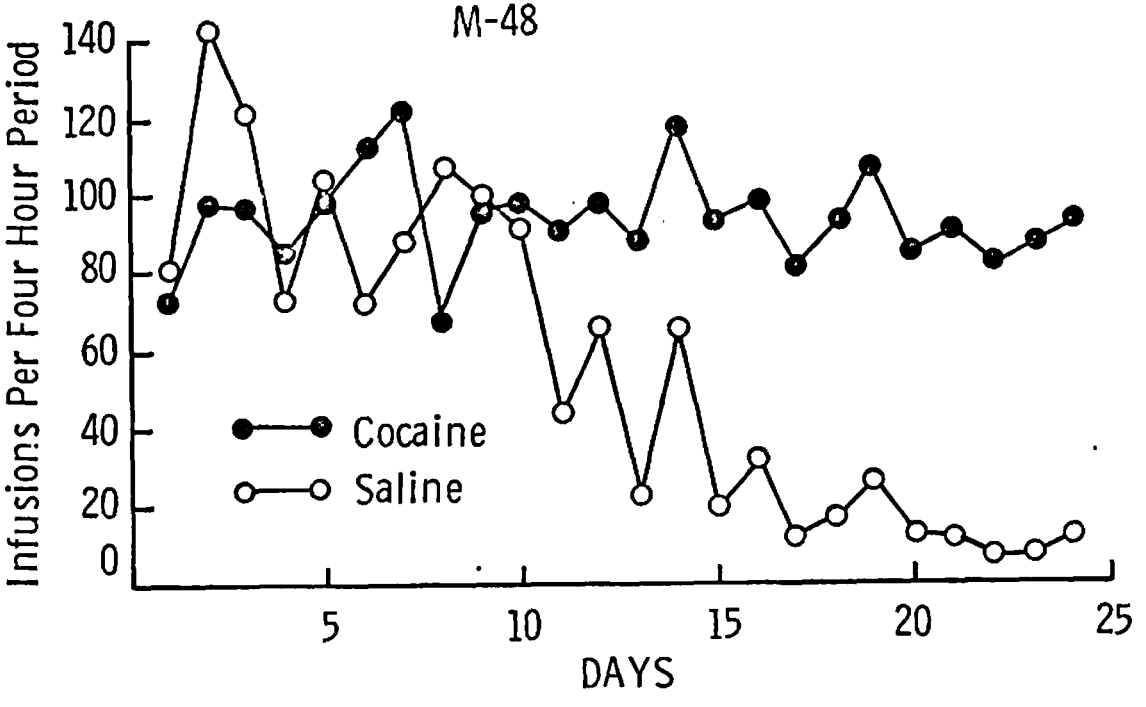


Figure 4c

positions were reversed each day to discourage position preference. Monkeys M-43 and M-45 failed to develop a discrimination during this simultaneous presentation. During the last 10 days of this condition, M-43 self-administered a mean of 88 infusions/day of cocaine and 100 infusions/day of saline while M-45 took 101 infusions/day of cocaine and 101 infusions/day of saline. Monkey M-44 who had developed and maintained a discrimination and choice during the successive presentation lost it after transfer to the simultaneous condition. Figure 5b shows that M-44's performance was slightly disrupted upon transfer to the simultaneous presentation, but he still maintained a weak discrimination. During the first 10 days following transfer, M-44 self-administered a mean of 56 infusions/day of cocaine and 36 infusions/day of saline. He lost the discrimination, however, after approximately 10 days. During the last 10 days of this condition, M-44 took a mean of 48 infusions/day of cocaine and 48 infusions/day of saline.

Transfer from Successive to Simultaneous Availability with Light Cues

The three animals who had previously had available drug associated light cues in the successive condition (M-46, M-47, and M-48) retained them when transferred directly to the simultaneous availability of the two solutions. This procedure allowed an assessment of the

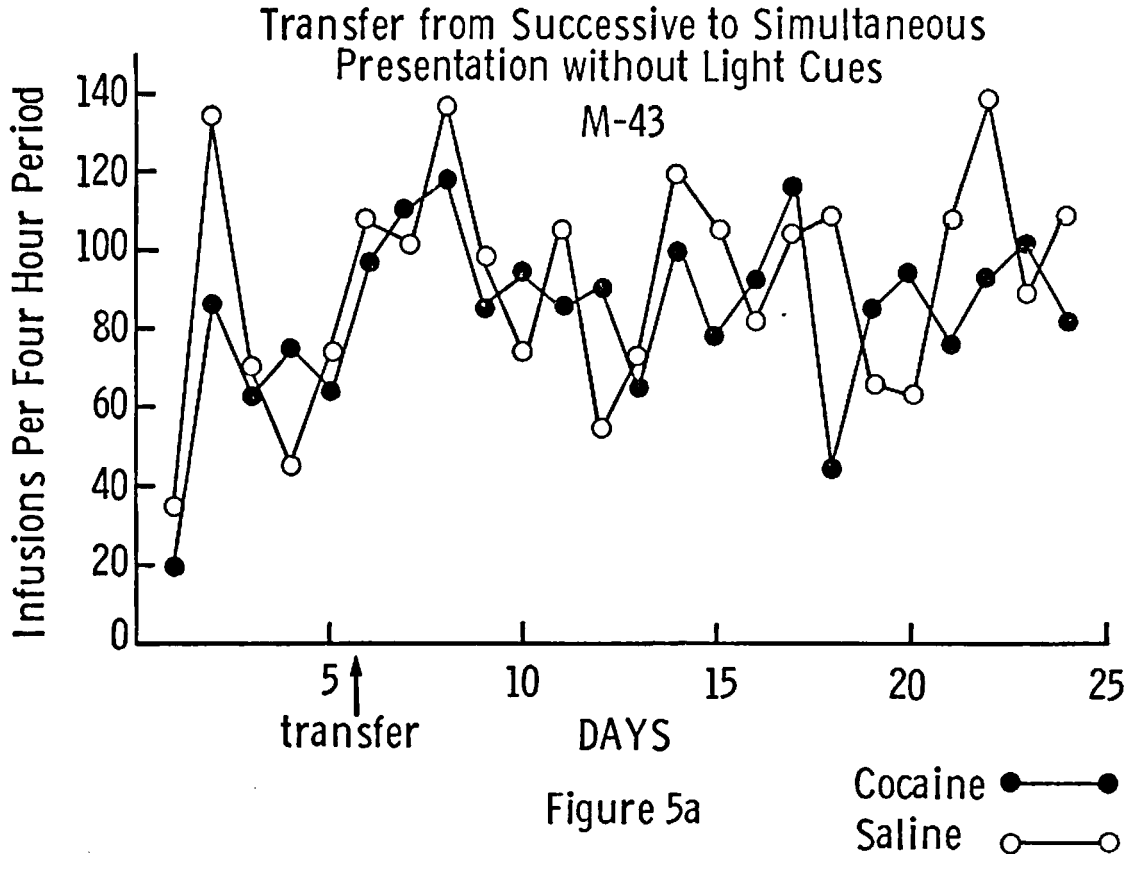


Figure 5a

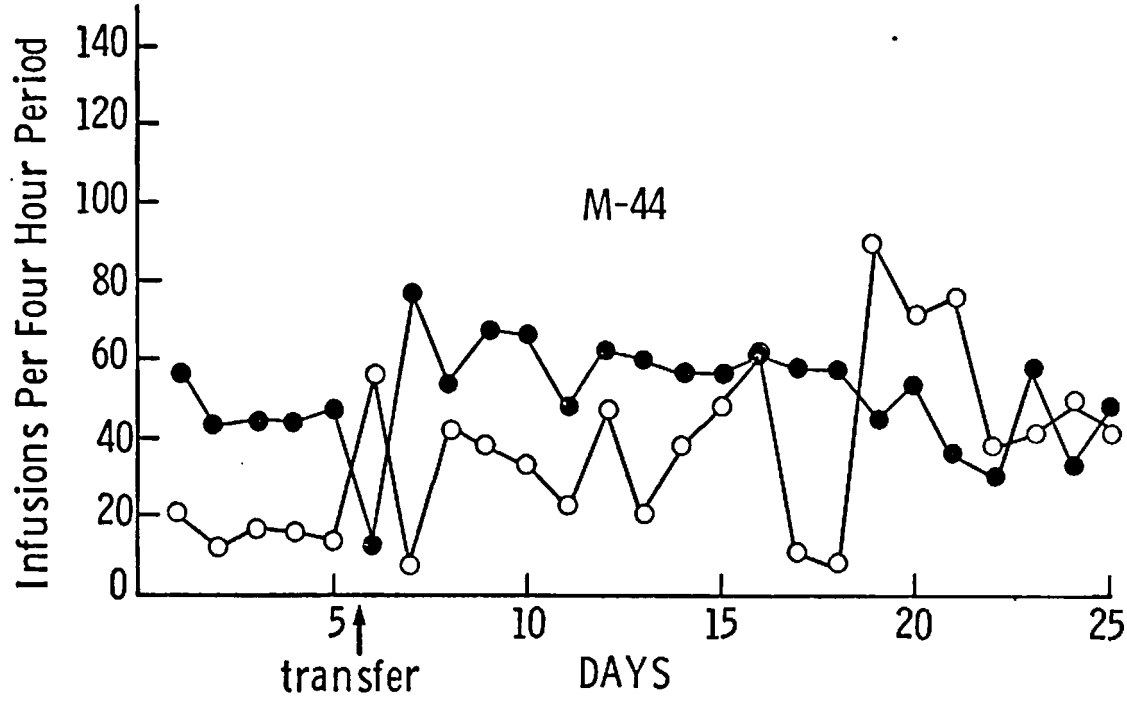


Figure 5b

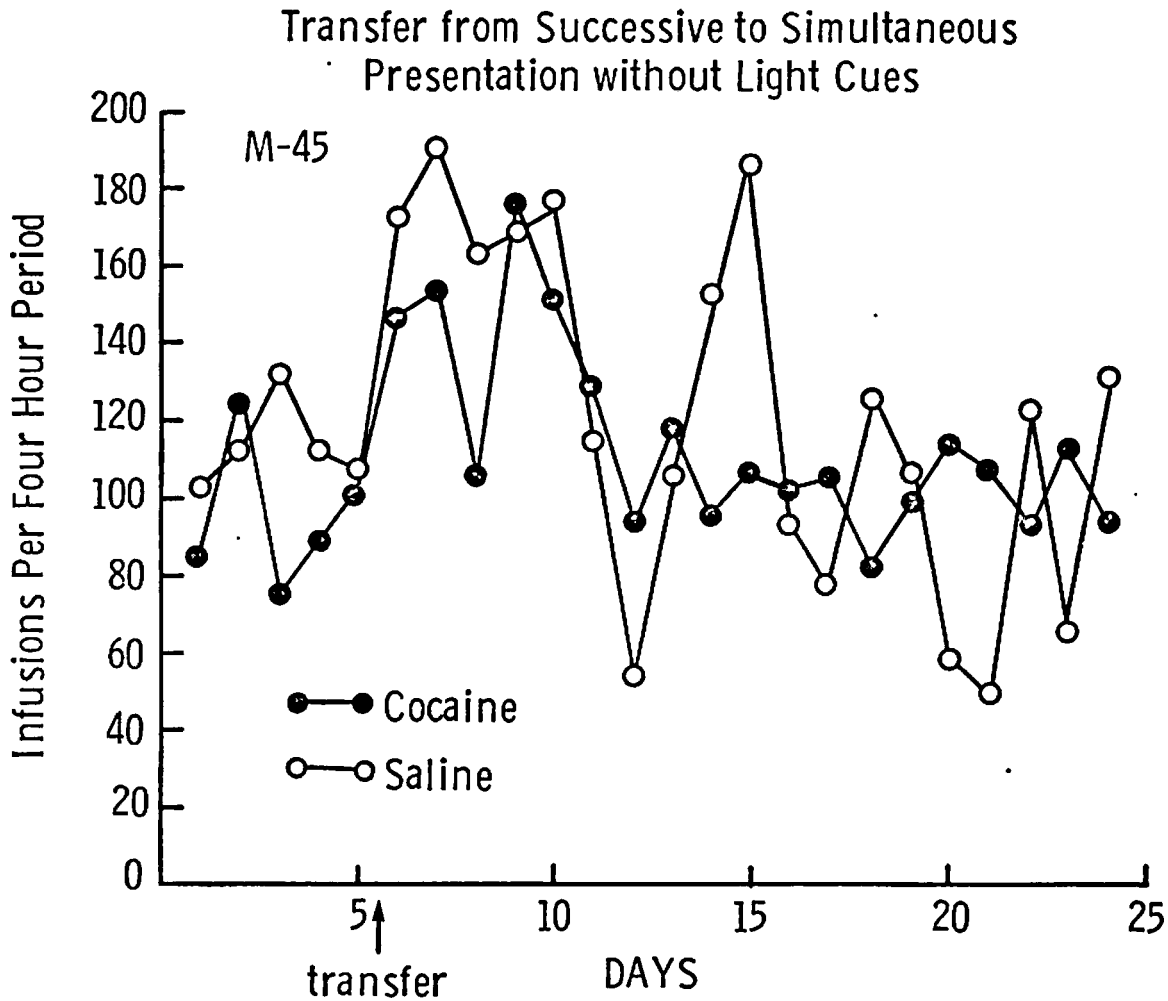

Transfer from Successive to Simultaneous
Presentation without Light Cues
M-45
Infusions Per Four Hour Period
200
180
160
140
120
100
80
60
40
20
0
Cocaine
Saline
5
10
15
20
25
transfer
DAYS

Figure 5c

stability of the light associated discrimination under simultaneous conditions. Data from the three animals is presented in Figure 6. It can be seen that all monkeys maintained and generally improved their discrimination. Figure 6a shows that M-46 experienced a slight disruption upon transfer to the simultaneous condition in the form of increased saline infusions on alternate days indicating preservation of a lever preference that diminished over time. During the last 10 days of this condition, M-46 self-administered a mean of 109 infusions/day of cocaine and 16 infusions/day of saline. Animals M-47 and M-48 improved their discrimination and tended to take less saline in the simultaneous condition. Animal M-47, during the final 10 days of this condition, took a mean of 54 infusions/day of cocaine and 4 infusions/day of saline while M-48 took 88 infusions/day of cocaine and 3 infusions/day of saline.

Transfer from Simultaneous with Light Cues to Simultaneous without Light Cues

In order to determine the importance of the light cues in maintaining the discrimination, the light cues were removed from those three animals (M-46, M-47, and M-48) who had developed a discrimination with light associated cues. Figure 7 illustrates the effect of this manipulation. Under this condition, all animals had available both active levers and solutions but no lights or lenses above the levers. It

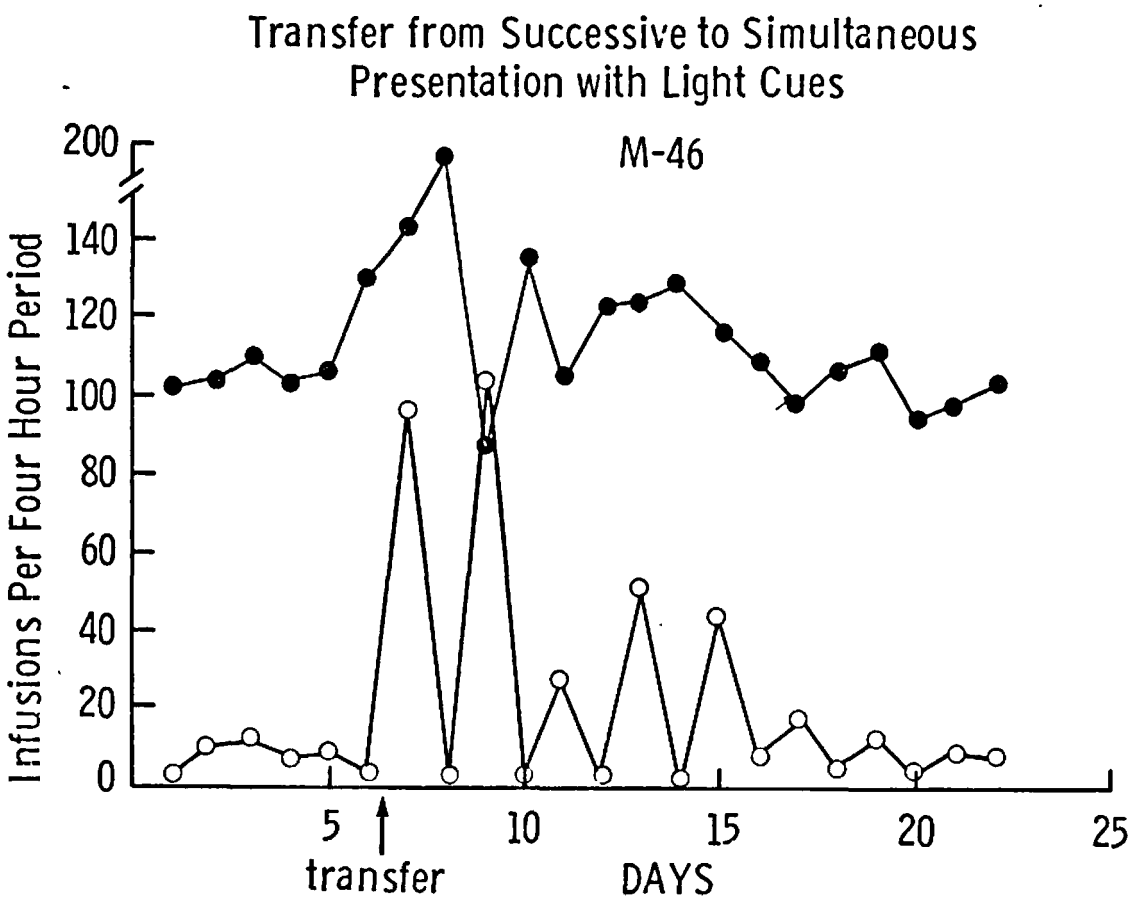


Figure 6a

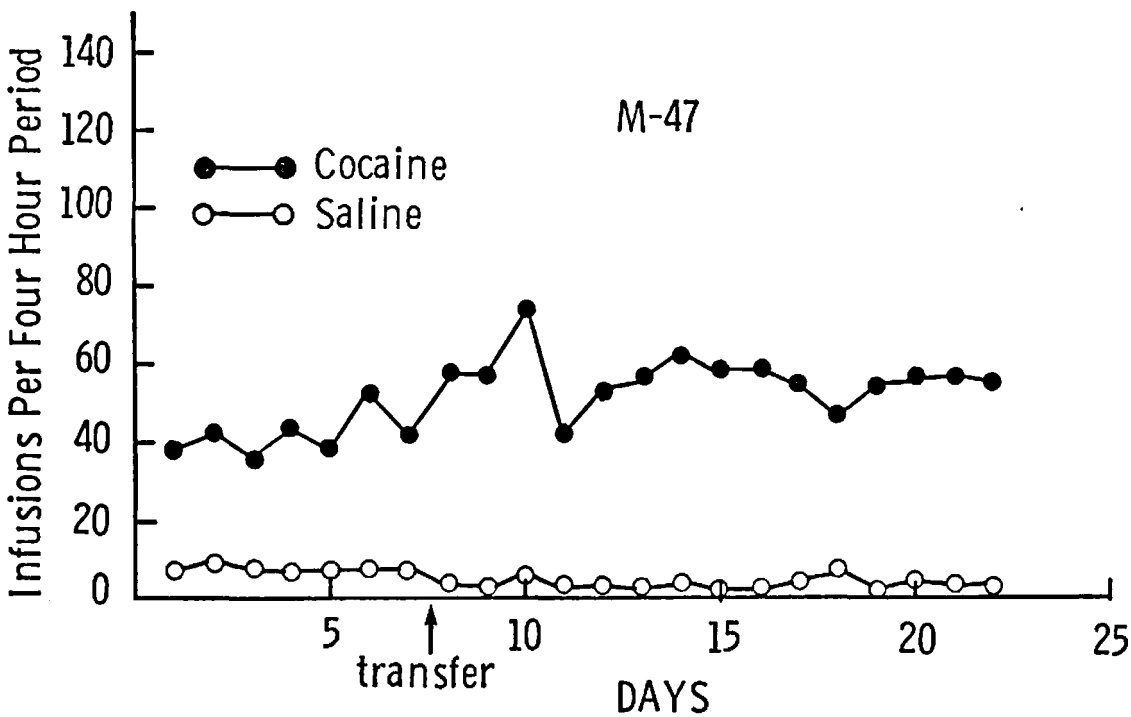


Figure 6b

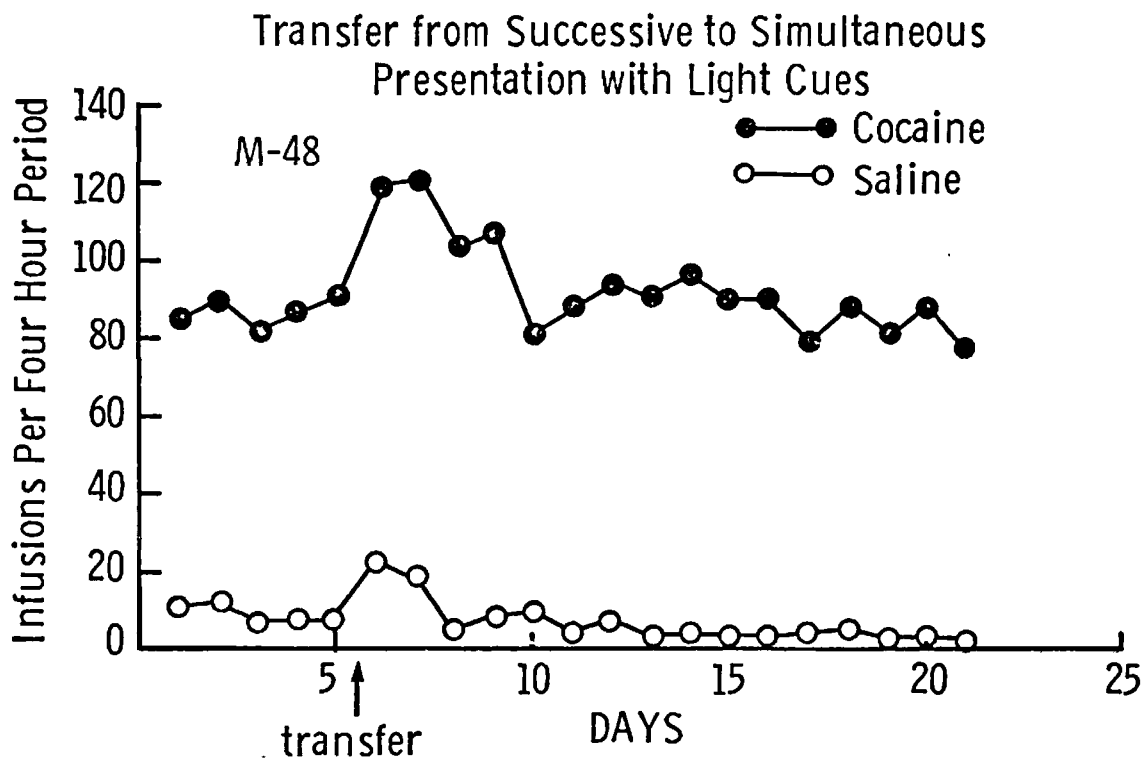

Transfer from Successive to Simultaneous
Presentation with Light Cues
M-48
Cocaine
Saline
Infusions Per Four Hour Period
140
120
100
80
60
40
20
0
5
10
15
20
25
transfer
DAYS

Figure 6c

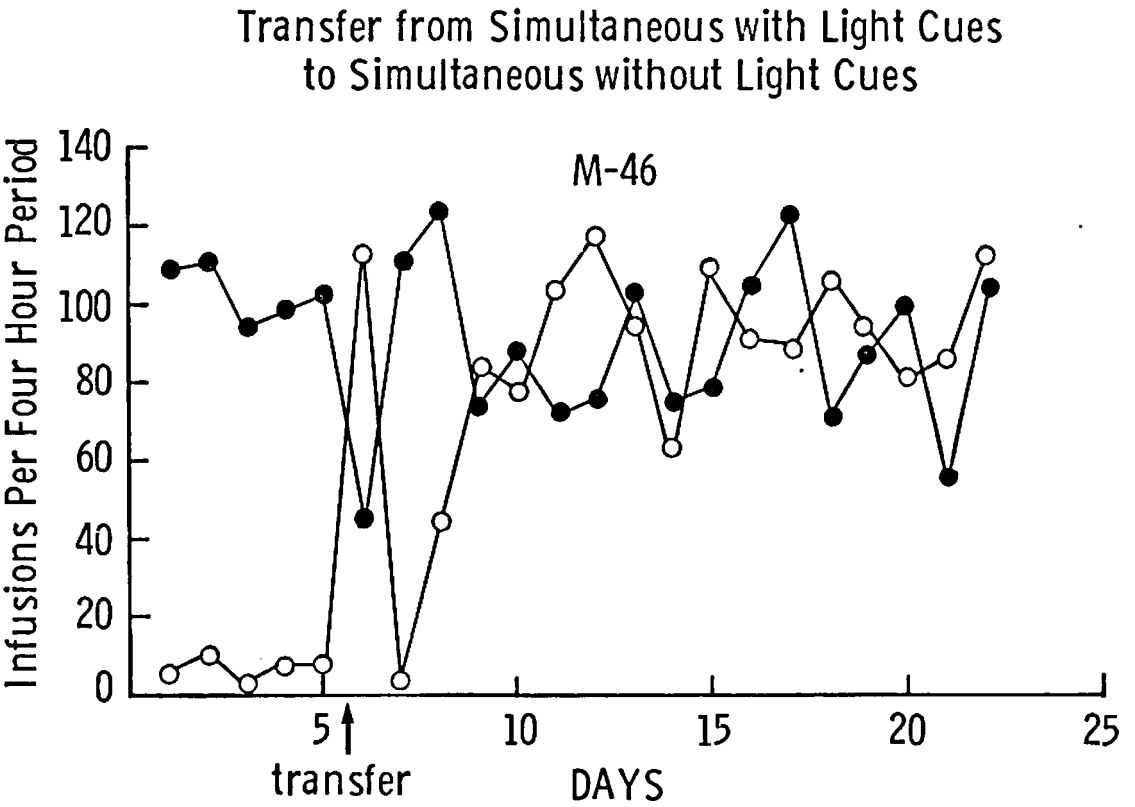


Figure 7a

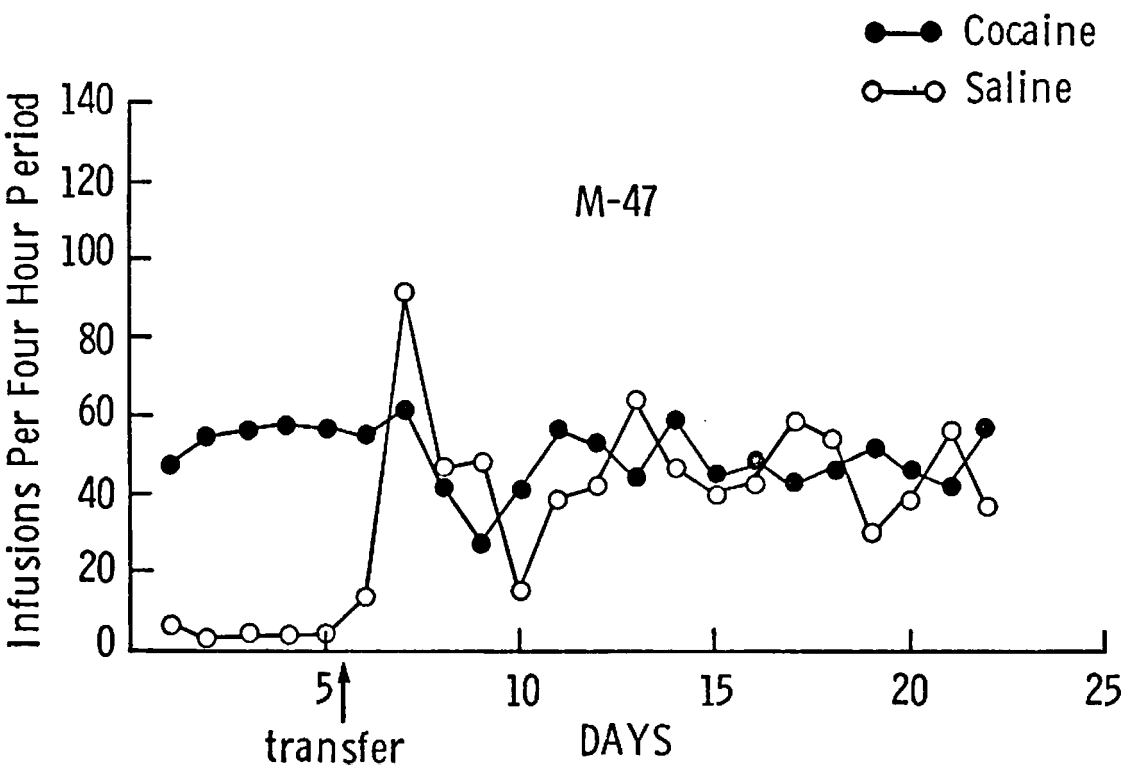


Figure 7b

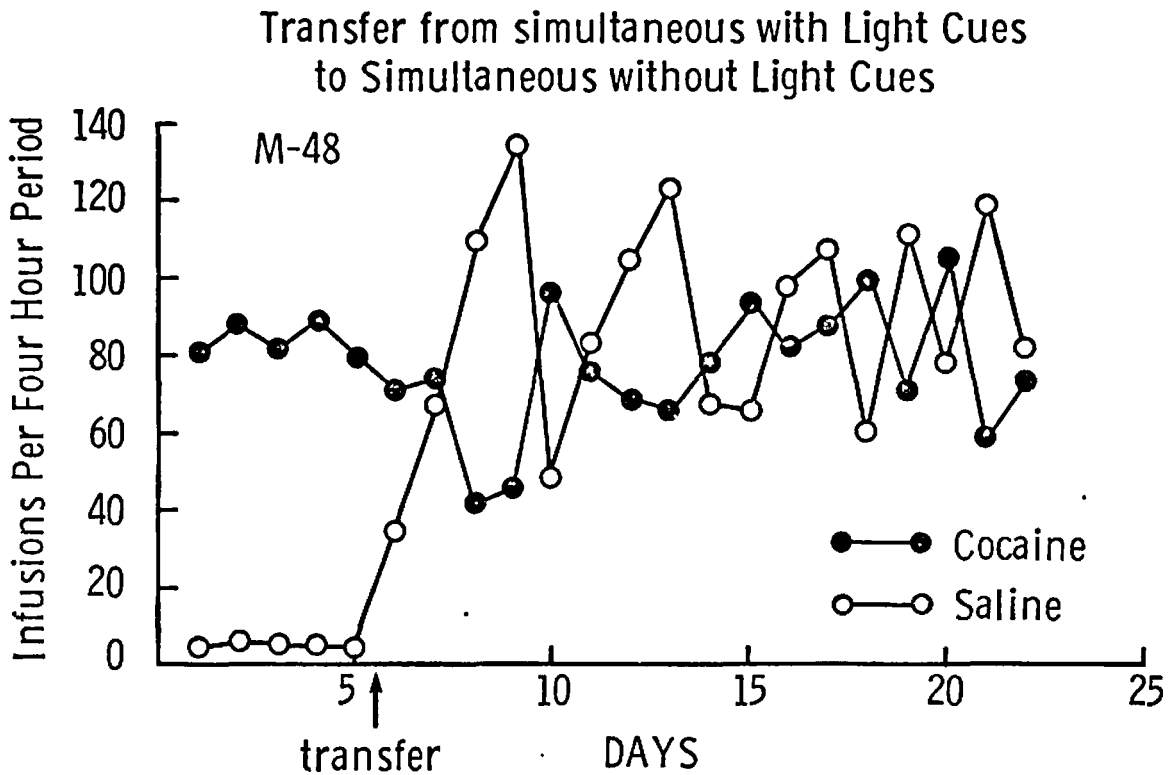

Transfer from simultaneous with Light Cues
to Simultaneous without Light Cues
M-48
Infusions Per Four Hour Period
140
120
100
80
60
40
20
0
5
10
15
20
25
transfer
DAYS
Cocaine
Saline

Figure 7c

can be seen that all animals lost their discrimination upon transfer to this condition and failed to discriminate during the 17 days of continued exposure to this condition. The animals continued to self-administer near average amounts of cocaine, but the saline intake rose to comparable levels. During the last 10 days of self-administration without light cues, M-46 self-administered a mean of 91 infusions/day of cocaine and 94 infusions/day of saline. During the same period of time, monkey M-47 took an average of 48 infusions/day of cocaine and 47 infusions/day of saline while M-48 self-administered a mean of 82 infusions/day of cocaine and 92 infusions/day of saline.

Effects of Cocaine Dosage Increase in a Simultaneous Presentation without Light Cues

Two (M-43 and M-45) of the three monkeys who had been on a simultaneous presentation without secondary light cues and had not developed a discrimination or expressed a choice were continued in this condition except that the unit dose of cocaine was increased from 200 μg./kg./infusion to 400 μg./kg./infusion. This was undertaken to determine if a greater cocaine infusion dosage would aid in the development of a discrimination. Animal M-44 was dropped from this investigation because of catheter complications.

Figure 8 presents the data from this procedure. It can be seen that for both monkeys the dosage increase did not aid in the development of discrimination. It can be

Effects of Cocaine Dosage Increase in
Simultaneous Presentation without Light Cues

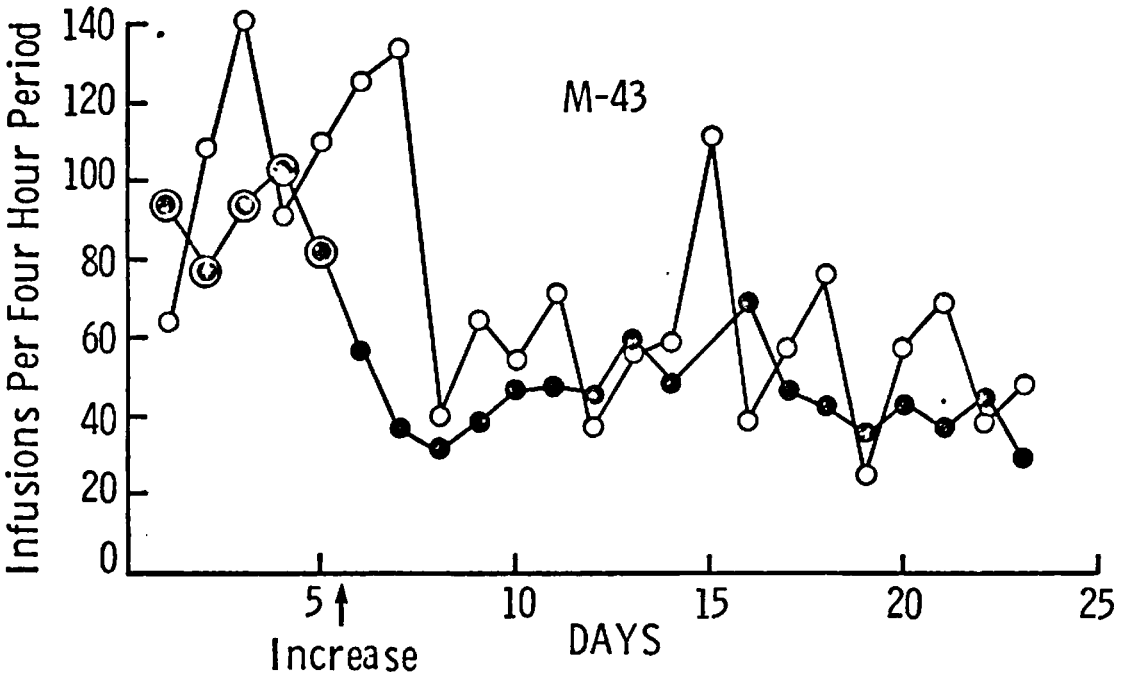
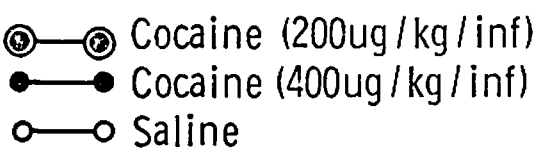


Figure 8a



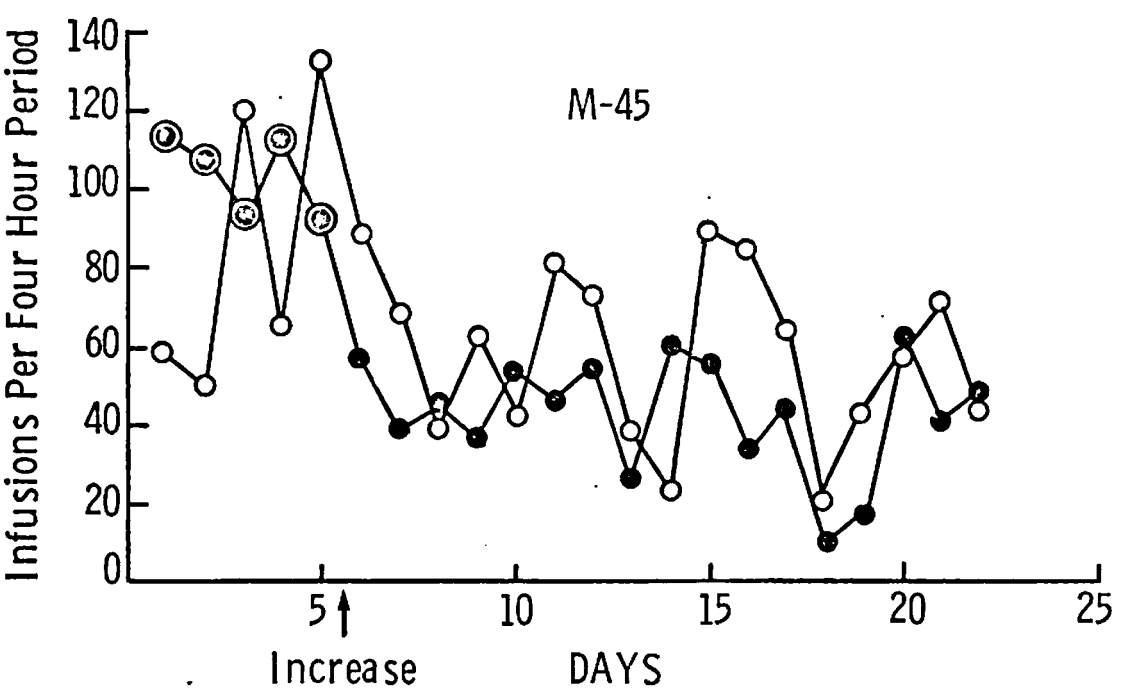


Figure 8b

observed from these figures, however, that the dosage increase resulted in a reduction of total infusions for both cocaine and saline. After 18 days in this condition, no discrimination or choice was apparent. Animal M-43 who had self-administered a mean of 88 infusions/day of cocaine and 100 infusions/day of saline before the dosage increase dropped to a mean of 45 infusions/day of cocaine and 58 infusions/day of saline during the last 10 days of the increased dose condition. This is approximately a 50% reduction in infusion volume and is characteristic of dose/response relationships common to self-administration investigations. This result is mirrored by the other animal in this condition (M-45). He dropped from a mean of 101 infusions/day of cocaine and 101 infusions/day of saline before the dosage increase to 40 infusions/day of cocaine and 54 infusions/day of saline after the dosage increase.

Simultaneous Self-Administration with Intermittent Light Cues

Three monkeys (M-46, M-47, and M-43) were trained under conditions of a simultaneous presentation of both solutions with intermittent light cues. In this condition, both solutions were available at all times during the four hour access period, but the location of the positions reversed every 15 minutes. The location of the cocaine lever was indicated by the presence of a white light over the

appropriate lever. No light was on over the saline lever. This procedure was an attempt to sensitize the animal to the discriminable properties of the drug by slowly reducing the duration of the light-on interval. Initially, the light was on at all times and reversed sides every 15 minutes as the drug location changed. After the monkeys learned the schedule and reliably self-administered cocaine and not saline, the duration of the light-on period was set at 4 minutes and the light-off period at 1 minute. Every 15 minute reversal in the solution location also resulted in the light coming on over the cocaine lever to indicate its new location. Over a period of 6 weeks, the light-on period was gradually decreased and the light-off period correspondingly increased until the discrimination began to break down.

Figure 9 illustrates the results of this procedure. It can be seen that all three animals maintained a discrimination until the light-on interval was reduced to 30 seconds in every 5 minutes in the case of M-46 (Figure 9a) and 1 minute in 5 for the other two monkeys. Disruption was in the form of increased saline intake. At this point, all animals were returned to a light-on interval that reinstated the discrimination. As the light-on interval was again reduced after stabilization, disruption again occurred. During the last 5 days of this condition, cocaine and saline self-administration were approximately equal.

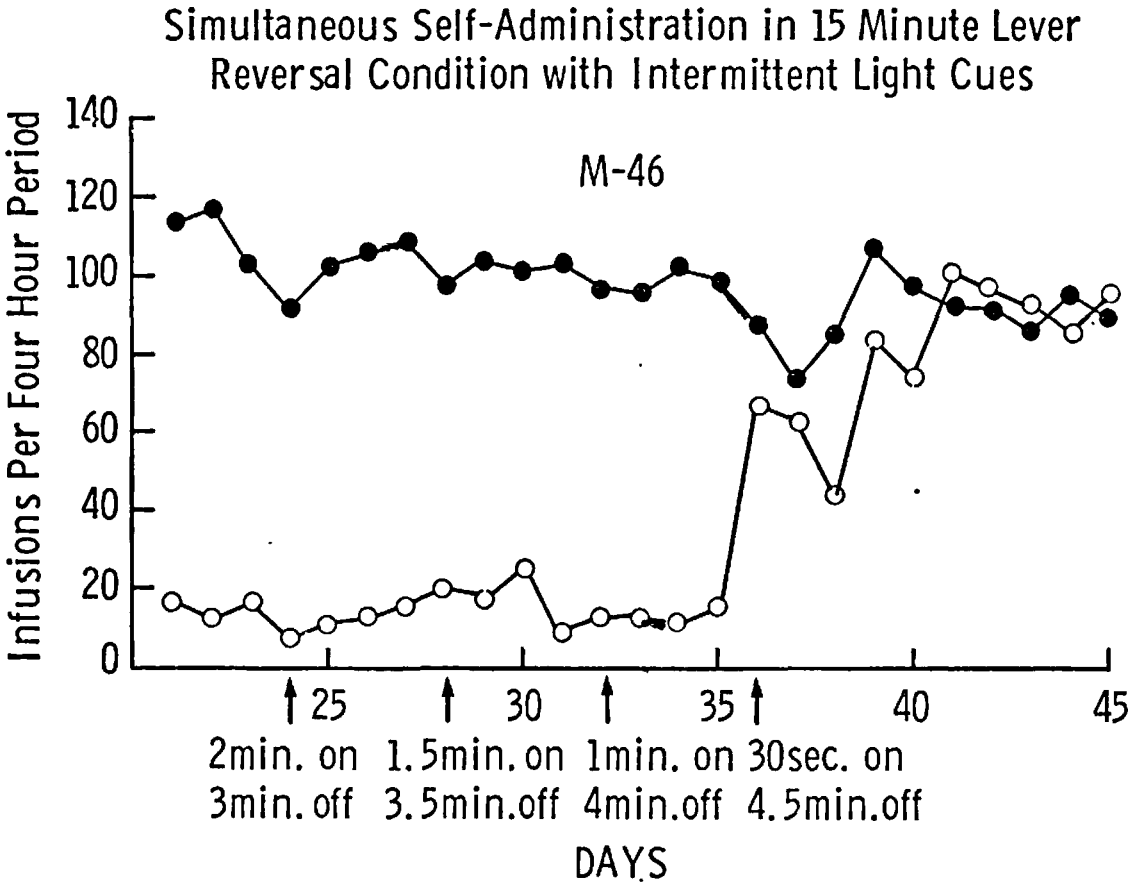


Figure 9a

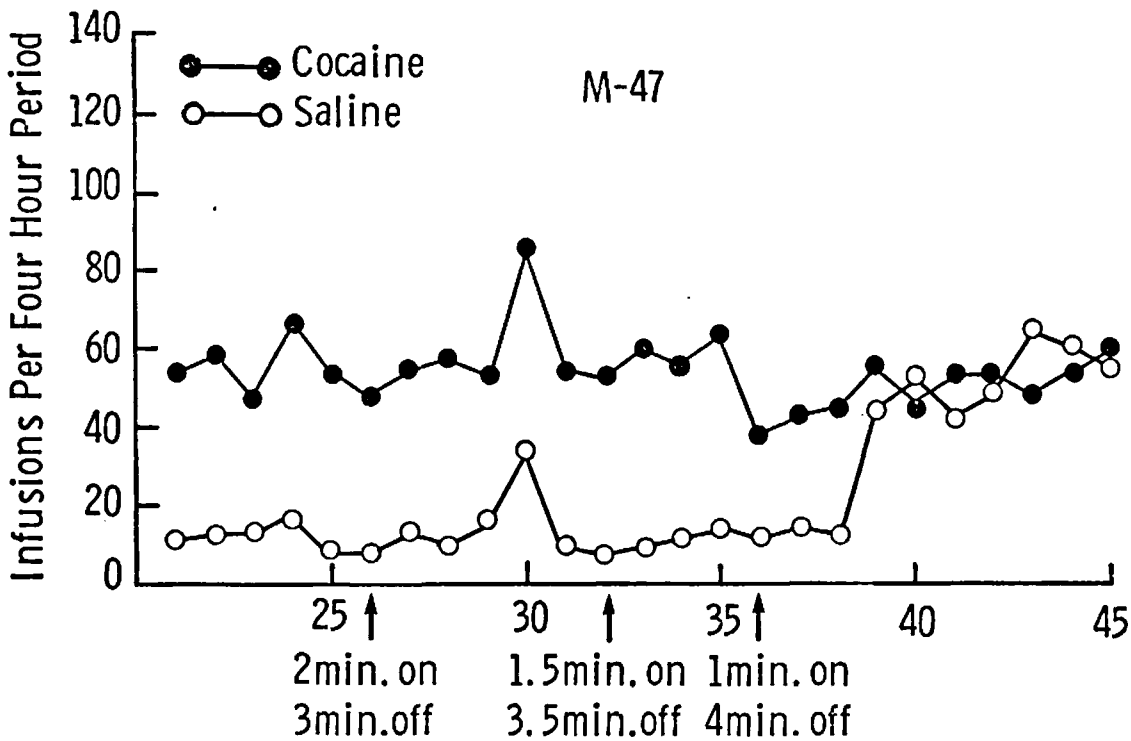


Figure 9b

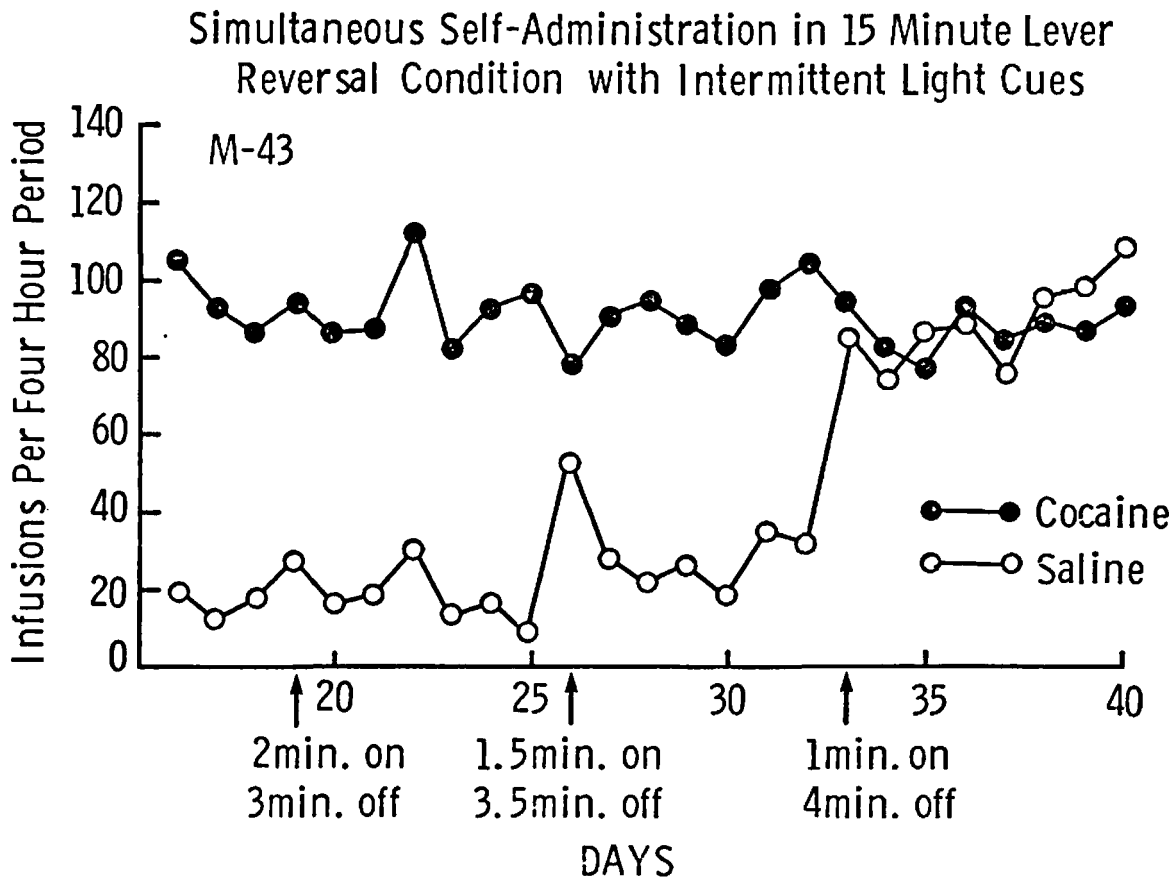

Simultaneous Self-Administration in 15 Minute Lever Reversal Condition with Intermittent Light Cues
M-43
Infusions Per Four Hour Period
140
120
100
80
60
40
20
0
Cocaine
Saline
20
25
30
35
40
2min. on
3min. off
1.5min. on
3.5min. off
1min. on
4min. off
DAYS

Figure 9c

During this period, M-46 self-administered a mean of 92 infusions/day of cocaine and 95 infusions/day of saline. During the same period of time, M-47 took a mean of 54 infusions/day of cocaine and 54 infusions/day of saline while M-43 self-administered a mean of 89 infusions/day of cocaine and 93 infusions/day of saline.

Simultaneous Self-Administration without Light Cues After Prolonged Experience and Sensitization.

In order to determine if the preceeding procedure and the prolonged experience with the two solutions during the investigation had increased the animal's ability to discriminate between the solutions, the same three monkeys (M-43, M-46, and M-47) were returned to the initial schedules of a simultaneous availability of cocaine and saline without secondary light cues.

Figure 10 presents the results of this condition. It can be seen from the figures that after three weeks experience with this condition, none of the animals discriminated or chose one solution over the other. Using the last 10 days as an index, M-47 self-administered a mean of 71 infusions/day of cocaine and 58 infusions/day of saline. Even though the cocaine intake was higher on the average than the saline for this animal, an examination of Figure 10a shows that no clear discrimination was present. Monkey M-43 self-administered a mean of 84 infusions/day of cocaine and 78 infusions/day of saline while M-46 took 127 infusions/day

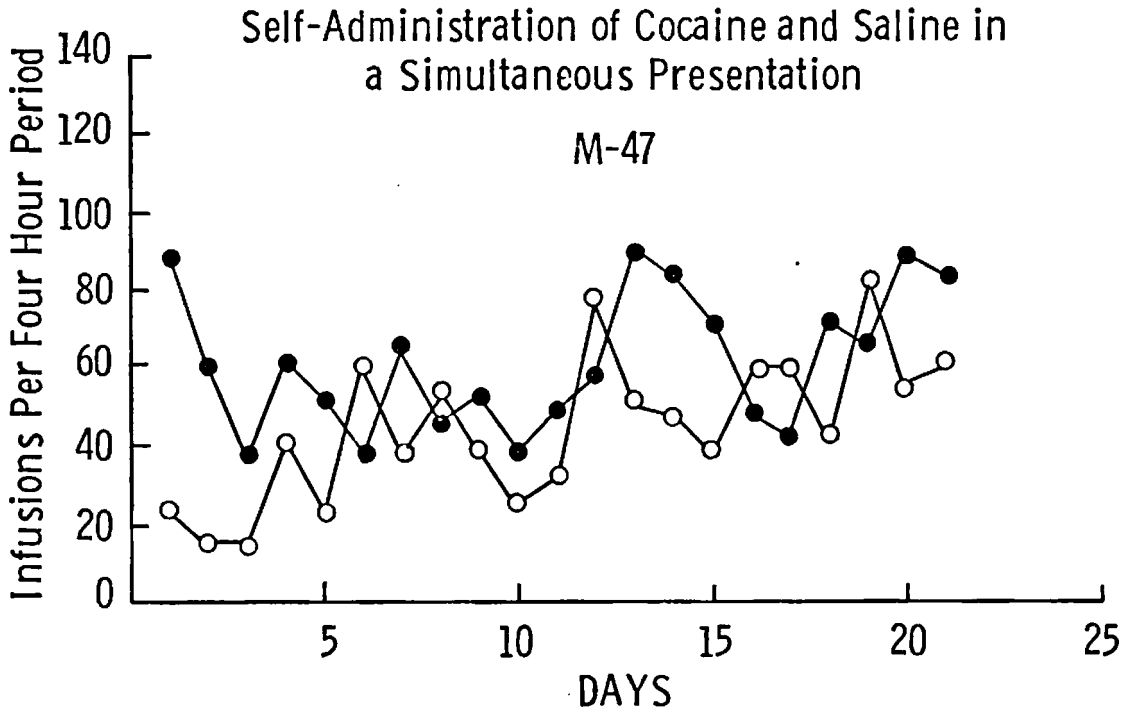


Figure 10a

Cocaine
Saline

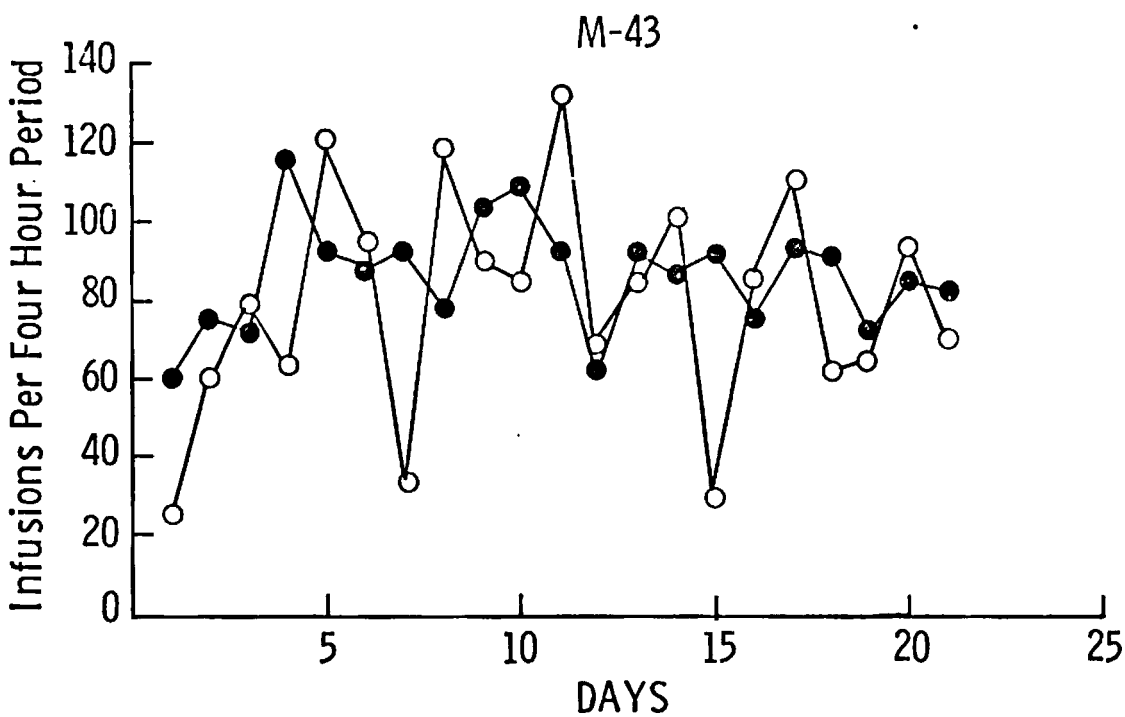


Figure 10b

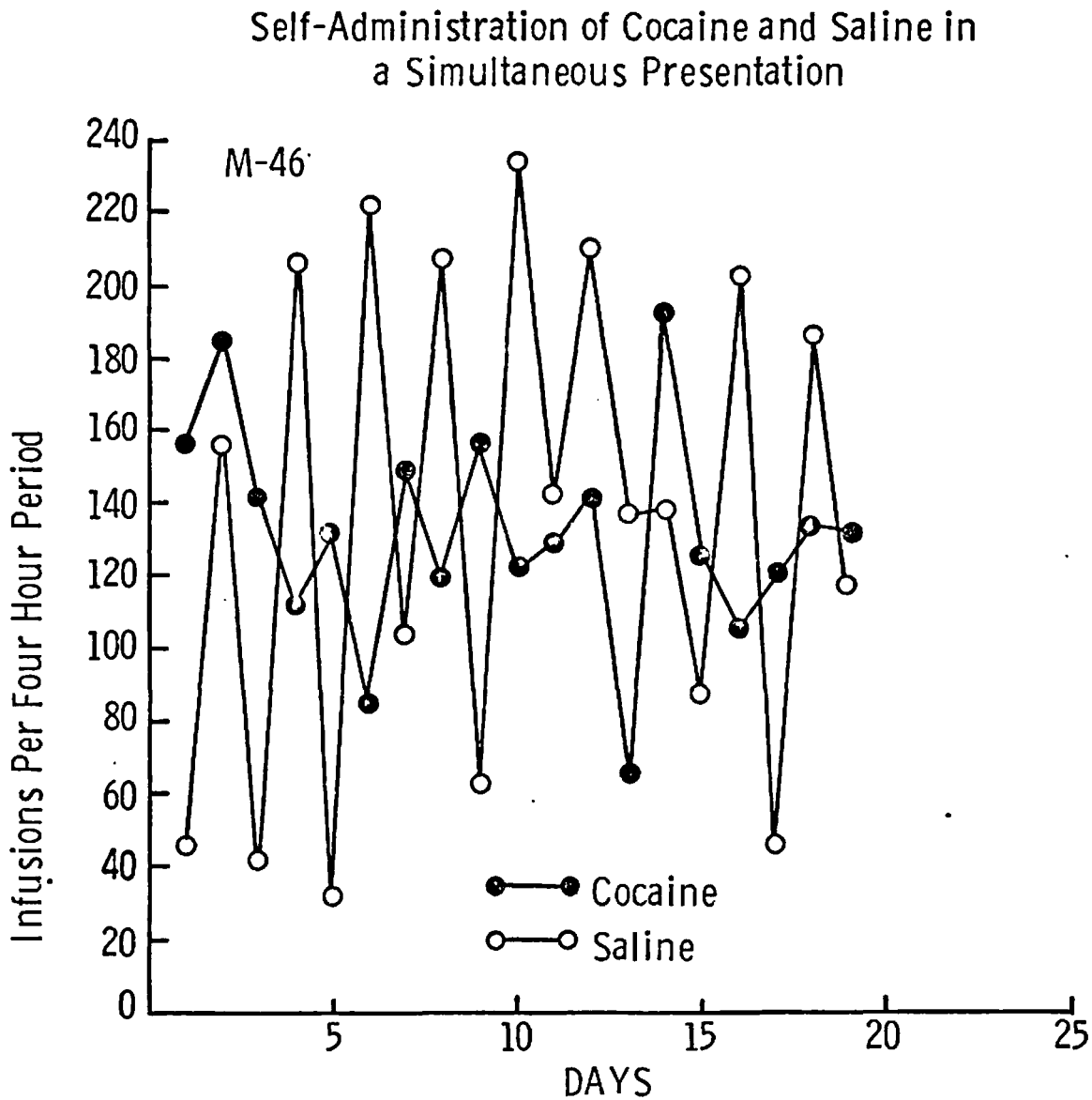

Self-Administration of Cocaine and Saline in
a Simultaneous Presentation
M-46
Infusions Per Four Hour Period
240
220
200
180
160
140
120
100
80
60
40
20
0
5
10
15
20
25
DAYS
Cocaine
Saline

Figure 10c

of cocaine and 150 infusions/day of saline. Figure 10c shows that M-46 developed a strong position habit and consequently self-administered large amounts of saline on alternate days.

Response Patterning

The response patterning apparent by examining cumulative records for the different conditions in this investigation indicates a typical cocaine pattern response only under those conditions where a strong discrimination was present. Under those conditions where saline intake was minimal and cocaine intake was high and stable, the cumulative records reflected a spaced cocaine self-administration pattern characteristic of cocaine self-administration in the typical single lever self-administration preparation. Cumulative records under other circumstances where no discrimination was evident and the animal consequently infused both solutions were not characterized by any discernable pattern. No instances were noted of any superstitious or response chaining behavior. On occasion, some monkeys resorted to pressing both levers simultaneously for a few infusions, but this did not occur frequently enough to represent any type of strategy on the part of the animal.

CHAPTER V

DISCUSSION

The primary objectives of this investigation were to determine the feasibility of a choice drug self-administration procedure for the rhesus monkey by assessing the degree to which it is able to discriminate between a drug and a non-drug solution and the extent to which it chooses one solution at the exclusion of the other. To this extent, this investigation indicates that rhesus monkeys can and will discriminate between a reinforcing and a non-reinforcing solution when both are available simultaneously. The extent of discrimination and the conditions under which it is most likely to occur, however, must be qualified.

The pilot work for this study and the initial replication of these results in the present investigation indicated that rhesus monkeys when given the opportunity to self-administer cocaine and saline simultaneously will self-administer both solutions in approximately equal amounts. The amount of cocaine infused in this preparation conformed to typical amounts of cocaine that is self-administered in a single solution self-administration procedure (Woods and Schuster, 1968). This clearly indicates that the animals were being reinforced for their lever pressing behavior

even though they were simultaneously infusing large amounts of non-reinforcing solution. They were therefore responding to their constantly changing drug state and not to the consequences of each individual bar press. Since the monkeys were not discriminating one solution from the other, either they could not or would not make the discrimination. In the initial condition, the only discriminative cues available to the monkey were the introceptive stimulus properties of cocaine or the lack of reinforcement from the saline infusion. This was probably confounded by the infusion itself which in this case functioned as an inappropriate secondary reinforcer or cue. Additionally, since the monkeys were being reinforced for their behavior by the cocaine intake and since the drug reinforced the animal across time and across infusions, it is possible that this continuous reinforcement masked the discriminative effect of the individual infusions. On the other hand, since the monkey was being reinforced for his behavior and could self-administer as much cocaine as he wanted, it was possible that since no particular incentive was present to make a choice, he was not motivated to do so. The procedural variations undertaken consequent to these findings were done so to examine these possibilities.

By comparing performance under successive and simultaneous availability, it could be determined if separate experience with each solution would aid in the development of a discrimination. Some investigators refer to this type

of procedure as sampling trials (Johanson, 1971). This procedure should have presumably eliminated some of the confounding involved if the persistence of cocaine in the animal's system was physiologically reinforcing all behaviors. This allowed the animal to experience the consequences of multiple bar-presses on each lever and the result of multiple infusions from the same solution.

The results of this manipulation were mixed. Although two monkeys tested under these conditions failed to develop a discrimination, one did. Besides suggesting that individual differences is a factor not to be ignored in these types of investigations, the results for this one monkey indicates that cocaine is adequately discriminable from saline in a successive presentation when the animal has as his only discriminable cue the stimulus or reinforcing properties of the drug itself. When this animal was transferred directly back to the simultaneous presentation, his discrimination, although maintained for a few days, eventually waned and was then lost. Since only one animal developed a discrimination under these conditions and lost it under the simultaneous presentation, it is probable that this technique allows the animal a better opportunity to make the discrimination by making the effects of the two solutions more discreet. These data, however, clearly indicate a monkey will choose a reinforcing solution over a non-reinforcing solution if the experimental conditions

are conducive to such a choice. Although not attempted in this investigation, it is possible that an increase in the successive intervals would encourage discrimination. This procedure, however, would move the task of the animal from pure choice, which is the focus of this investigation, to a multiple sampling technique. The data from this single subject supports the findings of other investigators (Johanson, 1971; Balster, Johanson, and Schuster, 1972). These two studies utilized sampling trials and also found that rhesus monkeys would choose cocaine over saline under these conditions. However, these two studies provided the animal with secondary discriminative cues in the form of different colored lights associated with the two solutions. The monkeys involved in the successive condition in the present investigation had the drug effect as the only cue indicating that this cue alone is sufficient for discrimination to develop and choice behavior to emerge under these conditions.

To determine if choice behavior would be more likely to develop if the experimental conditions presented to the animal were more perceptually distinct, a comparison was made of discrimination with and without secondary light cues under both simultaneous and successive availability. The results of this manipulation were very consistent and clear. All of the monkeys who had light cues available consistently and reliably chose cocaine over saline. Not

only did the animals make the choice under the successive condition, but they also maintained their discrimination when transferred back to the simultaneous condition. In fact, the discrimination was clearer and more stable in the simultaneous condition. These data clearly indicate that rhesus monkeys can and will respond positively to choice self-administration if the environmental conditions presented to the subject make his task perceptually clear. The importance of these secondary cues for this procedure and the reliance of the animal on them for making a discrimination is illustrated by the removal of these secondary discriminative cues. After removal, all apparent discrimination was lost, and no choice behavior re-developed without these additional cues. It is clear, then, that although rhesus monkeys can discriminate cocaine from saline without additional cues (at least to some extent), a strong and stable choice can be elicited if secondary cues are available to be used by the animal. Moreover, these animals were heavily if not completely dependent upon these cues to maintain the discrimination.

The effect of cocaine dosage on discrimination was also evaluated. By doubling the unit dose from 200 μg./kg./infusion to 400 μg./kg./infusion and observing this effect on discrimination and infusion rate, an analysis could be made of whether the animal has a tendency to discretely discriminate each infusion or whether he is

responding more to the consequences of multiple infusions in his efforts to maintain his drugged state. The results of this manipulation are unambiguous. The dosage increase did not in any discernable manner aid in discrimination but rather resulted in approximately a 50% drop in the number of both cocaine and saline infusions. Consequently, the animals maintained the same cocaine intake in spite of increased dosage. This result is consistent with those of Woods and Schuster (1968) who found that monkeys would self-administer approximately the same amount of cocaine over a wide range of infusion doses. This finding clearly indicates that these subjects maintain a controlled cocaine intake in a two lever as well as a single lever presentation. These animals, therefore, are maintaining a drugged state that each animal adjusts for himself. It follows from this that the contribution of each individual infusion is probably perceptually indiscriminable under these conditions, and the animal is probably responding to the consequences of several bar presses on the maintenance of his altered state.

Finally, an attempt to sensitize the animal to the discriminative properties of cocaine by providing intermittent light cues that would be faded out was unsuccessful. This manipulation was an attempt to transfer the animal from dependence on the visual cue to utilization of the introceptive cues of the drug by gradually reducing the

duration of the light cues. Apparently, the monkeys were completely dependent upon the light cues for the discrimination and they did not become more sensitive to the discriminable properties of cocaine. It is possible that the individual cocaine infusion is not discriminable when self-administered in this manner. Under these conditions, the animal would have to learn how to respond properly to the schedule in order to make a choice. It is possible that this is what was done by the single monkey who learned the discrimination without light cues.

It can be concluded from these results that rhesus monkeys can respond positively in a two solution choice self-administration preparation when the two solutions are available simultaneously if appropriate secondary cues are provided for the animal to use. Although discrimination and choice is possible solely from the drug effects alone, this discrimination is weak and easily susceptible to disruption. A schedule change, for instance, can abolish the weak discrimination. This technique, then, is a promising one for modified self-administration investigations. This procedure will allow a determination of drug preferences in rhesus monkeys and will therefore provide some insight into the relative reinforcing properties of various drugs. Most self-administrative studies allow the animal only one behavior--drug taking. If there are alternatives to drug self-administration or alternative drugs to infuse, the monkey may emit a wider and more meaningful range of behaviors.

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