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LA THÈSE A ÉTÉ  
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Termination of a Schedule-Complex Associated  
With Intravenous Injections of Naloxone and  
Cyclazocine in Morphine-Dependent and  
Post-Dependent Squirrel Monkeys

by Catherine A. Pink

Thesis presented to the Faculty of Social  
Sciences, School of Psychology, University  
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### Curriculum Studiorum

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### Abstract

The negative-reinforcing effects of dl-cyclazocine and naloxone were examined in morphine dependent and post-dependent squirrel monkeys. Five adult, male squirrel monkeys (Saimiri sciureus) were trained to emit 10 responses (FR 10) terminating a schedule-complex of light and masking noise associated with brief, intravenous injections of naloxone (.01 mg/kg/inj) and dl-cyclazocine (.003 mg/kg/inj). Animals had an experimental history of training to escape or avoid electric-shock presentation and intravenous drug injections. When the monkeys received a chronic intramuscular injection of morphine (10 mg/kg) one hour preceding daily sessions, responding to escape or avoid naloxone was well maintained. In two determinations, dl-cyclazocine injections were escaped or avoided but in a third, more injections were delivered. When morphine pretreatment was discontinued, post-dependent animals tolerated injections of naloxone or dl-cyclazocine. The negative-reinforcing capacity of these drugs with morphine-antagonist effects evidently depended upon whether or not monkeys were morphine dependent. It was suggested that both a reduced grade of physiological dependence and the small dose of dl-cyclazocine were responsible for the tolerance to dl-cyclazocine observed after protracted experimental manipulations.

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## INTRODUCTION

Opiate dependence continues to be a major problem throughout the world and has had an increasing impact on individual health and well-being as well as on society as a whole (Fink, Freedman, Resnick & Zaks, 1973; the World Health Organization, 1975). A drug is said to produce physiological dependence when an abstinence syndrome is observed upon withdrawal from the drug. Behavioural dependence, on the other hand, is a condition of compulsive drug-taking without an observable abstinence syndrome when the drug is removed. Both kinds of dependence are characterized by compulsive drug-seeking behaviour. In fact, dependence was first studied using the opiates (morphine) for which an abstinence syndrome as well as widespread non-medical self-administration in man had been commonly recognized. Research in areas as diverse as law enforcement, education and medicine has accelerated in an attempt to understand and alleviate this complex problem (Schuster & Balster, 1973). In the past 17 years, experimental psychologists have contributed to this work by developing techniques for the scientific study of the pharmacological and behavioural aspects of drug dependence. The general goals of behavioural pharmacology have been (a) to construct a laboratory model of dependence (including the underlying physiological and psychological mechanisms) and (b) to improve prediction of abuse potential of new

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x

drugs as substitutes are sought that have the potent analgesic effects of morphine without dependence-producing properties (Schuster & Balster, 1973; Goldberg, 1975; Kelleher & Goldberg, 1976).

Fundamental to the achievement of these goals has been the application of operant conditioning techniques developed by B.F. Skinner to the study of drug-behaviour interactions in animals. The operant model, in which behaviour is controlled by its consequences, can be applied to a vast range of behaviours (Kelleher & Goldberg, 1976) and has provided behavioural pharmacology with the methodology for objective measurement of the environmental and biological variables involved in drug-taking and drug-seeking behaviour (Pickens, 1977).

Also of importance for the study of the behavioural aspects of drug dependence, has been the development of techniques allowing experimental animals to self-administer drugs (Thompson & Schuster, 1969). Weeks (1961) first described intravenous self-administration in rats while Deneau, Yanagita and Seevers (1969) and Schuster and Thompson (1964) developed intravenous self-administration methods for rhesus monkeys. Using this procedure, experimental animals can control, by a behaviour such as lever pressing, the delivery of drugs from an infusion pump connected to an implanted, chronic-intravenous catheter.

The validity of infra-human primate research in drug dependence assumes the generalization of results to man. The World

Health Organization (WHO) has recognized primate research as the appropriate pre-clinical method of drug-dependence evaluation. This was based on the finding that many drugs commonly abused by man are also self-administered by laboratory animals (Schuster & Thompson, 1969; WHO, 1975). In addition to the ethical advantages of using animal subjects, such research allows greater experimental control while reducing reliance upon mentalistic constructs to explain drug-dependence (Schuster & Villarreal, 1968; Schuster & Thompson, 1969).

The extent to which drugs are self-administered is a measure of their reinforcing properties (Schuster & Thompson, 1969). Monkeys self-administer certain psychoactive drugs which are therefore described as being positively reinforcing or maintaining the behaviour leading to their delivery. Schuster and Thompson (1969) have reviewed in detail the classes of drugs that are self-administered by various species of experimental animals. They include: narcotic analgesic drugs, sedative-hypnotics, psychomotor-stimulant drugs and some minor tranquillizing agents.

Just as drugs can serve as positive reinforcers maintaining self-administration, they can also be aversive. Drugs function as aversive stimuli in two ways: (a) as a punisher, a drug infusion suppresses responding leading to its delivery; and (b) as a negative reinforcer, a drug maintains behaviour that either terminates the infusion (escape) or delays its presentation (avoidance).

Hoffmeister and Goldberg (1973) found that chlorpromazine (an anti-psychotic phenothiazine) was not self-administered by rhesus monkeys in experiments in which several drugs were cross-substituted for cocaine. They concluded that chlorpromazine had a punishing effect. In the same experiment, imipramine (a tricyclic anti-depressant) appeared to have no effect on behaviour and was therefore considered to be neither positively nor negatively reinforcing. In other research, Goldberg, Woods and Schuster (1971) found that morphine-dependent rhesus monkeys escaped or avoided injections of nalorphine (a mixed morphine agonist-antagonist) and naloxone (a potent morphine antagonist).

Much of the self-administration research has focused on the positive-reinforcing properties of psychoactive drugs while only recently have studies begun to assess the negative-reinforcing properties. Holz and Gill (1976) have reviewed the results of this recent area of study. They will be presented in detail in the final section of the Review of the Literature, (Chapter I).

The general purpose of research presented here was to continue investigation of the aversive properties of drugs using the self-administration procedure within the framework of the operant analysis of behaviour. dl-Cyclazocine was selected as the experimental drug to be studied in terms of its aversive properties. dl-Cyclazocine is a mixed morphine agonist-antagonist drug that has been used clinically in the treatment of heroin addicts (Martin, Fraser, Goro-detzky & Rosenberg, 1965; Fink et al., 1973) but has not been

thoroughly investigated in a pre-clinical setting. Results of two pieces of research suggested the work reported in this thesis. In the first, Hoffmeister and Wuttke (1973) found that cyclazocine (.01 to .0025 mg/kg/inj) generated and maintained escape/avoidance behaviour in drug-naive rhesus monkeys; that is, animals with no history of drug self-administration and not presently dependent on morphine. This was a unique finding since morphine antagonists or mixed agonist-antagonists are generally only aversive in morphine-dependent organisms (Woods, Downs & Carney, 1975; Kandel & Schuster, 1977). The second research of interest was by Tang and Morse (1976) who found that nalorphine (.01, .02 and .04 mg/kg/inj) maintained highly consistent escape/avoidance responding in morphine-dependent rhesus monkeys. Of key importance though was that such responding was not maintained in the same animals while they were in a post-dependent state. In other words, once morphine was withdrawn and the abstinence syndrome had diminished, animals no longer responded to escape or avoid injections of nalorphine. The two sets of results; that is, Hoffmeister and Wuttke (1973) and Tang and Morse (1976) appeared to be at odds in as much as cyclazocine and nalorphine are both mixed morphine agonist-antagonist drugs. Since cyclazocine had not been studied in morphine-dependent monkeys (Holz & Gill, 1976) or in post-dependent monkeys, the present research was designed (a) to replicate Hoffmeister and Wuttke's work (1973) with cyclazocine; (b) to explore the role of morphine dependence in the maintenance of cyclazocine escape/avoidance behaviour; and finally (c) to

compare these results with those of naloxone, a well known morphine antagonist.

In summary, the present research in behavioural pharmacology was designed to continue the investigation of the aversive properties of drugs; specifically to study the effects of morphine dependence and post-dependence on the aversive properties of dl-cyclazocine. As such, this work was situated within the larger framework of the operant analysis of drug-behaviour interactions and opiate dependence. The specific research questions will be presented at the conclusion of the Review of the Literature which follows in Chapter 1.

Chapter II describes the experimental procedure and methods of data acquisition. Chapter III contains the experimental results and the discussion and conclusion are found in Chapter IV.

## CHAPTER I

### REVIEW OF THE LITERATURE

Before reviewing the research concerned specifically with the aversive properties of drugs, a brief exposé of the behavioural pharmacology literature pertinent to the work presented here will be given. Such an exposé will not be in any way exhaustive but will attempt to give both the rationale for the experimental procedure as well as the necessary background against which results can be meaningfully interpreted. This information will be presented in several sections including: Operant Conditioning Techniques, the Determinants of Drug Action, Drug Self-Administration, The Behavioural Effects of Morphine and Morphine-Agonist and Antagonist Drugs, and the Aversive Properties of Drugs.

#### Operant Conditioning Techniques

The application of operant conditioning techniques developed by B.F. Skinner and his associates (Skinner, 1938; Ferster & Skinner, 1957) to studies of drug-behaviour interactions was established during the 1950's (e.g., Dews, 1955). At this time, the synthesis of psychoactive drugs was accelerating, beginning with the discovery of major tranquillizers; such as, chlorpromazine. While drug-screening research had been conducted since the 1920's the methodology was unsystematic and results fragmentary (Pickens, 1977). As



a result, several important papers called for the development of behavioural pharmacology as a basic medical science applying operant principles to the behavioural component of the drug-behaviour interaction (Dews, 1958; Sidman, 1959; Skinner, 1959).

Operant techniques provided a means of establishing and measuring a behavioural baseline sensitive to drug effects, against which the results of experimental manipulations could be compared (Sidman, 1960; Pickens, 1977). Typically, the behaviour measured was performed in a restricted experimental area and met the requirements of being (a) appropriate to the organism (e.g., key-pecking for pigeons and lever-pressing for rats and monkeys); (b) easily repeated by the organism; and (c) readily counted by automatic equipment (Kelleher & Morse, 1968). In addition to furnishing a method for measuring behaviour, operant techniques were valuable in that the principles of operant conditioning had been shown to be relevant and generalizable across species and behaviours (Kelleher & Morse, 1968; Kelleher & Goldberg, 1976).

The primary principle was that the frequency of occurrence of an operant or behaviour was controlled by its consequent event. This event was called a reinforcer when the behaviour it followed increased in frequency. Reinforcers could increase the frequency of behaviour leading to their delivery (as in positive reinforcement) as well as behaviour leading to their termination or postponement (as in negative reinforcement). Another event known as punishment controlled behaviour by suppressing the frequency of future

occurrence of the behaviour. Various events had been shown to act as reinforcers under suitable conditions. These included food and water presentation, the delivery of electric-shock and the delivery of drug injections. When drug injections were considered as consequent events (either as reinforcers or punishers) according to the operant model, their role in the maintenance of self-administration behaviour could be analysed functionally in the same manner as for other events that control behaviour (Kelleher & Goldberg, 1976; Spealman & Goldberg, 1978). It is within this operant framework, then, that the present research using drug injections has been designed.

While the consequent event itself is a key determinant of behaviour, the schedule governing its occurrence is at least as important (Kelleher & Morse, 1968). The rules stipulating the sequential and temporal relationship between a behaviour and its reinforcement are known as schedules of reinforcement (Kelleher & Goldberg, 1976). Each schedule engenders a characteristic pattern of responding (Kelleher & Morse, 1968) that must be taken into account when studying the reinforcing properties of drugs and their self-administration. The importance of schedules as well as other determinants of drug action for behaviour will be considered in the following section.

### The Determinants of Drug Action

Traditionally, drugs that affect behaviour have been classified as either stimulants or depressants and their inherent properties have been called upon to explain their effects. In recent years, however, such an account of the behavioural effect of drugs has not been supported by the research. In fact, preoccupation with the inherent properties of drugs may have encumbered understanding of drugs as reinforcers, (Kelleher & Morse, 1968; Kelleher & Goldberg, 1976; Spealman & Goldberg, 1978). The usual technique of holding environmental variables constant, masked the importance of such variables in the determination of drug action. Behavioural pharmacology has focused on environmental events and has found that under appropriate conditions, drugs formally classified as stimulants could increase or decrease responding while those regarded as depressants could also increase or decrease responding. The change in responding depended upon the ongoing rate and pattern of schedule-controlled behaviour (Kelleher & Morse, 1968).

Of all the environmental factors, the schedule-controlled rate and pattern of responding was found to be a primary determinant of drug action. As noted in the previous section, schedules were the rules establishing the temporal and sequential relationship between a behaviour and its reinforcement. They have been commonly classified according to whether the reinforcer follows a given number of responses (ratio schedules) or follows the first response

after a given period of time has elapsed (interval schedules) (Spealman & Goldberg, 1978). Under both regimes the response or time requirement could be fixed or variable. Dews (1955) was the first to show experimentally the differential effect of a drug, dependent on the schedule of reinforcement. Food-deprived pigeons were trained to peck at an illuminated key in an experimental chamber. Under the first schedule, every 50th response was reinforced by access to food (FR 50). Under the second, the first response after 15 minutes produced access to food (FI 15'). Two animals worked on each schedule. Control behaviour was typical of patterns engendered by fixed-ratio and fixed-interval schedules in that the FR 50 produced a steady, high response-rate while the FI 15' produced a long pause after reinforcement and then a progressive increase in rate of response throughout the interval. When baseline behaviour was established, the effect of pentobarbital sodium, a sedative-hypnotic (.25 - 5.6 mg i.m.) was studied. The 1 mg dose significantly increased responding under the FR 50 schedule but significantly decreased responding under the FI 15' schedule. In addition, a dosage of pentobarbital was found (.5 mg) that increased responding under the FI 15' condition. The assumption then, that pentobarbital sodium depressed behaviour did not bear out in Dews research. Although large enough doses would undoubtedly suppress responding, the effects of behaviourally active doses would be better understood by considering the rate of ongoing responding, a schedule-determined characteristic of behaviour. In a later

experiment, Dews (1958) went on to show that the effect of a psychomotor-stimulant drug, methamphetamine, was also dependent upon schedule-controlled rate of responding. When an FI 15' schedule maintained a low rate of responding, methamphetamine (.25 mg i.m.) increased responding over saline control. The same dose had no such stimulant action on behaviour maintained at a higher rate by an FR 50 schedule and a variable-interval, one minute (VI 1') schedule. A larger dose (1 mg i.m.) of methamphetamine decreased responding under all three schedules.

This pioneering work by Dews provided the framework for subsequent investigations of the parameters of schedule-controlled patterns of responding that modify drug effects. Kelleher and Morse (1968) have reviewed the vast number of studies in this area. For present purposes a brief resumé of the research results will be given. Dews original work (1955) has been supported using other species, drugs and types of reinforcers. Results confirmed that a single drug dose will differentially affect rates and patterns of responding engendered by different schedules and maintained by the same reinforcer. In addition, the parameters of a single schedule can modify drug effects. For example Morse (1962) reported that the higher doses of amobarbital, a sedative-hypnotic (10 mg i.m.) decreased responding more under the FR 33 schedule in which the control response rate was high, than under the FR 330 schedule which maintained a low control rate. This provided an example of

the importance of the rate of baseline responding. This variable is a major component of the schedule of reinforcement and a principle determinant of drug action.

Other experiments with drugs; such as, chlorpromazine and amphetamine have investigated the effect of holding constant the rate and pattern of control behaviour while varying the reinforcing event. The presentation of food, water, heat and intracranial stimulation have all been used as reinforcers in these studies. The drug effect on behaviour appears to be independent of the type of reinforcer. This finding is equally true when behaviour is controlled by negative reinforcement (the termination or postponement of noxious stimuli). Cook and Catania (1964) produced comparable patterns of responding in monkeys working under fixed-interval schedules of either food presentation or electric-shock termination. Chlorpromazine and imipramine decreased rates of responding with both reinforcing events, while certain doses of amphetamine, meprobamate and chlordiazepoxide increased rates of responding with both.

The consistent conclusion then, is that despite traditional assumptions regarding the inherent properties of drugs, their effects on behaviour depend on the schedule-controlled rate and pattern of responding and are generally independent of the reinforcing event.

Not to be overlooked in determining drug action is the effect of various drug doses on behaviour. Most drugs modify behaviour over a narrow range of doses and a single graded effect is rare although this has been found for simple in-vitro preparations



(Kelleher & Morse, 1968). Since large enough doses of any drug will eliminate responding it is essential in studying drug-behaviour interactions to establish dose-effect curves for a variety of drugs over several schedule-controlled patterns of responding (Kelleher & Morse, 1964).

The experiments noted in this section have dealt with the effects of acute drug injections on behaviour maintained by some other event such as food presentation or postponement of electric-shock. This type of work can be contrasted with self-administration studies in which the drug itself is the reinforcing event maintaining the behaviour. Schedule-controlled responding is also important in self-administration research and will be discussed in the following section.

#### Drug Self-Administration

A distinctive feature of drug dependence (both human and animal) is the persistent maintenance of behaviour leading to self-administration of the drug (Kelleher & Goldberg, 1976; Spealman & Goldberg, 1978). Recent technological advances that allow experimental animals to self-administer drugs have enhanced the laboratory model of drug dependence and furthered understanding of both drug-seeking behaviour and the reinforcing properties of drugs (Schuster & Thompson, 1969). Schuster and Thompson (1969) have reviewed the early self-administration work in which the oral route of drug

delivery predominated. In one method, animals were typically water-deprived prior to being given a choice of solutions to drink under varying conditions; such as, environmental stress. In addition, Falk (1961) observed that laboratory animals could be induced to self-administer drugs via adjunctive drinking. He discovered that rats trained on intermittent schedules of food reinforcement developed patterns of excess drinking during behavioural-testing sessions although they had not been fluid-deprived. This phenomenon, called schedule-induced polydipsia, has also been observed in monkeys (Schuster & Woods, 1966). There are, however, several major disadvantages to this route of administration. Position preference, degree of water deprivation and variability in time and amount of drug absorption may all confound results. Additionally, there is no record of the distribution or pattern of drug intake over time. Other routes of self-administration including inhalation (Goldstein, 1971) and intragastric have to date not been as thoroughly investigated as intravenous drug-taking behaviour.

Most recent work uses the intravenous self-administration technique first reported for use with rats by Weeks (1961). An indwelling-chronic venous catheter is connected to a drug injection pump which can be operated by the animals in the experimental chamber. This arrangement has also been described for rhesus monkeys and squirrel monkeys, (Schuster & Thompson, 1964; Yanagita, Deneau & Seevers, 1969; Stretch & Gerber, 1970).



Under suitable conditions, rats and monkeys have been shown to self-administer several compounds of the classes of drugs illicitly self-administered by man: narcotic analgesic drugs; sedative hypnotics including alcohol; psychomotor stimulants; and some minor tranquillizing agents (Schuster & Thompson, 1969). There is evidence that other drugs with psychoactive properties do not support compulsive drug-taking behaviour. They are the hallucinogens, major tranquillizers and certain narcotic compounds with mixed morphine agonist-antagonist effects (Holz & Gill, 1976).

The conditions or variables influencing the pattern and frequency of drug self-administration include (a) schedule of reinforcement; (b) drug dose and direct effects of the drug and (c) the animal's history of drug experience and current status of physiological dependence.

Schedules of reinforcement. Spealman and Goldberg (1978) reviewed the literature concerning the control of self-administration by schedules of reinforcement. They concluded that schedule-controlled rates and patterns of responding were more important than intrinsic drug properties in determining the effect of a drug on behaviour.

Providing certain conditions were met, it was possible to produce the rates and patterns of responding characteristic of each type of schedule when a drug acted as the consequent event. But on the fixed-ratio schedule for example, a high drug dose combined with frequent infusions could result in an accumulation of the drug

which disrupted behaviour. However, schedule-control could be improved by using the lower behaviourally-active doses and limiting the occasions of drug availability (Spealman & Goldberg, 1978).

For example, under an FR 30 schedule of cocaine (.003 mg/kg/inj) self-administration with intake limited to 48 inj/session, rhesus monkeys responded at a rate of one lever-press/sec which is comparable to the rate engendered by other reinforcers under the same schedule (Downs & Woods, 1974).

As with behaviour controlled by other events, rate of responding for drug self-administration varies directly with the size of the ratio requirement, over a large range of ratios (Schuster & Thompson, 1969). The pause after reinforcement, characteristic of ratio schedules varies in length directly with the ratio and drug dosage (higher ratios and doses producing longer pauses). While the fixed-ratio schedule has been studied most extensively, schedule-control has also been demonstrated with progressive-ratio, fixed-interval, variable-interval and second-order schedules of drug self-administration (Spealman & Goldberg, 1978). The powerful effect of schedule-control was demonstrated by Goldberg and Kelleher (1976). They studied the effect of increasing the doses of cocaine on self-administration behaviour in rhesus monkeys under a multiple fixed-interval 5 min, fixed-ratio 10 schedule. Alternating components of the schedule were separated by a 60 sec time-out. At doses of cocaine above .1 mg/kg/inj, rates of responding decreased in the fixed-ratio component to below those of the fixed-interval which itself was not

disrupted. A single dose of cocaine, therefore, had a different behavioural effect depending on the schedule of reinforcement. These results suggested that the fixed-interval schedule was more stable to the rate-decreasing effects of high doses of cocaine than was the fixed-ratio.

Drug dose and direct effects of the drug. A second variable to be considered when evaluating self-administration behaviour is drug dosage. Schuster and Thompson (1969) reviewed dose-effect results for several classes of compounds. Responding for morphine under a variable-interval schedule resulted in an inverted "V"-shaped curve as the dose increased from .01-1.0 mg/kg/inj, so that maximal response rates occurred for the intermediate doses. For the psychomotor stimulants (cocaine, d-amphetamine and methamphetamine) however, there was an inverse relation between doses and response rates across all self-administered doses.

A confounding variable in studying the reinforcing properties of drugs was the direct effects of the drug. These effects are called non-specific since they disrupt ongoing behaviour including the operant being measured (Schuster & Balster, 1973). As noted in the previous section, large doses of any drug will incapacitate the animal and result in cessation of behaviour. But even behaviourally-active doses, if accumulated and metabolized slowly, will disrupt behaviour and mask the reinforcing efficacy of the drug.

For example, Deneau, Yanagita and Seevers (1969) described the behavioural and somatic-toxic effects of cocaine and amphetamine

self-administration in rhesus monkeys. When each lever-press resulted in a drug injection with 24 hr access, drug accumulation produced among other symptoms: stereotypy, tremors and gross ataxia. In the case of cocaine, grand-mal convulsions were also observed. In contrast, when dose and schedule of cocaine self-administration were controlled, stable responding without disruption by direct effects was maintained (Stretch, 1977).

Much research has focused on ways of minimizing non-specific drug effects. Limiting the total number of infusions per session and using interval schedules gives the experimenter more control over total drug intake. Interposing time-out periods (during which the drug is not available) between drug trials also reduces cumulative drug effects. However, these methods provide only moderate control for short-acting compounds (Kelleher & Goldberg, 1976). Schuster and Balster (1973) have suggested that the use of rate of response as the dependent variable is not a foolproof indication of the reinforcing efficacy of a drug. For example, under an FR 10 schedule of morphine self-administration, rhesus monkeys responded at only low rates for any dose. However, morphine maintained high rates of responding when the schedule limited the frequency of injections (Spealman & Goldberg, 1978). Rate of response can also be misinterpreted when comparing reinforcing properties of different drugs. Schuster and Balster (1973) found that for rhesus monkeys responding on a 24 hr procedure, the highest rate of responding was for codeine (.05 mg/kg/inj) followed by propoxyphene, whereas

morphine (.01 - .05 mg/kg/inj) was self-administered at the lowest overall rate. Their data suggested that high doses of morphine are less reinforcing than the lowest codeine dose. This of course did not correspond with human clinical data and pointed out that direct drug effects can easily confound interpretation of a drug's function as a reinforcer.

An alternate approach to the rate of response as the dependent variable is use of choice procedures and measurement of the relative rates of responding to two or more drugs or doses of the same drug. As in single schedules, the average rate of responding on both levers would be partially influenced by direct drug effects. However relative rates of responding would allow an estimate of the control of the reinforcing events themselves (Kelleher & Goldberg, 1976). Studies using choice procedures with cocaine indicated that responding is maintained by the higher drug doses (Spealman & Goldberg, 1978). This procedure appears useful for evaluating high drug doses that under other schedules characteristically decrease responding.

Drug history. The drug history and current status of physiological dependence are also critical variables in self-administration behaviour. Previous experience with a drug can alter responding subsequently controlled by scheduled injections of that drug (Spealman & Goldberg, 1978). Experimental subjects may respond at higher rates and lower doses to a drug with which they have had considerable self-administration experience. Furthermore, experience

with one drug can affect responding maintained by another. For example, Schlichting, Goldberg, Wuttke and Hoffmeister (1971) found that rhesus monkeys on an FR 10 schedule of d-amphetamine self-administration responded at higher rates and with a more stable pattern when they had a history of cocaine self-administration than when responding had been previously maintained by pentobarbital or codeine.

Drugs can also exert differential effects depending on the current conditions of their self-administration (Spealman & Goldberg, 1978). If the experimental animal is physiologically dependent, the reinforcing effect of the drug is amplified, as a function of time since the last drug delivery (Schuster & Thompson, 1969). In addition, the morphine-dependent monkey will terminate injections of the morphine antagonists pentazocine or propiram while non-dependent animals will self-administer the same doses (Goldberg, Hoffmeister & Schlichting, 1972). There is an extensive literature concerning self-administration of morphine and its antagonists under various conditions of dependence which is immediately applicable to the present research and is therefore presented in a separate section. Suffice it to say for this section that drug dependence is another of the circumstances that affect self-administration behaviour.

In summary, the pattern and rate of responding to self-administer psychoactive drugs has been shown to be dependent upon

environmental factors rather than simply on inherent properties of the compounds.

Assessment of a drug's reinforcing efficacy must be carefully and cautiously interpreted considering the non-specific drug effects and limitations of the rate of responding as the dependent variable.

#### Behavioural Effects of Morphine and Mixed Morphine Agonist-Antagonist Drugs

A brief overview will be presented here of the major pharmacological characteristics of morphine and drugs with morphine-antagonist properties. No attempt has been made to provide an exhaustive account of the pharmacological nature of such compounds. This information is available elsewhere (Root, 1963; Martin, 1967; Goldstein, Aronow & Kalman, 1974; Goth, 1976).

As noted in the Introduction, behavioural pharmacology advanced rapidly as a separate scientific discipline largely in response to a need for the understanding of human opiate dependence and for the development of analgesic drugs devoid of dependence-producing properties. The recent investigations of self-administration behaviour in non-human primates have continued to elucidate the drug-behaviour interaction of morphine-agonist and antagonist drugs.

Morphine is an alkaloid found in opium, the dried juice of the poppy plant, Papaver somniferum. Morphine was isolated in 1803 and

remains the most important narcotic-analgesic drug (Goth, 1976). Narcotic analgesics are defined by their ability to suppress signs of abstinence in morphine-dependent subjects, as well as to produce morphine-like physiological dependence when administered chronically (Villarreal, 1973). Some other natural and synthetic narcotic analgesics are codeine, diacetylmorphine (heroin) and meperidine (Demerol). The analgesic effect of these drugs is found in classes of drugs other than the opiates, hence the definition of narcotic analgesics in terms of physiological dependence and abstinence. In humans, morphine (10-15 mg s.c.) produces drowsiness and euphoria as well as anxiety and nausea in some subjects (Goth, 1976). It is a potent analgesic for all modalities of pain and has widespread central nervous system effects, of which respiratory depression and pupillary constriction are most characteristic. Large doses of morphine can result in death due to respiratory failure. In addition to the central-depressant effects, morphine can be excitatory in certain circumstances (Goth, 1976; Holtzman, 1976). The effects of a single therapeutic dose last four to six hours whereas its metabolism takes much longer, with the half-life being approximately 24 hours (Goth, 1976).

Villarreal (1973) has described the effects of acute doses of morphine given to drug-naive monkeys. They include: central nervous system depression resembling intoxication, characterized by reduction of spontaneous activity and some loss of postural tone; reduction of spontaneous blinking with the animal instead, staring into space;



and marked reduction of responsiveness to stimuli. Large doses can result in coma and/or respiratory arrest. There is a notable similarity, then, in the physiological effects of morphine in humans and non-human primates.

Furthermore, for both humans and experimental animals of various species, tolerance develops to the central-depressant effects of morphine (Goth, 1974; McMillan, 1974; Kelleher & Goldberg, 1976). For humans, this means that progressively larger doses are required to obtain the same subjective effects so that the dose required for effective analgesia in a tolerant subject may be one that would be lethal to a non-tolerant subject. In laboratory animals, an initial dose of morphine that depresses; for example, the rate of responding for food reinforcement, will have no such effect after repeated trials, so that responding returns to the baseline rate (Schuster & Balster, 1973; McMillan, 1974; Adam-Carrière, Merali & Stretch, 1978).

Dependence is a phenomenon separate from tolerance but is also characteristic of the opiates and observed in both humans and experimental animals. Physiological dependence is inferred when (a) abrupt cessation of chronic drug delivery results in the abstinence syndrome and when (b) further administration of the drug relieves the syndrome (Schuster & Balster, 1973; WHO, 1975).

The abstinence syndrome is a group of specific symptoms and signs observed during drug withdrawal of a dependent organism or

as a consequence of precipitated abstinence (initiated by an acute dose of an antagonist drug). Seevers (1936) developed a detailed checklist of abstinence signs and grades of severity of the syndrome. Deneau (1956) revised this original classification so that it was possible to distinguish between eight grades of severity of abstinence. Briefly, some of the signs of abstinence in a dependent organism are: piloerection, emesis, diarrhea, miosis and hyperreflexia (Villarreal, 1973; Woods, Downs & Carney, 1975). Villarreal and his colleagues have used the checklist in the investigation of the dependence-producing capacity of some 900 compounds related to the narcotic analgesics. It had been determined that drugs which suppressed the signs of abstinence were themselves capable of producing morphine-like physiological dependence when chronically administered (Villarreal, 1973). In Villarreal's procedure (the single-dose suppression test), chronic morphine administration was abruptly withdrawn from rhesus monkeys and a single dose of an experimental drug was delivered in order to observe its ability to relieve the abstinence syndrome. Drugs that suppressed abstinence had high dependence-producing properties.

Although tolerance and physiological dependence are well-known phenomena that have been assessed for many pharmacological compounds, the mechanisms of action have not been conclusively determined.

Goldstein et al. (1974) explained that there are two kinds of theories of tolerance and dependence. The first assumes that the drug-receptor interaction remains the same as in non-tolerant and/or

non-dependent organisms, while the drug effects are compensated for in other biochemical pathways or neuronal systems. For example, it has been hypothesized that the primary drug effect activates various neural or hormonal pathways whose function it is to produce effects opposite to those of the drug. Homeostasis is thereby restored. In a tolerant organism a higher drug dose would be necessary to disrupt the homeostasis being maintained by increased stimulation of the various compensating pathways. Furthermore, withdrawal of the drug would result in symptoms associated with excess output of these pathways (e.g., the excitation observed upon withdrawal from morphine).

The second type of theory of tolerance and dependence has been labelled the "enzyme-expansion theory". In contrast to the theory above, the enzyme-expansion theory assumes that the drug produces changes in the drug-receptor interaction. To illustrate, in an attempt to maintain normal functioning at the synapse, enzyme production is increased to offset a drug-induced depression of synaptic firing. As more enzyme is produced, an increasing amount of drug is required to produce the same depressant effect (i.e., tolerance). When the drug is withdrawn the excess enzyme would not be immediately inhibited, causing the excitatory effect observed in the abstinence syndrome.

While both theories appear to account for both tolerance and the physiological disruption of withdrawal in drug-dependence organisms, it has, as yet, not been established which truly explains the two phenomena.

A third event observed in regard to psychoactive drugs is behavioural (or psychic) dependence. This is defined as the voluntary initiation and maintenance of drug self-administration without the observation of physiological disruption upon withdrawal (Deneau, Yanagita & Seevers, 1969; Schuster & Balster, 1973). Schuster and Balster (1973) noted that both physiological and behavioural dependence predispose the organism to self-administer opiates and can result in compulsive drug-seeking and self-administration. Society labels this behaviour as drug abuse when either physiological or behavioural disruptions dangerous to the individual or to society ensue.

One area of study in the control of opiate dependence has been with drugs displaying morphine-antagonist properties. These are substances with chemical structures that are a modification of the basic structure of morphine. Substitution of the methyl group of the basic nitrogen of narcotic analgesics by an allyl group, has yielded antagonists such as N-allylnormorphine (nalorphine) and N-allylnoroxymorphine (naloxone), (Fink et al., 1973; Blumberg & Dayton, 1973). Other N-cyclopropylmethyl substitutions have produced the N-methyl 6, 7 - benzomorphans, cyclazocine and pentazocine (Villareal, 1973). These and other antagonists are characterized by their ability to counteract the central-depressant effects of narcotic agonists, and to precipitate an acute abstinence syndrome in opiate-dependent organisms. They are however, ineffective against non-narcotic depressants like the barbiturates and alcohol.

An experimental clinical treatment for opiate dependence made use of antagonist actions. During extinction of drug-seeking behaviour, the relief of protracted, conditioned abstinence symptoms by narcotics was blocked by the administration of antagonists. By this method, self-administration of opiates, it was hypothesized, would have no reinforcing effect and would therefore decrease in frequency and finally disappear, (Martin et al., 1965; Fink et al., 1973). A complication in this procedure was that antagonists had direct effects of their own and most were better described as mixed agonist-antagonists.

Naloxone is the only relatively "pure" antagonist showing no antinociceptive activity in animals and basically no analgesic activity in man (Blumberg & Dayton, 1973). Furthermore, Jasinski, Martin and Heartzen (1967) demonstrated that in human subjects naloxone did not produce morphine-like subjective effects or physiological dependence. Naloxone has consequently been the drug of choice in the treatment of acute respiratory depression due to a narcotic overdose.

The drugs with mixed agonist-antagonist properties have been classified into two groups according to the type of agonist activity displayed (Villarreal, 1973; Jasinski, 1977). In the first are drugs like profadol and propiram that have morphine-like agonist effects, are dependence-producing and therefore an abstinence syndrome is observed upon their withdrawal or during precipitated abstinence. In the second group are nalorphine and cyclazocine-like

mixed agonist-antagonists. The central nervous system effects of these drugs differ from those of morphine in that there is a strong muscle-relaxant effect without severe respiratory depression or reduced responsiveness to environmental stimuli. For example, while monkeys gradually developed tolerance to .5 mg/kg of cyclazocine s.c. every 6 hrs, withdrawal of the drug or naloxone injections produced only yawning and self-scratching behaviour lasting 8-10 days (Villarreal, 1973). This suggested a very low level of physiological dependence, different from the morphine variety. In human studies, Jasinski (1977) reported that nalorphine and cyclazocine were experienced differently from the opiates. Subjects classified nalorphine and cyclazocine with the barbiturates and alcohol because of their sedative, drunken and disorienting effects. Morphine-like euphoria was not subjectively experienced. Tolerance to and physical dependence on nalorphine and cyclazocine were demonstrated but consistent with pre-clinical experiments, the withdrawal syndrome was not morphine-like. Human subjects reported a lack of concern over the mild symptoms and did not engage in drug-seeking behaviour (Martin et al., 1965). The difference between the agonist effects of these antagonists and those of morphine was further exemplified by the fact that while both nalorphine and cyclazocine precipitated abstinence in morphine-dependent subjects, neither successfully suppressed withdrawal symptoms, (Jasinski, 1977). A basic principle of behavioural pharmacology has been that the more potent a drug's pain-

relieving properties, the greater liability it has for producing morphine-like physiological dependence (Villarreal, 1973; Goldstein et al., 1974). Cyclazocine may be an exception to this rule since it has active analgesic properties (Fink et al., 1973) but apparently does not produce morphine-like physiological dependence.

Studies of the potential viability of cyclazocine as an analgesic as well as a morphine-antagonist in the treatment of drug dependence have shown that the drug has dysphoric and psychotomimetic effects in both opiate-dependent and opiate-naive human subjects, (Martin & Gorodetzky, 1965; Jasinski, Martin & Sapira, 1968; Fink et al., 1973). These side-effects however, may be antagonized by naloxone (Jasinski et al., 1968; Fink et al., 1973). As noted in the Introduction, preclinical work with cyclazocine has been much less extensive than investigations of nalorphine and naloxone, although there has been evidence of its clinical usefulness. The relative positive-reinforcing or aversive properties of cyclazocine have not been conclusively demonstrated.

In summary, opiate dependence has been a major focus of behavioural pharmacology research. Recent investigations of the role of narcotic antagonists and drugs with mixed agonist-antagonist properties (e.g., cyclazocine) indicate a possible role for these compounds in the treatment of drug dependence. However, further pre-clinical work is necessary to elucidate the drug-behaviour interactions of mixed agonist-antagonists and to establish their relative positive and/or negative-reinforcing properties.

### The Aversive Properties of Drugs

Until recently, drug self-administration research focused on the investigation of drugs as events that maintained responding leading to their delivery. In operant terms this process is known as positive reinforcement. In this section, work on the negative-reinforcing properties of drugs will be reviewed. The emphasis will be on the aversive properties of naloxone, nalorphine and cyclazocine in morphine-dependent, post-dependent and morphine-naïve monkeys, although reference will be made to research with other classes of drugs.

During some of the work done to assess the ability of various drugs to maintain self-administration behaviour, it was evident that certain substances appeared to have a punishing effect on drug-taking behaviour while others were neutral (neither positively reinforcing nor aversive). Deneau et al. (1969) found that when chlorpromazine (.1 and .5 mg/kg/inj) was cross-substituted in rhesus monkeys trained to self-administer morphine, responding decreased altogether. Similar results were obtained for nalorphine, for nalorphine-morphine mixture, mescaline and saline. Hoffmeister and Goldberg (1973) found that while rhesus monkeys consistently self-administered d-amphetamine and morphine, imipramine (.05 - .5 mg/kg/inj) failed to maintain rates of responding different from those seen during saline substitution. Response rates when chlorpromazine (.05 - .5 mg/kg/inj) was substituted were markedly suppressed. They concluded that chlorpromazine had aversive or punishing properties



and that imipramine was neutral. Holz and Gill (1976) reviewed other research in which standard substitution tests were used to assess drugs that failed to maintain self-administration. A punishing effect was commonly inferred if there was a more rapid decline in response rate than would be observed when saline was substituted. Such suppression of responding, however, might have been caused by factors other than aversive properties of the drug; such as, direct rate-depressing or behaviourally-disruptive effects. In addition, it was difficult to determine whether a drug was simply neutral in effect or was indeed aversive.

Recent work has used a direct method of analyzing a drug's negative-reinforcing properties. When responding is maintained by the termination of drug injections (escape) or the termination of a stimulus associated with the injections (avoidance), the drug is said to function as a negative reinforcer. The procedures used to study the negative-reinforcing properties of drugs are modifications of operant techniques originally designed to study responding maintained by escape from or avoidance of electric-shock (Goldberg, 1975). The point to note is that schedule-controlled behaviour can be maintained by a number of events including termination of various stimuli; for example, bright light, loud noise and intense heat (Holz & Gill, 1976) as well as electric-shock and drug injections. Such stimuli are defined as aversive not because they are subjectively unpleasant, but because of their effect on the future occurrence of

behaviour which terminates or avoids their presentation. Since experimental animals will respond to produce electric-shocks (e.g., Stretch; 1972) and will continue to self-administer drugs with severe side effects (Deneau et al., 1969), it is evident that consequent events cannot casually be described as positive or aversive according to subjective evaluation. Studies of negative reinforcement (e.g., Azrin, Holz & Hake, 1962) have shown that under appropriate conditions, rates and patterns of responding to terminate various stimuli can be similar to responding engendered by comparable schedules of positive reinforcement; such as, food presentation.

Goldberg, Hoffmeister, Schlichting and Wuttke (1971) were the first to use the negative-reinforcement paradigm with drug injections as the aversive event. Rhesus monkeys were maintained in a morphine-dependent state by automatic morphine injections delivered every four hours through a venous catheter. One hour after a morphine injection, animals were tested under a discrete avoidance/escape schedule. A 10 sec drug injection was delivered every 30 sec but could be escaped or avoided by completion of an FR 10 response requirement which was followed by a 60 sec time-out. Injections of the narcotic antagonists nalorphine (.01 - .05 mg/kg/inj) and naloxone (.0001, .0005 and .001 mg/kg/inj) were escaped or avoided, while saline injections were tolerated. Nalorphine and naloxone therefore, were considered to be aversive. Subsequent investigations of the negative-reinforcing properties of nalorphine and naloxone in morphine-

dependent monkeys confirmed these first results. Tang and Morse (1976) studied the role of morphine-dependence and fixed-ratio schedules in the maintenance of nalorphine escape/avoidance. Rhesus monkeys, previously trained to self-administer morphine, were injected daily with morphine (10 mg/kg/i.m.) to maintain physiological dependence. Animals were tested daily under a stimulus-complex similar to the one used in the present research. Nalorphine injections were scheduled to occur every 20 sec and after 5 injections an automatic 60 sec time-out was programmed. Completion of the fixed-ratio requirement (FR 3 or FR 30) before injections began, constituted avoidance and resulted in the 60 sec time-out. Injections already begun could be terminated by the same number of responses and this escape was also followed by time-out. More than 85% of nalorphine (.01 mg/kg/inj) injections were escaped or avoided under both FR 3 and FR 30 schedules. Response rates were higher for the FR 30 regime and fewer injections were tolerated. Larger nalorphine doses of .02 and .04 mg/kg/inj did not produce any major changes in response rate or number of injections received. When morphine pretreatment was discontinued, responding to escape or avoid nalorphine (.01 and .03 mg/kg/inj) diminished to near zero under both FR 3 and FR 30 schedules. There was further indication of the importance of the degree of morphine dependence for escape/avoidance behaviour. Monkeys normally received several nalorphine injections at the beginning of each session before starting to respond. But when a pre-session nalorphine injection was given,

responding began immediately and continued throughout the session even though saline was being delivered intravenously in place of nalorphine. The authors concluded that the withdrawal state produced by nalorphine was the major influence on behaviour to terminate nalorphine injections or stimuli associated with nalorphine even when saline was substituted. The presence or absence of morphine-dependence was therefore considered the underlying factor in the aversiveness of nalorphine.

Kandel and Schuster (1977) also studied nalorphine in morphine-dependent and post-dependent monkeys. They used an escape-only paradigm and a continuous (rather than discrete-trials) injection of nalorphine (.001 or .002 mg/kg/10 sec). Animals were allowed four, one hour periods of morphine self-administration daily to maintain physiological dependence. Drug-escape trials began 2 hours after a morphine self-administration session. Nalorphine was consistently escaped under FR 1 and FR 5 schedules of drug termination. When morphine self-injection sessions were gradually eliminated over one week, responding to escape nalorphine injections continued for approximately one month. Little change was observed when the dose of nalorphine was increased to .004 or .005 mg/kg/10 sec. Kandel and Schuster suggested that the maintenance of escape behaviour might be due to an increased sensitivity of post-dependent animals to the aversive properties of the antagonist. While results of the several experiments agreed, that nalorphine was escaped or avoided



in morphine-dependent monkeys, there were discrepancies in observations for post-dependent animals keeping in mind that the experimental procedures were not identical across studies. Hoffmeister and Wuttke (1973) also found that nalorphine was escaped/avoided in non-dependent rhesus monkeys. Their subjects, however, were morphine-naive and had been trained to escape/avoid electric-shock presentations before intravenous drug-injection trials began. In addition, they used much higher doses of nalorphine (.01 - .5 mg/kg/inj) than Kandel and Schuster (1977). Hoffmeister and Wuttke concluded that certain psychopharmacological effects of nalorphine were probably responsible for its aversive properties in the non-dependent monkeys. In the same experiment, injections of cocaine, codeine, pentazocine and propiram fumarate (all .05 mg/kg/inj) were tolerated, as were injections of naloxone (.1 - .005 mg/kg/inj). Cyclazocine (.01 - .0025 mg/kg/inj) generated and maintained escape/avoidance behaviour similar to nalorphine. A smaller dose of cyclazocine (.0001 mg/kg/inj) was tolerated somewhat more than saline injections as a control procedure. The authors noted that while monkeys did not salivate or vomit when injection of cyclazocine were delivered, they were very sedated for the first few sessions when drug intake was high. Despite sedation, the animals did begin to avoid cyclazocine reliably on the second or third day of drug trials. This was the only published report of work with cyclazocine (using the negative-reinforcement paradigm). This drug is also the only morphine

antagonist, amongst those that have been investigated in a negative-reinforcement procedure, that has not been studied in morphine-dependent monkeys (Holz & Gill, 1976). The research reported here was designed to elucidate the nature of cyclazocine escape/avoidance with morphine-dependent and post-dependent subjects.

Goldberg's et al. (1971) research results with naloxone were also confirmed by subsequent experiments. Downs and Woods (1975) for example, found that morphine-dependent rhesus monkeys reliably escaped or escaped/avoided injections of naloxone (.0001 - .02 mg/kg/ing) on an FR 30 schedule. In the escape-only segment of the experiment, response rates to escape a continuous drug injections were dose related. The largest and smallest doses of naloxone produced the lowest response rates while an intermediate dose was escaped at high rates of responding. Small doses of naloxone apparently failed to have aversive effects while large doses resulted in gradual accumulation of the drug which disrupted behaviour by the end of the session so that responding diminished or became erratic. When animals were tested under a discrete-trial procedure with an avoidance contingency, they avoided almost all injections so that little naloxone was accumulated and the dose-related performance was not as clear.

While it seemed generally true that morphine-dependent monkeys would avoid or escape non-contingent injections of morphine antagonists, results were cautiously interpreted since some investigations

have shown that such animals will also press a lever to obtain antagonist injections. Downs and Woods (1976) reported that morphine-dependent rhesus monkeys responded to produce naloxone injections for at least a limited period of time under a second-order schedule. The animals had been responding to avoid naloxone under an FR 30, escape/avoidance procedure when the schedule was changed. Under the second-order regime, each 30-response fixed-ratio component was followed by a brief (1.5 sec) flash of the houselight. Ten such components produced .002 mg/kg/inj of naloxone and a 60 sec time-out. Subjects responded at high rates for two blocks of sessions (8 and 10 days respectively), separated by control days during which the naloxone pump was disconnected and responding abruptly decreased. When naloxone was made available for a third determination however, responding was maintained at low rates with little naloxone being delivered. The authors speculated that the decrease in responding was comparable to that found for similar fixed-ratio schedules of response-produced electric-shock; but that perhaps responding would be maintained indefinitely under a fixed-interval schedule as it is under conditions of electric-shock presentation.

While much of the work concerning the negative-reinforcing properties of drugs has focused on nalorphine and naloxone, other morphine antagonists have been studied, as have drugs belonging to classes other than the narcotic analgesics and their antagonists. Briefly, pentazocine and propiram fumarate (both weak morphine antagonists

with strong agonist properties) were escaped or avoided by morphine-dependent monkeys but were tolerated more than saline in morphine-naive monkeys (Hoffmeister and Wuttke, 1973). The hallucinogens, lysergic acid diethylamide (LSD) and {1-(2,5-dimethoxy-4-methyl-phenyl) 2-propylamine hydrochloride} (STP) supported escape/avoidance responding in non-dependent rhesus monkeys (Hoffmeister, 1975; Hoffmeister & Wuttke, 1976). Chlorpromazine, the phenothiazine derivative, (a major tranquilizer) was avoided or escaped by non-dependent monkeys while imipramine (a tricyclic anti-depressant drug) was tolerated at levels comparable to saline (Hoffmeister and Wuttke, 1976). Pentobarbital, codeine and cocaine were all tolerated more than saline by non-dependent animals under a negative-reinforcement schedule (Hoffmeister and Wuttke, 1973; Hoffmeister and Wuttke, 1976). Perphenazine (another major tranquilizer), studied in post-dependent rhesus monkeys, was reliably escaped in an escape-only paradigm (Kandel & Schuster, 1977).

Generally, drugs shown to be aversive to rhesus monkeys in the negative-reinforcement procedure are the same ones that are not abused by man. Heroin addicts certainly avoid narcotic antagonists that produce the abstinence syndrome and dislike the psychotomimetic side-effects of nalorphine and cyclazocine. While chlorpromazine is a frequently used tranquillizer, patients find it disagreeable and self-maintenance of the drug programme is often a problem. Drugs which are abused, such as pentobarbital, codeine and cocaine are not



escaped or avoided by rhesus monkeys. The hallucinogens seem to be the solitary exception to this general pattern. They are not tolerated by experimental animals but have been self-administered by humans. However, the widespread use of LSD in the 1960's may have been a relatively short-lived cultural phenomenon. The abuse of LSD is associated with the acute psychotoxic effects and does not resemble compulsive abuse. There has been no evidence to demonstrate that LSD has pharmacological properties that are reinforcing.

This review of the aversive properties of drugs has concentrated on naloxone, nalorphine and cyclazocine as they are most pertinent to the present research report. While few studies have been published concerning cyclazocine, much more work has been done with nalorphine. This has been reviewed here due to the similarities between nalorphine and cyclazocine. The issue of why certain drugs are aversive has not been conclusively determined. Some research supports the idea of the importance of morphine dependence while others have found certain antagonist drugs to be aversive in the absence of morphine-dependence. Even though research has demonstrated that certain drugs can function as negative reinforcers, the experimental conditions, previous drug history and schedule parameters must be further investigated in an attempt to understand the process.

The objectives of the experimental work reported here can be stated as follows: (a) to examine, in squirrel monkeys, Hoffmeister and Wuttke's finding (1973) that cyclazocine exhibited negative-



reinforcing properties in rhesus monkeys with no history of exposure to morphine, (b) to explore the role of morphine dependence and post-dependence in the maintenance of cyclazocine escape/avoidance behaviour, and, (c) to compare the results of (b) above with those for naloxone, a potent morphine antagonist.

## CHAPTER II

### METHODS

#### Subjects

Five adult, male squirrel monkeys (Saimiri sciureus) designated 221, 222, 223, 224 and 225, weighing 500-600 gm were used. The animals were housed in pairs in a temperature and humidity-controlled colony room with free access to food, water and vitamin supplements except during experimental sessions when they were removed individually to behavioural-testing cubicles. None of the animals had participated in previous experiments; each animal completed preliminary training and the pilot work described below. Monkey 223 was removed from the experiment at the end of the pilot study due to inability to retain implanted catheters. Monkey 225 died shortly after beginning the main experiment; the probable cause of death was a chronic respiratory infection. Results, therefore, will be presented for all five animals for preliminary training and pilot work and for three animals (221, 222 and 224) for the main experiment.

#### Apparatus

Each monkey was tested daily in a small, primate restraining chair (BRS/LVE) inside a ventilated, but sound-attenuating cubicle. The response lever was located above the waist lock, 8-10 cm in front of the seated monkey. A cue lamp (BRS/LVE 111-05) was

situated above the response lever; provision was made for a white houselight and low level (75 dB) masking noise in each cubicle. Each lever-press closed a microswitch, constituting a response for recording purposes. Experimental conditions were controlled by standard relay, timing and counting equipment located in an adjacent room. Responses and electric-shock presentations or drug injections were tabulated by digital counters and plotted by a Gerbrands cumulative-response recorder. Intravenous injections of drugs or control solutions (e.g., saline or the vehicle in which dl-cyclazocine was dissolved) were delivered by a Sage Model 341 syringe driver.

#### Procedure

Preliminary training. Under a discrete-trials electric-shock escape/avoidance procedure, the monkeys were trained to complete a fixed-ratio requirement of 10 lever-presses (FR 10). The onset of a white houselight and masking noise signalled the presentation, after 30 sec, of a red light associated with intermittent electric-shocks, at an intensity of 5 ma, each of .25 sec duration for a total of 10 sec. Shocks were delivered to a shaved portion of the monkey's tail. Completion of 10 responses during the first 30 sec terminated the houselight and sound, avoiding electric-shock presentation and producing a 60 sec time-out. Completion of 10 responses after shocks had begun terminated the houselight, red cue light and shocks (designated as an escape) producing the 60 sec

time-out. During time-out, lights and noise were switched off, no electric-shocks were delivered and responses had no programmed consequences. Each session terminated after 50 min or 50 shocks, whichever came first. After responding stabilized over 12 sessions so that electric-shocks were delivered only infrequently, electric-shock presentation was discontinued and over 15 consecutive sessions fixed-ratio responding was subjected to experimental extinction. The extinction procedure marked the end of preliminary training.

Catheter implantation. Using procedures described by Stretch and Gerber (1970) subjects were surgically fitted with an intravenous catheter. PVC tubing (.38 mm I.D., .76 mm O.D.) was inserted under pentobarbital anesthesia into the external jugular or femoral vein. Each catheter was sealed with a stylet wire and rested in a pouch on the back of the leather vest worn by each animal at all times as a means of achieving catheter protection. Throughout the experiment it was necessary to replace catheters due to blocking or rejection, requiring a period of at least seven days for the surgical work and subsequent post-operative recovery. During this period, experimental sessions were not conducted. The number of consecutive sessions under any condition, therefore, occasionally varied between animals although the sequence of treatments was identical.

Pilot work. Pilot work was undertaken initially to replicate Hoffmeister and Wuttke's study (1973) of the aversive properties of

dl-cyclazocine. After evaluating the initial results of this work the protocol was revised in favour of another methodology using the procedure described by Tang and Morse (1976) which allowed further exploration of the aversive properties of dl-cyclazocine. While this pilot work was not the major focus of the research presented here, it is nevertheless described in sufficient detail to substantiate the finding that Hoffmeister and Wuttke's results (1973) were difficult to replicate in the squirrel monkey. In addition, such a description provides essential information on the experimental history of each animal prior to participation in the main experiment.

Following catheter implantation and post-operative recovery, the monkeys were exposed to a schedule of discrete-trials identical to that of the preliminary electric-shock escape/avoidance procedure except that electric-shock presentation was replaced by non-contingent saline injections. Later, as described below, saline injections were replaced by drugs with morphine-antagonist properties. The onset of the white houselight and masking-noise signalled the delivery, after 30 sec, of a 10 sec drug injection ( $.25 \text{ cm}^3$  of solution) accompanied by a red light. If the FR 10 response requirement was completed during the first 30 sec, the injection was avoided, light and noise were switched off, automatically instituting a 60 sec time-out period. The time-out period could likewise be initiated by escaping the injection if the response requirement was completed before the drug injection-ended. An automatic time-out was imposed

following the injection if the monkey failed to complete the FR 10 requirement. Each experimental session lasted for 50 min or until 50 injections had been delivered, whichever came first. Each drug or control solution was available for six consecutive sessions or until a criterion was met. In the first manipulation saline was injected through the catheter until at least 70% of the injections were tolerated over six consecutive sessions. This provided a measure of baseline responding and a control for naloxone vehicle. Subsequently, naloxone (.01 mg/kg/inj) was substituted for saline until the same criterion was met. dl-Cyclazocine vehicle was then substituted for naloxone to provide a control for dl-cyclazocine. Finally, dl-cyclazocine (.005 mg/kg/inj) was made available.

Due to the failure of the animals to respond to avoid or escape dl-cyclazocine (.005 mg/kg/inj) it became evident that Hoffmeister and Wuttke's results (1973) were not susceptible to replication in the squirrel monkey. In addition, lever-press responding was severely suppressed. Before the protocol change to the Tanq and Morse (1976) procedure could be made and the main experiment begun, it was essential to have evidence that lever-pressing behaviour was again established as part of the animals' behavioural repertoire. Rather than return to the electric-shock escape/avoidance training to reinstate lever-pressing in already-catheterized monkeys, a procedure using response-contingent intravenous injections of cocaine hydrochloride (.015 or .03 mg/kg/inj) as a reinforcer was adopted for this purpose.

Main experiment. Training to terminate a schedule-complex associated with brief injections of naloxone (.01 mg/kg/inj) began. For this procedure, each monkey received a daily intramuscular injection of morphine (10 mg/kg) 60 min before behavioural testing. Chronic daily administration of morphine preceeding individual sessions was undertaken to establish physiological dependence; discontinuation of daily morphine pretreatment as an experimental manipulation enabled comparison of the relative aversiveness of drugs with morphine-antagonist properties in morphine-dependent and post-dependent monkeys.

During experimental sessions, injections of naloxone were delivered every 20 sec after the onset of a green light and low-level masking noise. Each injection duration was 1 sec and .15 cm<sup>3</sup> of drug was delivered. Following the procedure of Tang and Morse (1976), five such injections, in the absence of responding, completed the time-in period and were followed by an automatic time-out of 60 sec during which the light and noise were switched off and responding had no scheduled consequences. One complete cycle, therefore, had a total duration of 100 sec. Under a fixed-ratio 10 schedule (FR 10), 10 lever-press responses were required to terminate the light and masking noise to produce the 60 sec time-out. Monkeys could therefore avoid injections if the FR response-requirement was completed during the first 20 sec of the cycle, or escape from injections by completing the requirement after the sequence of 5 injections had begun. At the end of the time-out period, the light and noise were



presented again and the cycle was repeated. Each experimental session lasted 100 min or until 100 injections had been delivered.

Once responding to terminate the naloxone stimulus-complex under the FR 10 schedule was well-maintained and stable, sequences of consecutive sessions were conducted in which: (a) morphine pretreatment was discontinued; (b) morphine pretreatment was reinstated and saline was substituted for naloxone; (c) dl-cyclazocine injections (.003 mg/kg/inj) were substituted for naloxone under circumstances in which morphine pretreatments were given or discontinued; and, (d) injections of the vehicle in which dl-cyclazocine was dissolved were substituted for dl-cyclazocine as a control procedure. Since different numbers of consecutive sessions under the various conditions were given to each of the monkeys, results will be presented on an individual basis.

#### Drug Preparation

Morphine sulphate and naloxone hydrochloride were dissolved in and diluted with .9% saline solution using sterile procedures; doses are expressed in terms of the salts. dl-Cyclazocine base was dissolved in three parts of 8.5% lactic acid and two parts 1.0 N sodium hydroxide following the procedure described by Holtzman (1976).

#### Data Analysis

Preliminary training (shock escape/avoidance). For each animal, the mean number of responses made, shocks avoided, escaped and/or

delivered were calculated for the first and second six-day periods. For the condition of experimental extinction of responding, the mean number of escape and avoidance responses as well as the mean total responses were determined for each animal in the absence of electric-shock presentation.

Pilot work (discrete-trials drug escape/avoidance). The results of this work will be presented briefly in terms of the mean number of injections completed per session for all animals together (with the standard deviation and standard error of the mean) over all sessions for each experimental condition.

Main experiment. The mean number of injections delivered per session and mean response rate per second (plus the standard deviation and standard error of the mean) under consecutive sequences of experimental conditions were calculated for each monkey individually.

## CHAPTER III

### RESULTS

The present chapter contains the results of the experimental manipulations described in Chapter II. The data are divided into three distinct sections corresponding to the three major procedures detailed in the methodology. They are: results of the Preliminary Training (Electric-Shock Escape/Avoidance); data obtained from the Pilot Work (Discrete-Trial Drug Escape/Avoidance); and finally, the results of the Main Experiment (Stimulus-Complex Termination). Discussion of the experimental findings follows in Chapter IV.

#### Preliminary Training (Electric-Shock Escape/Avoidance)

Results of the discrete-trials FR 10 electric-shock escape/avoidance training are shown in Table 1. Data are divided into two blocks: one shows the first six days during which the acquisition of escape/avoidance behavior took place; and the second illustrates the final six days of stable behavior. By the end of training, all animals avoided an average of more than 49 of the 50 shocks available during each session. Monkeys 221, 222, 223 and 225 reduced the average number of escapes from shocks begun as well as the average number of shocks delivered by the final six sessions. Monkey 224, on the other hand, avoided all shocks

Table 1

Mean Number of Responses Made and Shocks  
Delivered<sup>a</sup> per Session during the Electric-Shock  
Escape/Avoidance Procedure

| Monkey                       | Shocks<br>Delivered | Responses |        |       |
|------------------------------|---------------------|-----------|--------|-------|
|                              |                     | Avoidance | Escape | Total |
| First six days               |                     |           |        |       |
| 221                          | 13.8                | 38.7      | 11.3   | 112.0 |
| 222                          | .8                  | 49.3      | .7     | 91.0  |
| 223                          | 1.8                 | 48.3      | 1.7    | 188.3 |
| 224                          | 0                   | 50.0      | 0      | 155.7 |
| 225                          | .2                  | 49.8      | .2     | 200.2 |
| Second six days <sup>b</sup> |                     |           |        |       |
| 221                          | .3                  | 49.7      | .3     | 93.5  |
| 222                          | .3                  | 49.8      | .3     | 69.0  |
| 223                          | .3                  | 49.8      | .3     | 174.5 |
| 224                          | 0                   | 50.0      | 0      | 118.8 |
| 225                          | .3                  | 49.8      | .3     | 183.3 |

<sup>a</sup> The maximum number of shocks per session was 50.

<sup>b</sup> The means for monkeys 222, 223, 224 and 225 are based on four sessions.

throughout the training. A reduction of the average total number of responses per session was seen for each animal by the time that stable behaviour had been established.

Table 2 shows the data for the extinction period divided into (a) the first 10 days during which behaviour was in transition from a condition of non-contingent electric-shock presentation to one without electric-shock; and (b) the final five days of stable behaviour. During the first ten days the mean number of avoidance responses increased substantially for monkeys 221, 223 and 225 over those of the final six days of electric-shock escape/avoidance (see Table 2). Mean avoidance responses for monkeys 222 and 224 showed a minor decrease. The mean number of escape responses however, showed a clearly detectable increase for all animals during the first 10 days of extinction.

Subsequently, for the final five days of extinction the mean number of avoidance responses dropped by between 45.9% and 80.7% from the first 10 days. Corresponding decreases in mean escape responses ranged from 6.4% to 71.4%. As the mean total responses also decreased from between 32.2% to 75.4% from the first 10 days it was evident that responding had undergone experimental extinction.

Representative cumulative recordings of electric-shock escape/avoidance and extinction of responding for monkey 221 are presented in Figure 1. A and B show the second and final days of electric-shock escape/avoidance respectively. Each diagonal stroke on the

Table 2

Mean Number of Responses Made per Session  
During Extinction of Responding to  
Escape/Avoid Electric-Shock

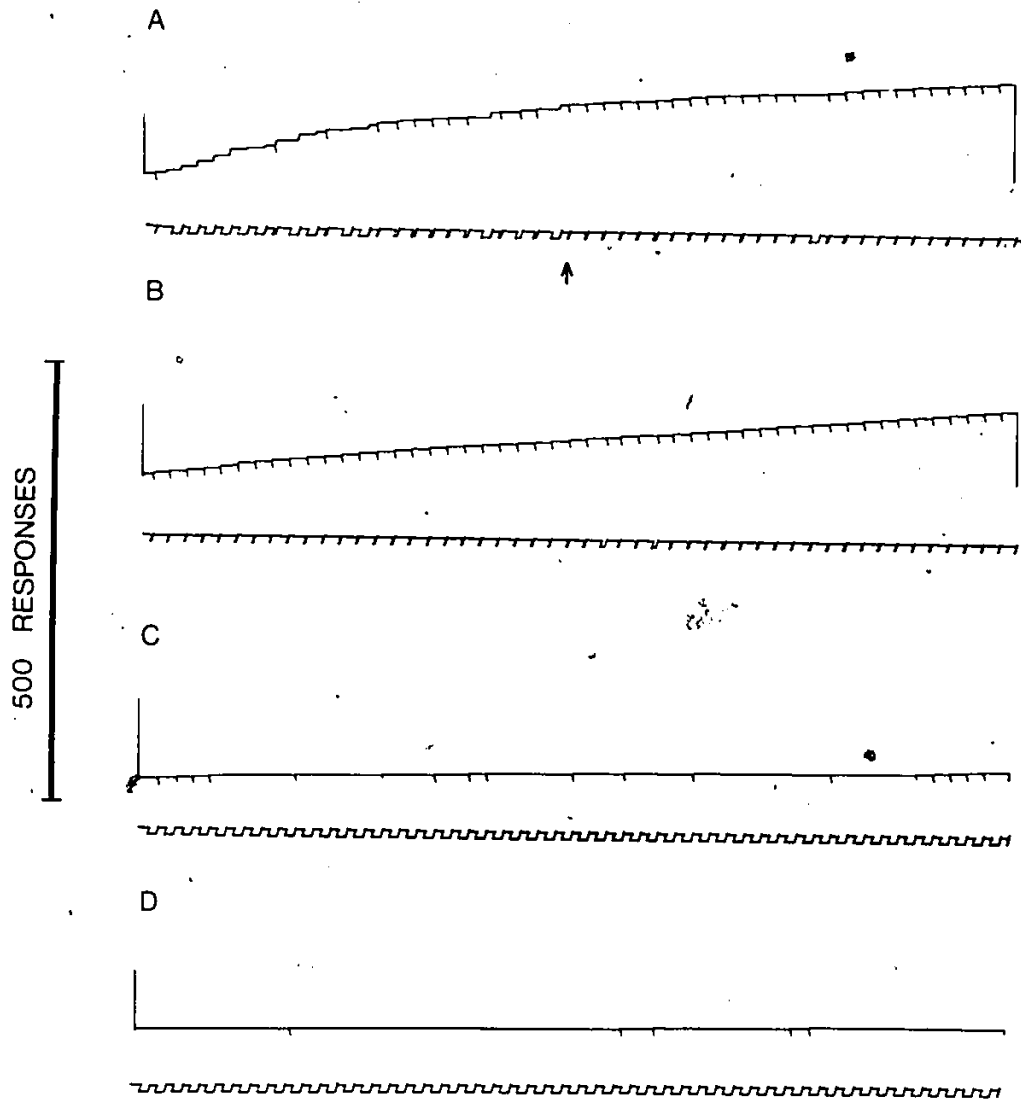
| Monkey           | Responses |        |       |
|------------------|-----------|--------|-------|
|                  | Avoidance | Escape | Total |
| First 10 days    |           |        |       |
| 221              | 84.1      | 8.3    | 104.0 |
| 222              | 42.4      | 7.8    | 63.4  |
| 223              | 119.9     | 19.4   | 199.9 |
| 224              | 33.2      | 4.2    | 51.2  |
| 225              | 89.1      | 10.9   | 126.9 |
| Final five days  |           |        |       |
| 221 <sup>a</sup> | 35.0      | 7.3    | 58.0  |
| 222              | 11.2      | 3.8    | 27.4  |
| 223              | 66.0      | 12.6   | 135.6 |
| 224              | 6.4       | 1.2    | 12.6  |
| 225              | 48.2      | 10.2   | 74.6  |

<sup>a</sup> The means for monkey 221 are based on four sessions.

Figure 1

Cumulative-response recordings for monkey 221, showing responding to escape/avoid electric-shock presentation and performance during experimental extinction of responding. A and B represent days 2 and 12 of electric-shock escape/avoidance training. C and D represent days 1 and 14 of extinction of responding. Each diagonal stroke on the cumulative recording indicates an avoidance response. Each downward stroke of the event pen refers to the beginning of time-in while an upward stroke marked commencement of time-out.

MONKEY 221





cumulative recording was an avoidance response (completion of the FR 10 requirement during the first 30 sec of time-in). Each downward stroke of the event pen marked the beginning of time-in, while each upward stroke marked commencement of the 60 sec time-out. A shock delivered was therefore indicated by an extended time-in period. Escape responses were not indicated on the recording. A shows that on the second day of training, monkey 221 made only 12 avoidance responses and received 12 shocks during the first half of the session (to the left of the arrow) but completed 25 avoidance responses and received only one shock during the remainder of the session. By the final day of training (B) 50 avoidance responses were made and no shocks delivered. Graphs C and D show the first and final days of experimental extinction of responding. On these graphs the diagonal strokes on the cumulative recording represented escape responses. C shows that on the first day of extinction, escape responses were made to the first four trials, whereafter escape responding became sporadic until the final five trials. By the final day (D) when shocks were no longer delivered, only five escape responses were made intermittently over the 50 min session. Comparable recordings were collected for all animals during preliminary training.

#### Pilot Work (Discrete-Trial Drug Escape/Avoidance)

In Table 3 are the results of substituting for electric-shock, the various drug and control solutions in the FR 10 drug escape/

Table 3

Mean Number of Injections Completed  
per Session<sup>a</sup> During the Drug  
Escape/Avoidance Procedure

| Drug or Control Solution        | Injections Completed <sup>b</sup> |
|---------------------------------|-----------------------------------|
| Saline                          | 45.8 ± 4.4 (SD); SEM = .8 (30)    |
| Naloxone (.01 mg/kg/inj)        | 39.9 ± 7.5 (SD); SEM = 1.4 (29)   |
| dl-Cyclazocine Vehicle          | 46.8 ± 2.0 (SD); SEM = .4 (24)    |
| dl-Cyclazocine (.005 mg/kg/inj) | 39.3 ± 14.7 (SD); SEM = 3.8 (15)  |

<sup>a</sup> The total number of injections available was 50.

<sup>b</sup> Numbers in parentheses indicate the number of sessions completed for each drug or control solution; SD refers to one standard deviation; SEM refers to the standard error of the mean.

avoidance procedure. Shown are the mean number of injections completed per session for the final six days of each condition out of a maximum possible 50 injections per session. The numbers represent the mean for all animals and sessions taken together for each condition. The data clearly show that non-contingent injections of naloxone (.01 mg/kg/inj), dl-cyclazocine (.005 mg/kg/inj) as well as saline and dl-cyclazocine vehicle were tolerated; that is, none of these drug manipulations reinstated lever-press responding to terminate the drug-stimulus complex. The relatively greater variance in number of injections completed for naloxone and dl-cyclazocine was due to the performance of monkey 221. This animal consistently escaped or avoided more injections of both drugs than any of the other monkeys.

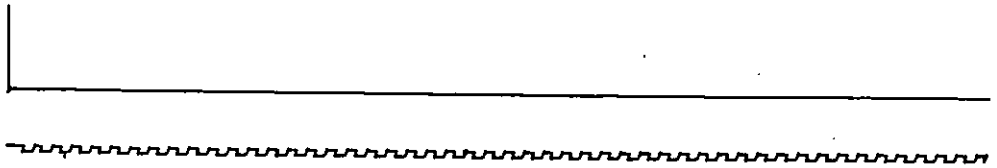
Figure 2 contains representative cumulative records for the pilot work collected from monkey 222 and shows the following conditions: A - saline; B - naloxone (.01 mg/kg/inj); C - dl-cyclazocine vehicle; and D - dl-cyclazocine (.005 mg/kg/inj). There was no responding under conditions of saline, dl-cyclazocine vehicle or dl-cyclazocine substitution during which all infusions were tolerated. This animal made seven avoidance responses during the session shown when naloxone substitution was made. Comparable cumulative recordings were collected for each animal during the pilot work.

Figure 2

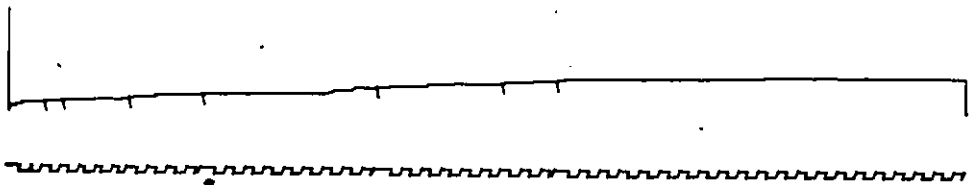
Representative cumulative recordings for the pilot work collected from monkey 222. A- demonstrates a session in which saline injections were delivered and no responses were made to terminate or postpone them. B- a session in which 7 avoidance responses were made to postpone injections of naloxone (.01 mg/kg/inj) which were otherwise tolerated. C- dl-cyclazocine vehicle was delivered in the absence of responding, as was dl-cyclazocine in record D.

MONKEY 222

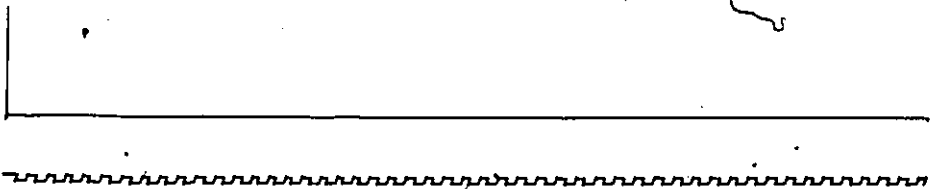
A



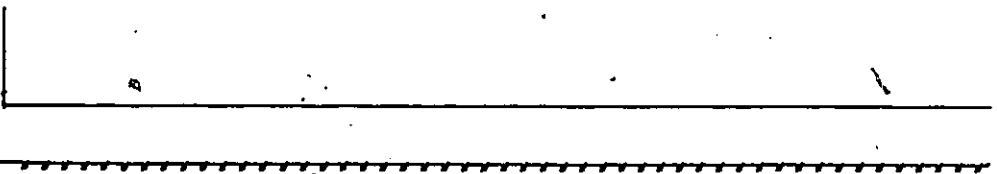
B



C



D



20 MINUTES

### Main Experiment

Results will be initially presented for each animal separately over the sequence of conditions of morphine-dependence and post-dependence. Subsequently, a comparison will be made across animals and representative cumulative recordings of the various experimental manipulations will be shown.

Results are given in graphical form (e.g., Fig 3) with data points referring to the mean number of injections delivered per session  $\pm$ SEM on one graph, and the mean number of responses per second  $\pm$ SEM on another. Two points were plotted for each experimental manipulation. The first datum point represents the mean for the first five days or transition period while the second refers to the mean of the remaining sessions (the number of which varied over different conditions). These two data points allowed evaluation of the behavioural effects of introducing and discontinuing morphine pretreatment several times throughout the experiment. The first five sessions after a change in pretreatment procedure marked a transition period that, in the case of discontinuing pretreatment, was characterized by the morphine abstinence syndrome. The severe state of withdrawal disrupted all behaviour including lever-press responding. After approximately five days the abstinence syndrome was no longer observed and lever-pressing behaviour generally stabilized with the animal in a post-dependent state. This stable behaviour is then presented in the second datum point. Similarly, behaviour was disrupted when morphine pretreatment was reintroduced. The transition

period was marked by the gradual development over several days of physiological dependence on and tolerance to morphine. By separating out the transition periods then, the effects of the stable state of either morphine-dependence or post-dependence on termination of a drug-stimulus complex could be observed.

Two data points were likewise presented for each manipulation during which a different drug or control-solution substitution was conducted, while either morphine-dependence or post-dependence was maintained.

Figure 3 contains graphs showing for monkey 221 the effects of morphine pretreatment and absence of pretreatment upon the mean rate of responding (upper graph) and mean total number of non-coincident injections delivered per session (lower graph) during the sequence of consecutive experimental manipulations.

In Table 1 of the Appendix are found the corresponding standard deviation, standard error of the mean and number of sessions for each datum point.

A- Morphine pretreatment; naloxone (.01 mg/kg/inj). During the first five sessions of morphine pretreatment (A, 1) monkey 221 produced an average .6 responses/sec and tolerated 20 inj/session of naloxone. Responding stabilized at .5 responses/sec on the average, with 32.3 inj/session being completed (A, 2). Variability of responding decreased during the final 8 sessions.

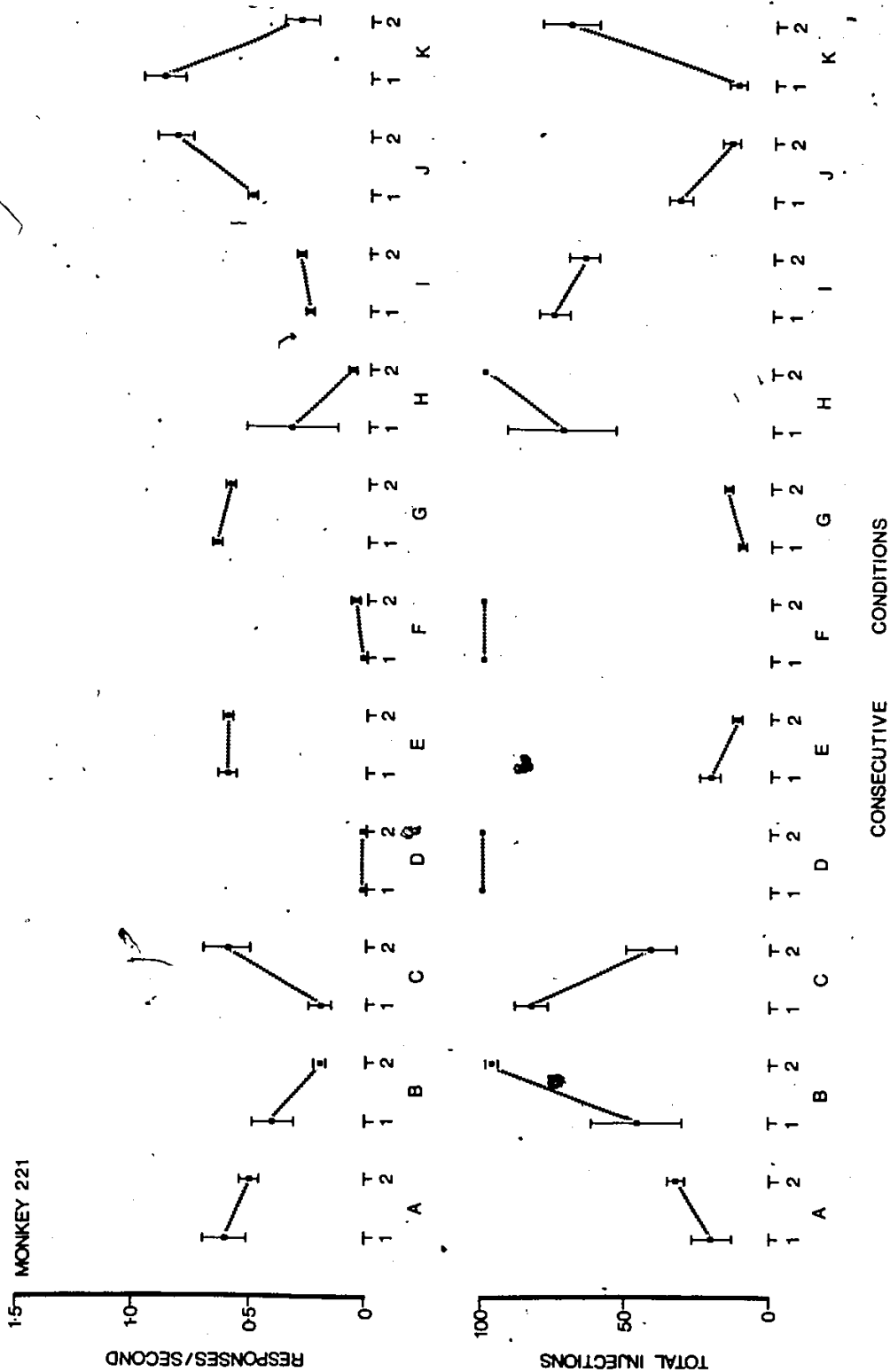
B- No morphine pretreatment; naloxone (.01 mg/kg/inj). When morphine pretreatment was withdrawn, responding began to decrease

Figure 3

Graphs showing for monkey 221, the responses/sec (upper graph) and total injections (lower graph) for consecutive sessions of schedule-complex termination. Data points refer to the mean  $\pm$  SEM for observations of each experimental condition. Numbers appearing on the horizontal axes refer, for each condition designated by a letter, to the first five sessions in every instance above the numeral 1, and a variable number of additional consecutive sessions above the numeral 2.

- Condition A: morphine 10 mg/kg; naloxone .01 mg/kg/inj  
1: 5 sessions                      2: 8 sessions
- Condition B: no morphine pretreatment; naloxone .01 mg/kg/inj  
1: 5 sessions                      2: 5 sessions
- Condition C: morphine 10 mg/kg; naloxone .01 mg/kg/inj  
1: 5 sessions                      2: 12 sessions
- Condition D: morphine 10 mg/kg; saline  
1: 5 sessions                      2: 5 sessions
- Condition E: morphine 10 mg/kg; dl-cyclazocine .003 mg/kg/inj  
1: 5 sessions                      2: 5 sessions
- Condition F: morphine 10 mg/kg; dl-cyclazocine vehicle  
1: 5 sessions                      2: 5 sessions
- Condition G: morphine 10 mg/kg; dl-cyclazocine .003 mg/kg/inj  
1: 5 sessions                      2: 5 sessions
- Condition H: no morphine pretreatment; dl-cyclazocine .003 mg/kg/inj  
1: 5 sessions                      2: 5 sessions
- Condition I: morphine 10 mg/kg; dl-cyclazocine .003 mg/kg/inj  
1: 5 sessions                      2: 10 sessions
- Condition J: morphine 10 mg/kg; naloxone .01 mg/kg/inj  
1: 5 sessions                      2: 2 sessions
- Condition K: no morphine pretreatment; naloxone .01 mg/kg/inj  
1: 5 sessions                      2: 11 sessions





immediately and dropped from .4 to .2 responses/sec (B,1 & B,2). During transition, a mean of 46.0 naloxone injections was completed with great variability, compared to 96.6 for the remaining sessions of stable behaviour.

C- Morphine pretreatment; naloxone (.01 mg/kg/inj). When morphine pretreatment was reinstated, responding to escape/avoid naloxone did not change initially (.2 responses/sec) and a mean of 83.0 inj/session was tolerated (C,1). This transition period was marked by considerable variability in performance. While responding increased to .6 responses/sec and only 41.5 inj/session of naloxone were completed during the final 12 sessions (C,2), variability of performance was still evident.

D- Morphine pretreatment; saline. When saline was substituted for naloxone as a control procedure, monkey 221 made no responses to escape/avoid the injections throughout the 10 sessions. All 100 inj/session were tolerated (D,1 & D,2).

E- Morphine pretreatment; dl-cyclazocine (.003 mg/kg/inj). When saline injections were replaced with dl-cyclazocine, responding to escape/avoid quickly increased to .6 responses/sec while only 21.8 inj/session were completed (E,1). After this transition period, responding remained at the same rate (although with more stability) and injections-completed decreased to 12.0 per session.

F- Morphine pretreatment; dl-cyclazocine vehicle. To control for the possible effects of dl-cyclazocine vehicle, this solution

was substituted for dl-cyclazocine under conditions of morphine pretreatment. Responding immediately decreased, stabilizing at .1 responses/sec (F,2); all 100 inj/session were tolerated for the duration of the substitution (10 sessions).

G- Morphine pretreatment; dl-cyclazocine (.003 mg/kg/inj). A second dl-cyclazocine substitution was made, reproducing condition E. Monkey 221 increased escape/avoidance responding to .7 responses/sec (G,1), and maintained a rate of .6 responses/sec (G,2) after the transition period. Initially, 10.0 inj/session of dl-cyclazocine were tolerated (G,1) increasing to an average of 14.6 during the final five sessions (G,2). This stable behaviour was comparable to that observed for condition E when dl-cyclazocine was first introduced.

H- No morphine pretreatment; dl-cyclazocine (.003 mg/kg/inj). In this manipulation, morphine pretreatment was discontinued. During withdrawal, responding to escape/avoid dl-cyclazocine was highly variable with responding decreased to .3 responses/sec and an average of 72.6 inj/session tolerated (H,1). For the remaining five sessions however, lever-pressing further diminished to a constant .1 responses/sec with all 100 inj/session being delivered.

I- Morphine pretreatment; dl-cyclazocine (.003 mg/kg/inj). Morphine pretreatment was reinstated so that conditions similar to E and G were in force. Responding to escape/avoid dl-cyclazocine increased slightly to .3 responses/sec during transition (I,1) and settled at that rate during the final 10 sessions (I,2). Initially,

74.0 inj/session were tolerated (I,1), decreasing minimally to 65.7 per session (I,2). A clearly greater number of injections of dl-cyclazocine were tolerated on reinstatement of morphine-dependence than during E and G, and responding was maintained at only half of the previous rates.

J- Morphine pretreatment; naloxone (.01 mg/kg/inj). In order to further explore the failure of monkey 221 to respond to escape/avoid dl-cyclazocine at the previous rates, naloxone was substituted for dl-cyclazocine while continuing morphine-dependence. In contrast to the response to dl-cyclazocine (in condition I), naloxone was escaped or avoided with behaviour similar to that during the original naloxone substitutions (A and C). Monkey 221 increased lever-pressing to .5 responses/sec during transition while tolerating 32.6 inj/session (J,1). Responding was fixed at an average of .8 responses/sec for the remaining two sessions with only 15.2 inj/session completed.

K- No morphine pretreatment; naloxone (.01 mg/kg/inj). As a final determination of the influence of morphine-dependence and post-dependence on drug escape/avoidance behaviour, morphine was withdrawn while non-contingent injections of naloxone were delivered. During the withdrawal state (K,1), responding increased to .9 responses/sec and few naloxone injections were tolerated (12.4 inj/session). As the abstinence syndrome subsided, lever-pressing diminished to .3 responses/sec and 71.7 inj/session of naloxone were completed during the remaining 11 sessions. The final six days of this condition were characterized by toleration of all 100 inj/

session, indicating that the behaviour was comparable to that of condition B,2 during which naloxone was also delivered while monkey 221 was in a stable post-dependent state.

In summary, for monkey 221, the pattern of results showed that naloxone was tolerated when morphine pretreatment was withdrawn but escaped/avoided following morphine pretreatment. dl-Cyclazocine was likewise tolerated when the animal was in the post-dependent state. When morphine pretreatments were given, monkey 221 responded to escape/avoid dl-cyclazocine during the first two determinations of this condition but not during a third. Injections of saline and dl-cyclazocine vehicle were consistently tolerated during sessions following morphine pretreatment.

Figure 4 illustrates the main experiment results for monkey 222. Each condition is represented by two data points with three exceptions (B, H and I) that will be noted below. Table 2 of the Appendix contains the standard deviation, standard error of the mean and number of sessions for each condition.

A- Morphine pretreatment; naloxone (.01 mg/kg/inj). During the first five sessions of morphine pretreatment, monkey 222 responded to escape/avoid naloxone injections at .9 responses/sec, while tolerating an average of 21.6 inj/session (A,1). There was a notable variation in performance among different sessions. For the final five sessions lever-pressing decreased to .7 responses/sec and 32.6 inj/session were completed (A,2). Variability diminished to a minor degree.

Figure 4

Graphs showing for monkey 222, the responses/sec (upper graph) and total injections (lower graph) for consecutive sessions of schedule-complex termination. Data points refer to the mean  $\pm$  SEM for observations of each experimental condition. Numbers appearing on the horizontal axes refer, for each condition designated by a letter, to the first five sessions in every instance above the numeral 1, and a variable number of additional consecutive sessions above the numeral 2.

Condition A: morphine 10 mg/kg; naloxone .01 mg/kg/inj  
1: 5 sessions                      2: 5 sessions

Condition B: no morphine pretreatment; naloxone .01 mg/kg/inj  
1: 12 sessions                      2: 7 sessions (asterisk denotes  
3: 7 sessions                      FR 30)

Condition C: morphine 10 mg/kg; naloxone .01 mg/kg/inj  
1: 5 sessions                      2: 5 sessions

Condition D: morphine 10 mg/kg; saline  
1: 5 sessions                      2: 5 sessions

Condition E: morphine 10 mg/kg; dl-cyclazocine .003 mg/kg/inj  
1: 5 sessions                      2: 5 sessions

Condition F: morphine 10 mg/kg; dl-cyclazocine vehicle  
1: 5 sessions                      2: 5 sessions

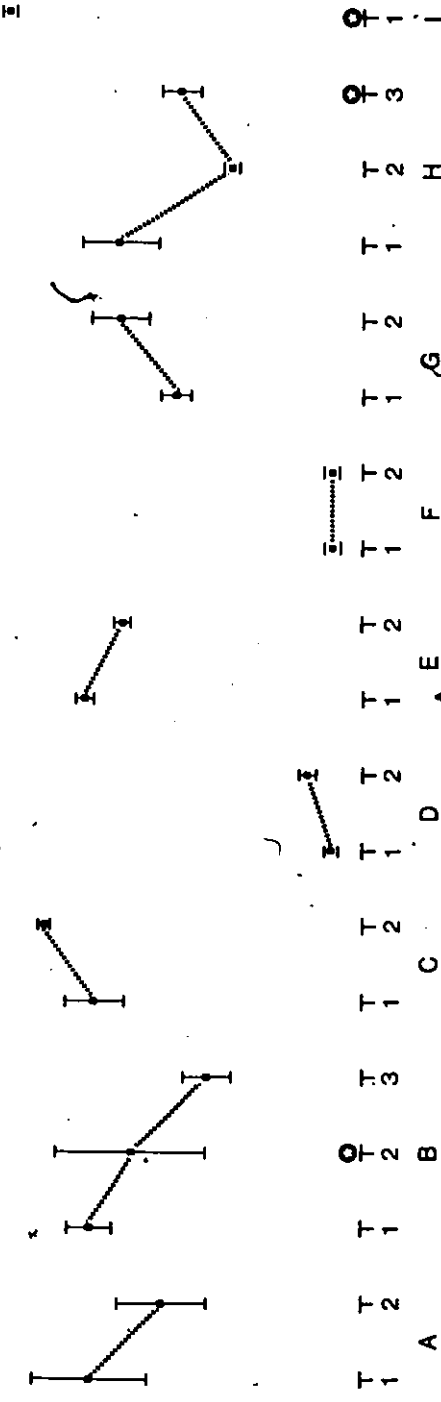
Condition G: morphine 10 mg/kg; dl-cyclazocine .003 mg/kg/inj  
1: 5 sessions                      2: 3 sessions

Condition H: no morphine pretreatment; dl-cyclazocine .003 mg/kg/inj  
1: 5 sessions                      2: 16 sessions  
3: 10 sessions (asterisk denotes FR 30)

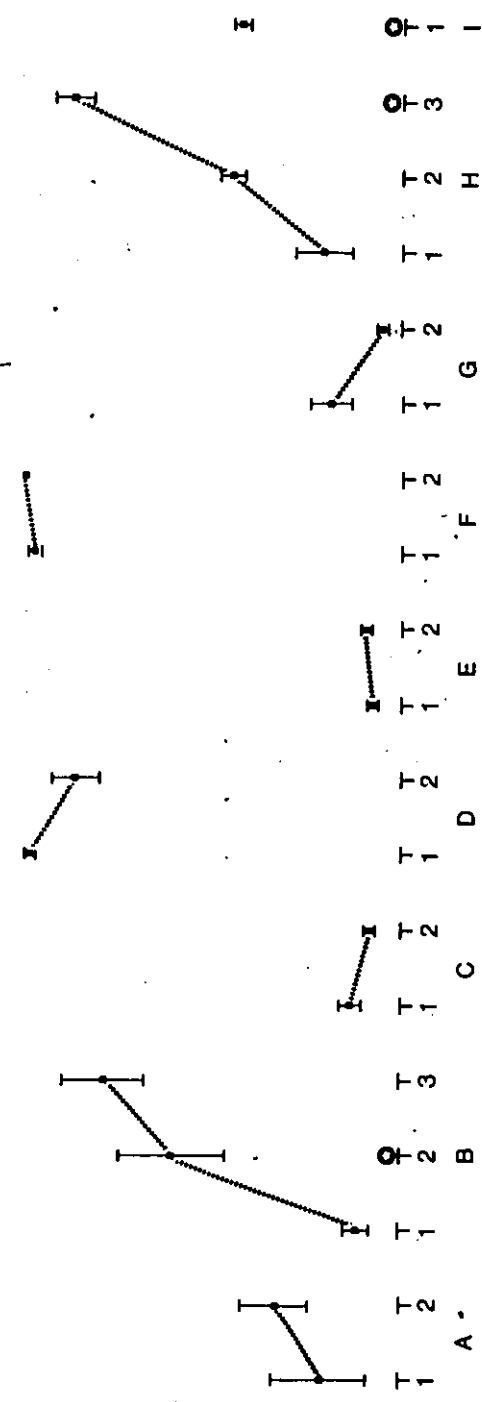
Condition I: morphine 10 mg/kg; dl-cyclazocine .003 mg/kg/inj  
1: 3 sessions (asterisk denotes FR 30)

MONKEY 222

RESPONSES / SECOND



TOTAL INJECTIONS



CONSECUTIVE CONDITIONS

B- No morphine pretreatment; naloxone (.01 mg/kg/inj). When morphine pretreatment was discontinued, responding to escape/avoid naloxone increased to .9 responses/sec and only 11.3 inj/session were delivered (B,1). These results represent 12 sessions during which monkey 222 continued to escape/avoid naloxone even after the usual five-day recovery from the withdrawal syndrome. In order to assess whether continued responding was due to the aversiveness of naloxone or simply to persistence of lever-pressing in this animal, the fixed-ratio requirement was increased from FR 10 to FR 30 for seven sessions (B,2). Responding decreased to a mean of .8 responses/sec with high variability in performance; 60.9 inj/session were tolerated on the average, again with high variability. For a final series of seven sessions (B,3) the fixed-ratio requirement was returned to FR 10. Responding diminished further to a more constant .5 responses/sec; 78.9 inj/session of naloxone were completed (with variability still evident).

C- Morphine pretreatment; naloxone (.01 mg/kg/inj). When morphine pretreatment was reintroduced, escape/avoidance responding increased to .9 responses/sec (C,1) and stabilized at 1.1 responses/sec during the final five sessions of this condition (C,2). While a mean of 12.2 inj/session was completed during transition (C,1), only 8.2 were tolerated when behaviour reached a steady state (C,2). There was considerably less variation in performance for condition C than for either A or B.



D- Morphine pretreatment; saline. Lever-pressing declined quickly to .1 responses/sec when a saline control substitution was made for naloxone; Monkey 222 tolerated 98.5 inj/session (D,1). During the final five sessions responding increased to .2 responses/sec while an average of 86.4 inj/session of saline were completed (D,2).

E- Morphine pretreatment; dl-cyclazocine (.003 mg/kg/inj). With monkey 222 still in a morphine-dependent state, dl-cyclazocine was substituted for saline. Responding to escape/avoid injections increased to .9 responses/sec with only 7.6 inj/session being tolerated (E,1). Lever-pressing settled at .8 responses/sec during the remaining five sessions; 9.2 inj/session of dl-cyclazocine were completed:

F- Morphine pretreatment; dl-cyclazocine vehicle. As a control procedure, dl-cyclazocine vehicle was substituted while monkey 222 continued to receive daily morphine injections. Responding immediately diminished to .1 responses/sec (F,1) and remained there for the duration of the experimental manipulation (F,2). While 97.8 inj/session were delivered during the first five sessions (F,1), this increased to 100 inj/session for F,2.

G- Morphine pretreatment; dl-cyclazocine (.003 mg/kg/inj). In a second determination of escape/avoidance of dl-cyclazocine, the transition period was characterized by lever-pressing at .6 responses/sec and 18.2 inj/session being completed (G,1). For the final three days, responding increased to .8 responses/sec while only 5 inj/

session were tolerated (G,2). These results were comparable to those of condition E in which monkey 222 worked to escape/avoid dl-cyclazocine while in a morphine-dependent state.

H- No morphine pretreatment; dl-cyclazocine (.003 mg/kg/inj).

During the first five sessions after morphine pretreatment was discontinued (H,1), responding to escape/avoid injections remained at a relatively high rate (.8 responses/sec), while only 21.0 inj/session were tolerated. For the next 16 days (H,2) lever-pressing decreased to .4 responses/sec, with 44.7 inj/session being delivered. Monkey 222 continued to respond to escape or avoid more than 50% of the dl-cyclazocine injections, even after a normal period of recovery from the abstinence syndrome (as was seen in condition B with naloxone). Therefore, contingencies were altered as before so that 30 responses were required to escape or avoid drug injections. During the 10 sessions on the FR 30 schedule (H,3), responding increased to .6 responses/sec but inj/session tolerated reached an average of 87.5.

I- Morphine pretreatment; dl-cyclazocine (.003 mg/kg/inj).

For a final determination of relative aversiveness of dl-cyclazocine, morphine pretreatment was reinstated. During three sessions at FR 30 (I,1) monkey 222 responded at 1.2 responses/sec while tolerating 42.3 inj/session of dl-cyclazocine. Although this condition was similar to E and G, results were not comparable since the animal was in transition from a post-dependent to a morphine-dependent state and the experiment was terminated due to time considerations, before stable behaviour had been established.

In summary, for monkey 222, naloxone was tolerated while the animal was in a post-dependent state and escaped or avoided when sessions were preceded by a morphine injection. dl-Cyclazocine was also tolerated in the absence of morphine pretreatment. When monkey 222 was morphine-dependent, dl-cyclazocine was escaped or avoided during two determinations; a third was inconclusive because of a limited number of sessions. On two occasions it was necessary to increase the fixed-ratio requirement in order to demonstrate tolerance of naloxone and dl-cyclazocine in the post-dependent state. Saline and dl-cyclazocine vehicle were tolerated while the animal was morphine-dependent.

Figure 5 shows the results of the main experiment for monkey 224. Table 3 of the Appendix contains the standard deviation, standard error of the mean and number of sessions for each datum point plotted on the graphs.

A- Morphine pretreatment; naloxone (.01 mg/kg/inj). For the first five days of morphine pretreatment, monkey 224 responded with .2 responses/sec while tolerating 47.8 inj/session of naloxone (A,1). During the remaining eight sessions, the response rate increased to .4 responses/sec and average inj/session became more stable at 27.3 (A,2).

B- No morphine pretreatment; naloxone (.01 mg/kg/inj). When morphine was withdrawn, performance was erratic during transition (B,1). Responding to escape/avoid naloxone injections remained at .4 responses/sec while 54.4 inj/session were delivered. When behaviour became stabilized (B,2), responding decreased altogether and all 100 inj/session were tolerated.

Figure 5

Graphs showing for monkey 224, the responses/sec (upper graph) and total injections (lower graph) for consecutive sessions of schedule-complex termination. Data points refer to the mean  $\pm$  SEM for observations of each experimental condition. Numbers appearing on the horizontal axes refer, for each condition designated by a letter, to the first five sessions in every instance above the numeral 1, and a variable number of additional sessions above the numeral 2.

Condition A: morphine 10 mg/kg; naloxone .01 mg/kg/inj  
1: 5 sessions                      2: 8 sessions

Condition B: no morphine pretreatment; naloxone .01 mg/kg/inj  
1: 5 sessions                      2: 5 sessions

Condition C: morphine 10 mg/kg; naloxone .01 mg/kg/inj  
1: 5 sessions 2: 12 sessions

Condition D: morphine 10 mg/kg; saline  
1: 5 sessions 2: 5 sessions

Condition E: morphine 10 mg/kg; dl-cyclazocine .003 mg/kg/inj  
1: 5 sessions. 2: 8 sessions

Condition F: morphine 1.0 mg/kg; dl-cyclazocine vehicle  
1: 5 sessions 2: 5 sessions

Condition G: morphine 10 mg/kg; dl-cyclazocine .003 mg/kg/inj  
1: 5 sessions 2: 2 sessions

Condition H: no-morphine pretreatment; dl-cyclazocine .003 mg/kg/inj  
1: 5 sessions                      2: 5 sessions

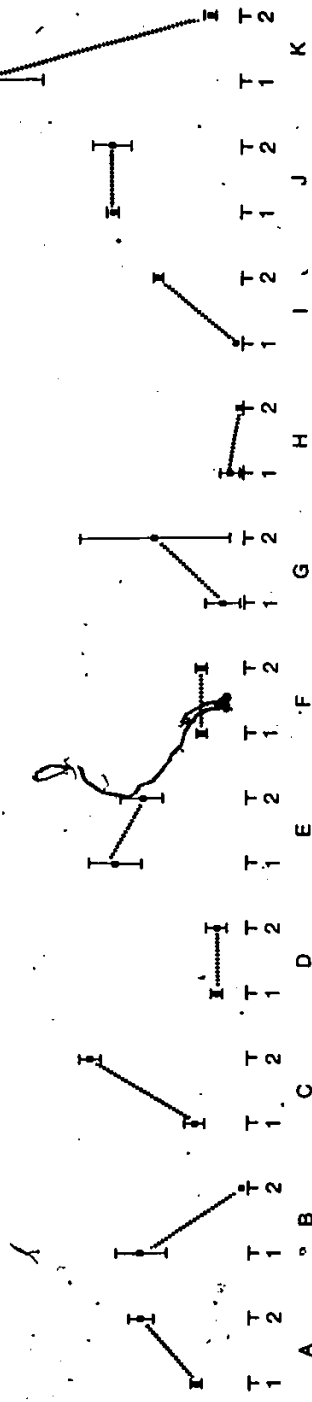
Condition I: morphine 10 mg/kg; dl-cyclazocine .003 mg/kg/inj  
1: 5 sessions                      2: 19 sessions

Condition J: morphine 10 mg/kg, naloxone .01 mg/kg/inj  
1: 5 sessions 2: 2 sessions

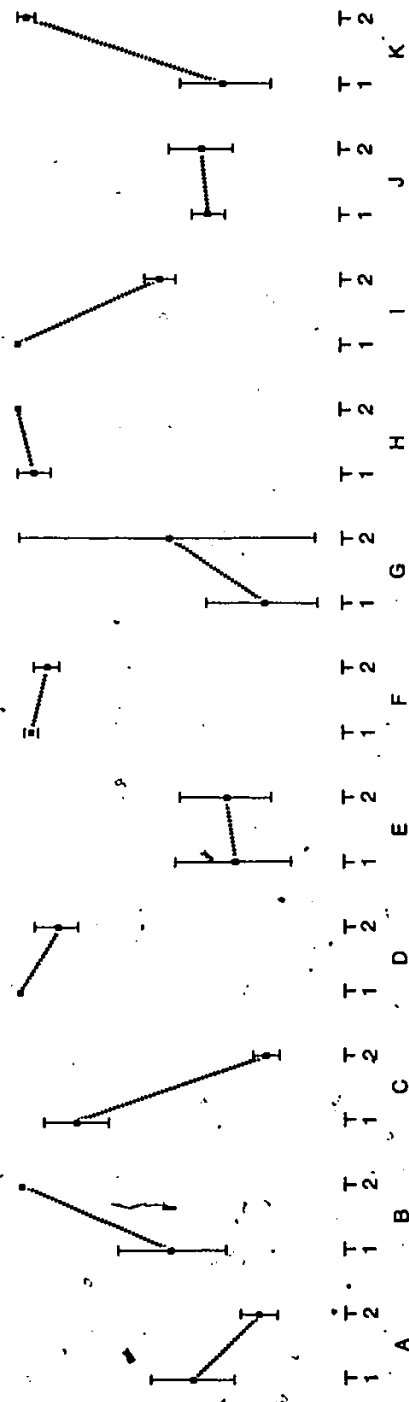
Condition K: no.morphine pretreatment; naloxone .01 mg/kg/inj  
1: 5 sessions                      2: 6 sessions

MONKEY 224

RESPONSES/SECOND



TOTAL INJECTIONS



CONSECUTIVE CONDITIONS

C- Morphine pretreatment; naloxone (.01 mg/kg/inj). Performance again was marked by high variability during reinstatement of morphine-dependence (C,1). Responding to escape/avoid naloxone was at .2 responses/sec; a mean of 83.8 inj/session were completed. For the final 12 sessions, .6 responses/sec were made and only 24.3 inj/session were delivered (C,2). This stable performance was similar to that of A,2 in which the same experimental conditions prevailed.

D- Morphine pretreatment; saline. While maintaining morphine-dependence, a saline control substitution was made. Responding immediately decreased to .1 responses/sec (D,1) and settled at this rate for the duration of the substitution (D,2). Initially, 100 inj/session of saline were delivered, dropping to 88.6 for the last five sessions during which time performance was also more variable.

E- Morphine pretreatment; dl-cyclazocine (.003 mg/kg/inj). When dl-cyclazocine injections were delivered non-contingently, monkey 224 produced, during the transition period, a mean of .5 responses/sec and tolerated 35 drug inj/session (E,1). Escape/avoidance behaviour was highly variable during transition as well as the final eight sessions. Responding decreased slightly to .4 responses/sec (E,2) during this last series of sessions; 36.8 inj/session on the average were delivered.

F- Morphine pretreatment; dl-cyclazocine vehicle. This control-solution substitution was carried out while monkey 224 was morphine-dependent. An immediate decrease in escape/avoidance responding to

.2 responses/sec was observed and 97.4 inj/session of dl-cyclazocine vehicle were completed (F,1). The response rate remained the same for the remaining five sessions although a mean of 91.8 inj/session were delivered.

G- Morphine pretreatment; dl-cyclazocine (.003 mg/kg/inj).

A second determination was made of responding to escape/avoid dl-cyclazocine when sessions followed a morphine injection. As in the initial determination (E) responding was highly variable, particularly so for the datum point (G,2) which represented only two sessions. For the first five sessions (G,1), .1 responses/sec were produced while 25.2 inj/session of dl-cyclazocine were tolerated. Responding increased to .3 responses/sec for the final sessions; 54 inj/session being completed (G,2).

H- No morphine pretreatment; dl-cyclazocine (.003 mg/kg/inj).

Morphine injections were discontinued while dl-cyclazocine injections continued to be delivered non-contingently. Lever-pressing diminished quickly to .1 responses/sec during the abstinence period (H,1) and stabilized at 0 responses/sec during the final four sessions (H,2). Initially, monkey 224 tolerated 94.8 inj/session of dl-cyclazocine (H,1) but finally allowed all 100 injections to be completed (H,2) while in the post-dependent state.

I- Morphine pretreatment; dl-cyclazocine (.003 mg/kg/inj).

Pre-session morphine injections were reinstated for a third evaluation of escape/avoidance responding for dl-cyclazocine. During transition to the morphine-dependent state, monkey 224 produced no

responses and tolerated all 100 inj/session (I,1). For a further 19 sessions, an average of .3 responses/sec were made to escape/avoid dl-cyclazocine; 56.2 inj/session were completed (I,2). These results for the stabilized sessions were comparable to the earlier determination, G,2, but showed a greater number of inj/session completed on the average than E,1; E,2 and G,1. In addition, variability of performance was considerably lower for condition I than for the previous similar conditions.

J- Morphine pretreatment; naloxone (.01 mg/kg/inj). Since monkey 224 did not respond to escape/avoid more than 44% of the dl-cyclazocine injections, a subsequent naloxone substitution was made to determine if this behaviour was attributable to dl-cyclazocine in particular, or would also be seen in response to naloxone injections. The animal worked to escape/avoid naloxone at .5 responses/sec for the duration of the experimental manipulation (J,1 & J,2). The average inj/session tolerated was also relatively consistent throughout, with 41.2 naloxone injections delivered per session for the first five days and 43 for the final two days. Variability in performance was somewhat greater for the second datum point representing, as it did, only two sessions. Although monkey 224 responded to escape or avoid more naloxone injections than cyclazocine injections, more naloxone was tolerated in this substitution than in the stable sessions of A and C.

K- No morphine pretreatment; naloxone (.01 mg/kg/inj). When morphine injections were discontinued in a final series of sessions,



escape/avoidance behaviour immediately increased to 1 response/sec during the transition period (K,1); an average of 35.6 inj/session was tolerated. As the abstinence syndrome subsided, responding decreased to .1 responses/sec and 96.3 inj/session of naloxone were completed (K,2). Both the variability of the transition period and stability of the final performance were comparable to condition B in which morphine pretreatment was withdrawn while naloxone injections continued to be delivered non-contingently.

In summary, monkey 224 responded to terminate the stimulus-complex associated with injections of naloxone while in a morphine-dependent state. In a third determination however, a relatively greater number of naloxone injections was tolerated. Naloxone injections were not escaped or avoided when the animal was in a post-dependent state. Injections of dl-cyclazocine were likewise tolerated after morphine pretreatment was discontinued. While morphine-dependent, this animal generally escaped/avoided 40-80% of the dl-cyclazocine injections. However performance was highly variable for two of the three determinations. Injections of saline and dl-cyclazocine vehicle were consistently tolerated while monkey 224 was morphine-dependent.

The general pattern of results for the three animals was the same. All monkeys responded to escape or avoid non-contingent injections of naloxone and dl-cyclazocine when experimental sessions were preceded by a morphine injection. When morphine was withdrawn

and a post-dependent state established, the animals did not terminate or avoid injections of either drug. Both control solutions (i.e., saline and dl-cyclazocine vehicle) were tolerated by all monkeys while they were morphine-dependent.

There were some notable individual differences in responding to terminate the stimulus-complex that prevailed irrespective of both pretreatment regime and drug substitutions. For example, in comparing the upper graphs (responses/sec) for the three animals (Figs 3, 4 and 5) it was evident that the overall response rate varied. The lever-pressing of monkey 222 was almost twice as frequent as that of monkey 224 throughout the experiment, while monkey 221 responded at rates between the other two.

Despite these individual differences in tendency to lever-press, response rates and inj/session completed were alike for all animals when saline and dl-cyclazocine vehicle substitutions were conducted. Responding typically decreased to between 0 and .2 responses/sec while more than 86% of the injections were tolerated.

Results of dl-cyclazocine escape/avoidance under conditions of morphine-dependence revealed a consistent phenomenon across all three animals. More injections of dl-cyclazocine were tolerated in the final determination (I) than in the previous two series (E & G). Monkeys 221 and 222 responded at between .6-.8 responses/sec allowing only 5-14.6 inj/session to be delivered during conditions E, 2 and G, 2. For datum point I, 2, 42.3-65.7 inj/session were tolerated while

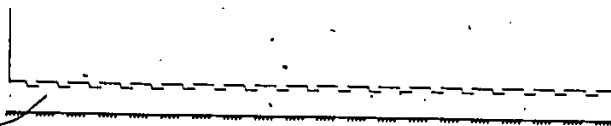
responding decreased to .3 responses/sec for monkey 221. Monkey 222, on a higher response-requirement regime (FR 30), increased responding to 1.2 responses/sec but still tolerated more drug injections. The performance of monkey 224 ranged between .3-.4 responses/sec with considerable variation over the three determinations; the average inj/session completed, increased in the second determination and remained approximately the same in the final series. This animal generally tolerated the greatest number of injections of dl-cyclazocine throughout the experiment.

Figure 6 contains representative cumulative recordings of the experimental conditions in which control-solution substitutions were conducted. A and B show typical sessions of saline and dl-cyclazocine vehicle escape/avoidance respectively, for monkey 221. Each downward deflection on the cumulative recording marked the beginning of the 60 sec time-out. Each upward deflection marked time-in, during which the pen moved vertically with each response. Each diagonal stroke of the event pen represented an injection begun. Both sessions shown followed morphine pretreatment and all 100 injections were delivered. Monkey 221 did not produce any responses during the saline substitution; 21 responses were made during the dl-cyclazocine vehicle session. Records C and D show the performance of monkey 222 under the same experimental conditions. They illustrate the individual differences in tendency to lever-press. This animal also allowed all 100 available injections of both saline (C) and dl-cyclazocine vehicle

Figure 6

Representative cumulative-response recordings of experimental sessions in which control-solution substitutions were conducted. Each downward deflection of the cumulative recording pen marked the commencement of the 60 sec time-out period. Each upward deflection marked time-in. Each diagonal stroke of the event pen represented an injection begun. Records A and B show the response of monkey 221 to saline and dl-cyclazocine vehicle injections respectively. All 100 injections were delivered in both sessions. Records C and D show the performance of monkey 222 under the same experimental conditions and illustrate the individual differences in tendency to lever-press. All 100 injections of saline (C) and dl-cyclazocine vehicle (D) were delivered although monkey 222 produced many more responses than did monkey 221.

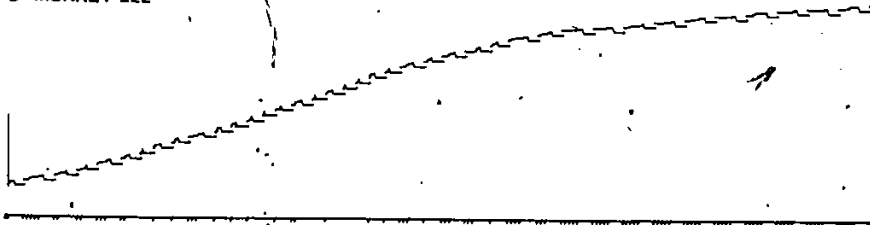
A MONKEY 221



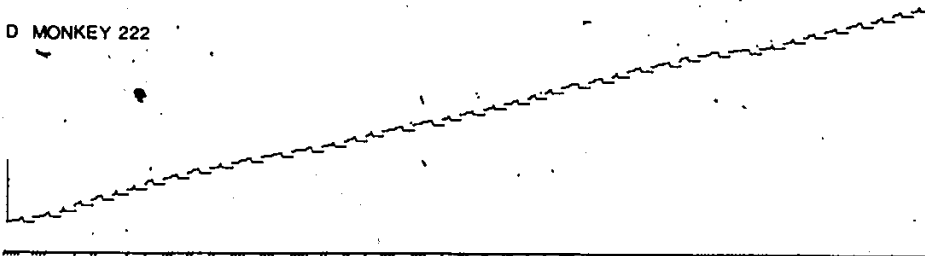
B MONKEY 221



C MONKEY 222



D MONKEY 222



500 RESPONSES

20 MINUTES

(D) to be delivered. In contrast with monkey 221 however, 342 and 405 responses were made during the time-in components of the respective sessions.

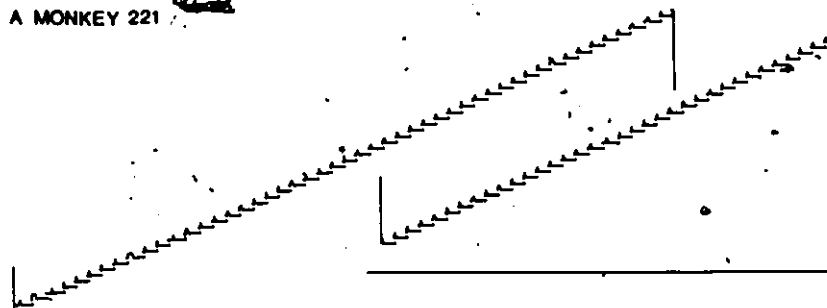
Figure 7 illustrates the effects of morphine pretreatment and discontinuation of pretreatment on responding to escape/avoid injections of naloxone. Record A for monkey 221 and C for monkey 224 show the usual pattern of responding seen for all animals when morphine injections preceded the experimental sessions. A few injections were commonly delivered at or near the beginning of the session while responding to avoid subsequent injections was orderly and consistent for the remainder (the graphs form a straight line). Records B and D illustrate normal steady-state performances observed when morphine had been withdrawn and naloxone was delivered non-contingently. In B, for monkey 221, all 100 injections of naloxone were tolerated despite 473 time-in responses. In D, monkey 224 produced only 48 responses while 100 injections were delivered.

In Figure 8 are presented cumulative recordings for monkey 221, showing experimental manipulations with dl-cyclazocine under conditions of morphine pretreatment or discontinuation of pretreatment. Record A represents a performance typical of all animals during the first and second determinations of dl-cyclazocine escape/avoidance when morphine pretreatments were given. Several drug injections were tolerated at the beginning of the session and then responding to avoid further injections became steady and even. B illustrates the usual results when morphine pretreatment was discontinued and dl-cyclazocine continued to be delivered. In this example, monkey 221 made 209

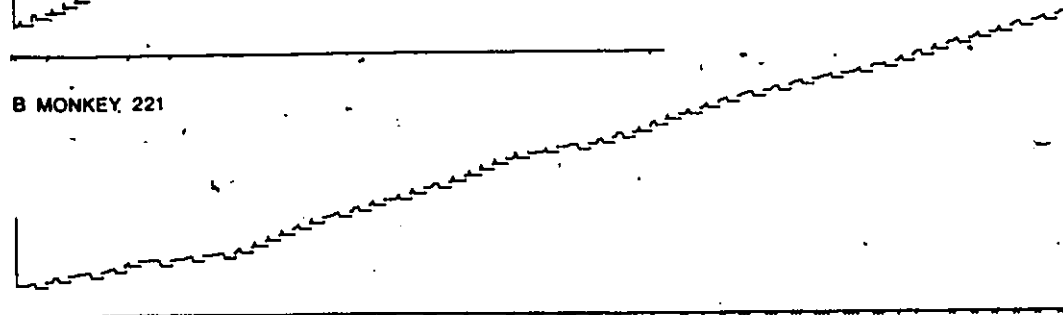
Figure 7

Cumulative-response recordings showing the performances of monkeys 221 and 224 under conditions in which morphine pretreatment was given (A and C) and then discontinued (B and D) while non-contingent injections of naloxone (.01 mg/kg/inj) were delivered. When morphine injections preceded the session, monkey 221 (A) and monkey 224 (B) typically tolerated several naloxone injections at the beginning of the session and then responded steadily to avoid further drug delivery. When morphine was withdrawn, the post-dependent animals tolerated all 100 naloxone injections. Monkey 221 (B) continued to respond, while allowing injections to be delivered while the responding of monkey 224 (D) underwent experimental extinction.

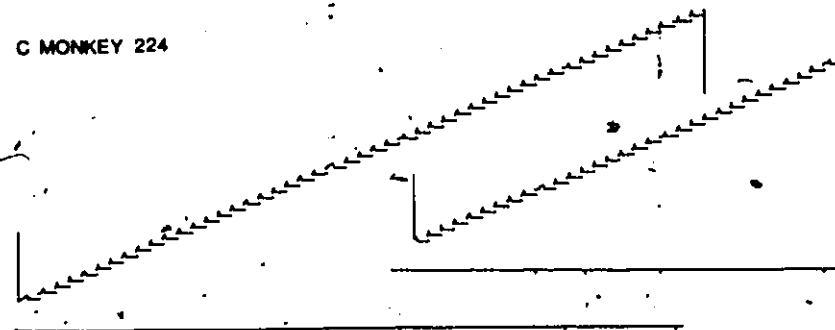
A MONKEY 221



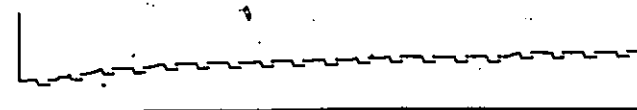
B MONKEY 221



C MONKEY 224



D MONKEY 224



500 RESPONSES

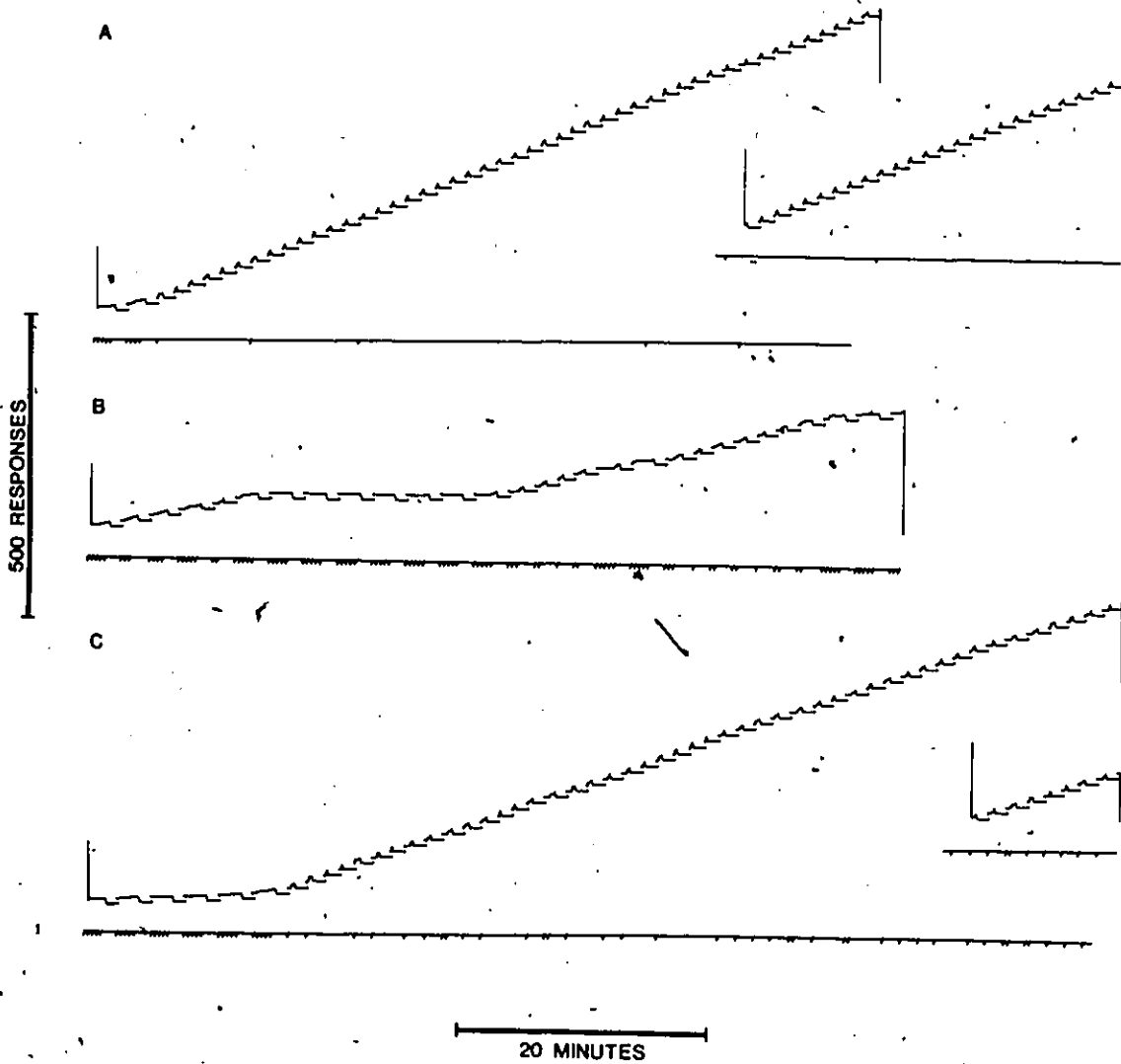
20 MINUTES



Figure 8

Cumulative-response recordings for monkey 221 showing responding to escape or avoid injections of dl-cyclazocine (.003 mg/kg/inj) under conditions of morphine pretreatment or discontinuation of pretreatment. When morphine pretreatment was given (A) the animal reliably avoided dl-cyclazocine after receiving several injections at the beginning of the session. Responding decreased when morphine pretreatment was discontinued (B) so that all 100 dl-cyclazocine injections were delivered. Record C shows the change in responding that was observed during the third determination of the aversiveness of dl-cyclazocine. More injections were tolerated when the session started and further drug injections were delivered consistently throughout the remaining trials.

MONKEY 221



responses while allowing all 100 injections to be completed. Record C is included as an example of the change in responding noted previously; that is, the increase in number of injections of dl-cyclazocine delivered during the third determination of stimulus-complex termination. Typical of the performances of all animals, monkey 221 produced 577 time-in responses while allowing 76 drug-injections to be completed, even though the session followed a morphine pretreatment.

A discussion of the preceding results of the main experiment as well as those of the preliminary training and pilot work follows in Chapter IV.

## CHAPTER IV

### DISCUSSION AND CONCLUSIONS

To maintain continuity and for easy reference to the methods and results chapters, the following discussion will be divided into three sections: Preliminary Training (Electric-Shock Escape/Avoidance), Pilot Work (Discrete-Trials Drug Escape/Avoidance), and the Main Experiment (Stimulus-Complex Termination).

#### Preliminary Training (Electric-Shock Escape/Avoidance)

The electric-shock escape/avoidance training before catheterization was undertaken in preparation for replicating Hoffmeister and Wuttke's work (1973). Their rationale for electric-shock training was to establish in the behavioural repertoire, responding to terminate an aversive stimulus. Once learned, this behaviour would generalize to drug injections (but not to saline) as a measure of the aversiveness of the drug. Hoffmeister consistently used electric-shock training in research in which the experimental animals were morphine-naive and had not been trained in drug self-administration; that is, the monkeys were not maintained in a morphine-dependent state nor had they previously received any morphine in their experimental histories (Hoffmeister & Wuttke, 1974; Hoffmeister, 1975; Hoffmeister & Wuttke, 1976). For experiments in which morphine-dependence was a variable, electric-shock training was not used. Animals were typically trained to self-administer morphine until

tolerance and dependence developed. Physiological dependence was then maintained either by programmed self-administration sessions or by daily intramuscular injections. The negative-reinforcement schedule of drug-injection termination was subsequently introduced without prior training to terminate an aversive stimulus (e.g., Goldberg et al., 1971; Kandel & Schuster, 1977). Since the first goal of the present research was to examine the aversiveness of dl-cyclazocine in squirrel monkeys that had not previously received morphine, an electric-shock escape/avoidance procedure according to Hoffmeister and Wuttke (1973) was adopted. The procedures were identical except that sessions were 50 minutes in length rather than two hours and the monkeys were trained on an FR 10 schedule of stimulus termination rather than FR 1.

As predicted by Hoffmeister and Wuttke's results, animals reliably escaped or avoided most of the scheduled electric-shock presentations within 12 days of training (Table 1). The mean number of total responses decreased in the second six days as expected, as responding came under discriminative control of the stimulus complex. When electric-shock presentation was discontinued, extinction of responding was established in approximately two weeks, consistent with the time taken in Hoffmeister and Wuttke's study. When electric-shocks were first discontinued, both avoidance and escape responding generally increased as the animals attempted to terminate the stimulus light previously associated with electric-shock. After several

sessions of exposure to the extinction contingency however, responding decreased as illustrated in Figure 1 (D).

#### Pilbt Work (Discrete-Trials Drug Escape/Avoidance)

After the monkeys had been trained to terminate electric-shock or the red light conditioned-stimulus, and had been catheterized, sessions were begun in which drug injections replaced electric-shock presentation. As expected, injections of physiological saline were not aversive and were tolerated by all monkeys. Likewise, the vehicle in which dl-cyclazocine was dissolved was also tolerated. Consistent with Hoffmeister and Wuttke (1973), injections of naloxone (.01 mg/kg/inj) were not escaped or avoided by the monkeys but were tolerated somewhat less than saline. Downs and Woods (1976) were the only investigators to show that naloxone was escaped by non-dependent rhesus monkeys. However, the drug doses necessary to support responding were over 1000 times greater than those maintaining similar behaviour in dependent animals. This was further evidence of the fact that large enough doses of any drug will have the general effect of disrupting behaviour.

When injections of dl-cyclazocine (.005 mg/kg/inj) were substituted for dl-cyclazocine vehicle in the present experiment, animals continued to tolerate drug injections at the same levels as for naloxone; that is, they tended to escape or avoid a few more dl-cyclazocine injections

than either saline or dl-cyclazocine vehicle. Doses of .01 and .0025 mg/kg/inj of dl-cyclazocine were consistently escaped or avoided by Hoffmeister and Wuttke's animals. The dose used in the present research falls between these two and would be expected to be aversive had it been used by Hoffmeister and Wuttke. They also found that a dose of .001 mg/kg/inj was terminated but that the smallest dose used, .0001 mg/kg/inj, was tolerated like saline. At first glance, these results suggested that perhaps higher doses of dl-cyclazocine might be necessary to initiate and maintain escape/avoidance behaviour in the squirrel monkey. Since it was clear that comparable doses of dl-cyclazocine were causing different results in rhesus and squirrel monkeys subjected to the same experimental procedure perhaps a species-specific effect was a critical determinant. Indeed, non-contingent injections of dl-cyclazocine had different physiological effects in the two species. Hoffmeister and Wuttke reported that the drug injections did not produce salivation or vomiting in any of their rhesus monkeys but that the animals were highly sedated during the first few days, then began to terminate injections on the second or third day of experimental sessions. In the present work however, under repeated injections of dl-cyclazocine, squirrel monkeys salivated profusely and vomitted, appearing to be completely debilitated while in the experimental chamber. Recovery took two to three hours after experimental sessions terminated. The strong muscle relaxant effect of the drug may have been so potent

as to make lever-pressing behaviour virtually impossible so that responding did not begin even after several consecutive sessions. Villarreal (1973) reported a similar effect when non-dependent rhesus monkeys received injections of .5 mg/kg of cyclazocine s.c.. With this much higher dose, animals were totally immobile in their home cages for two to three hours; but with chronic injections, tolerance developed to these central-relaxant effects. No evidence of tolerance to the severe effects of dl-cyclazocine was seen in one animal tested for four consecutive days in the current study. It is not known whether tolerance would have developed over an extended period of exposure to the drug. It could not be concluded then, that dl-cyclazocine was aversive to morphine-naive rhesus monkeys but not to squirrel monkeys; and clearly, a higher drug dose in the squirrel monkey would not have initiated escape or avoidance behaviour, considering the debilitating direct muscle-relaxant effects. On the other hand, if a species-specific effect was responsible for the divergent observations, perhaps a lower dose of cyclazocine could be found that would maintain escape/avoidance but not produce debilitating direct effects. A still lower dose might be tolerated as it was in the rhesus monkey, again without side effects.. Such hypotheses remain to be tested.

Since dl-cyclazocine had not been escaped or avoided by squirrel monkeys as it had in rhesus monkeys, the Tang and Morse (1976) procedure was adopted to allow further exploration of the possible aversive properties of this drug.



### Main Experiment (Stimulus-Complex Termination)

Experimental conditions were revised so that brief drug injections (of 1 sec duration) were scheduled to occur every 20 sec after the onset of a green light and masking noise. Five injections, in the absence of fixed-ratio responding, were followed by an automatic 60 sec time-out. Monkeys could either escape or avoid injections by completing the FR 10 requirement. Under these conditions the possible aversive properties of dl-cyclazocine were compared to those of naloxone under conditions of morphine-dependence and post-dependence.

Despite minor individual differences in tendency to lever-press to terminate the stimulus-complex, naloxone injections (.01 mg/kg/inj) were reliably escaped/avoided when the monkeys were morphine dependent. On the other hand, saline-control injections were not terminated under the same conditions of chronic morphine pretreatment. When morphine was withdrawn and animals were in a stable, post-dependent state, naloxone injections were tolerated like saline. Results strongly suggested that it was indeed the state of morphine dependence that determined whether or not naloxone was aversive and not attributable merely to acute morphine pretreatment. This was indicated by experimental condition C (see Figs 4, 5, and 6) when morphine dependence was re-established after a period of post-dependence. During the transition to tolerance and dependence (C,1) more injections of naloxone were tolerated than when the dependent state had stabilized (C,2). If dependence had not been a critical determinant of the aversiveness of naloxone,

there would have been an immediate response to terminate naloxone injections after acute morphine pretreatment. The present results were in agreement with those found for morphine-dependent rhesus monkeys by Goldberg et al (1971), Downs and Woods (1975, 1976) and Woods et al. (1975) in which both discrete and continuous injections of naloxone were avoided or terminated. This study has extended previous information on naloxone aversiveness to include the post-dependent animal.

When dl-cyclazocine injections (.003 mg/kg/inj) were delivered without reference to behaviour, they were tolerated when the animals were in the stable, post-dependent state. Like the morphine-naive condition of the animals in the pilot work, post-dependence was not conducive to maintaining stimulus-complex termination. It is interesting to note here, that Kandel and Schuster (1979) found that in post-dependent rhesus monkeys, continuous injections of nalorphine continued to be escaped for at least a month following morphine withdrawal. Rather than attributing this behaviour to an inherent aversive property of nalorphine, the authors concluded that an increased sensitivity to the negative-reinforcing properties of nalorphine developed as a result of previous morphine dependence. While post-dependent squirrel monkeys tolerated dl-cyclazocine in the present experiment, they did not salivate profusely or vomit when the drug accumulated (in contrast to the pilot work) but did exhibit the same strong, muscle-relaxant direct effect. When morphine-

dependence was established, dl-cyclazocine injections were clearly aversive in experimental conditions E and G. The control solution, dl-cyclazocine vehicle was not responsible for the aversiveness of dl-cyclazocine in the morphine-dependent monkey, since it was tolerated like saline. Similar to results with naloxone, the aversiveness of dl-cyclazocine seemed to be due to the presence or absence of morphine dependence rather than to an inherently aversive property of the drug itself. In addition, results suggested that simply the presence of acute morphine was not responsible for maintaining stimulus-complex termination; physiological dependence on morphine was important. This was seen in experimental condition I when morphine-dependence was re-established after a period of post-dependence. Monkeys 221 and 224 tolerated more dl-cyclazocine during the transition period than during the final sessions of stable morphine-dependence (the experiment was terminated before monkey 222 completed this manipulation). In this final determination of the aversiveness of dl-cyclazocine, the animals' behaviour changed so that more dl-cyclazocine was tolerated even though morphine-dependence had been established and maintained. This suggested that perhaps after protracted exposure, dl-cyclazocine injections were no longer as aversive as they had been initially. Indeed, the monkeys were not severely debilitated as they had been during the pilot work when dl-cyclazocine was first delivered.

The pattern of responding was also significantly different. During the pilot work, the animals typically tolerated several drug

injections at the beginning of each session, then avoided or escaped dl-cyclazocine for a few trials and finally tolerated all remaining injections, being unable to lever-press due to the drug accumulation. In the main experiment (condition I) this cessation of responding was not seen. After tolerating the first few cycles of dl-cyclazocine delivery, responding began and remained at a steady rate. Completed drug injections were evenly spaced throughout the session. Failure to escape or avoid most of the dl-cyclazocine injections could not be explained by the direct effects of the drug.

In order to determine whether or not this failure to terminate drug injections at previous rates was specific to dl-cyclazocine, injections of naloxone (.01 mg/kg/inj) were substituted in two animals. Responding to terminate the stimulus-complex immediately increased from .3 responses/sec for dl-cyclazocine to .9 response/sec for naloxone (monkey 221). Monkey 224 had also been responding at .3 responses/sec to terminate dl-cyclazocine injections and increased this to .5 responses/sec when naloxone was substituted. The failure to continue to terminate dl-cyclazocine at previous rates then, did not generalize to naloxone but was specific to the effects of dl-cyclazocine.

It has been well documented in human clinical studies that tolerance develops to the agonist properties of cyclazocine, including the central depressant effect, subjective psychotomimetic changes, somnolence and irritability (e.g., Martin et al., 1965; Fink et al., 1973). No human or animal studies, to date, have reported tolerance

to the antagonist effects of the drug. In fact, Martin, Gorodetzky and McClane (1966) found that in human subjects, tolerance did not develop to the ability of cyclazocine to antagonize the pharmacological actions of morphine. Subjects received chronic injections of cyclazocine which consistently antagonized the toxic and euphoric effects of large doses of heroin and morphine. This of course was a different experimental procedure so that a direct comparison with the negative-reinforcement procedure was not possible. Nevertheless, it was evident that these results with the squirrel monkey were unique. Based on the assumption that morphine antagonist drugs are aversive in dependent organisms due to their ability to precipitate the abstinence syndrome, the current results suggested that dl-cyclazocine did not continue to precipitate abstinence after prolonged sequences of delivery and was therefore tolerated to a greater degree in the morphine-dependent squirrel monkey.

It was possible that a higher dose of cyclazocine might have been more aversive and would have been escaped or avoided. Preliminary results of such observations with squirrel monkeys (Stretch; Note 1) showed that in morphine dependent animals, responding was reliably maintained so that most injections of dl-cyclazocine (.01 mg/kg/inj) were avoided or escaped.

When morphine was withdrawn, animals in a stable post-dependent state continued to respond to terminate injections of dl-cyclazocine for an extended period. These observations were similar to those mentioned above in which post-dependent rhesus monkeys continued to escape nalorphine injections (Kandel & Schuster, 1977).

The fact that a larger dose of dl-cyclazocine was consistently escaped or avoided in morphine-dependent animals suggested an explanation to account for the decrease in aversiveness of the .003 mg/kg/ inj dose. It was possible that over the six months of chronic morphine pretreatment, tolerance developed to the dose of morphine administered (10 mg/kg i.m.). In effect, the low-grade physiological dependence engendered by this dose initially, might have diminished over time due to the well-documented characteristic of tolerance to the central-depressant effects of morphine. If this was indeed the case, then the level of morphine-dependence would not have been sufficient to result in a severe abstinence syndrome when a small dose of dl-cyclazocine was delivered. Naloxone, however, continued to be aversive with this hypothesized reduced degree of physiological dependence. This may be explained by the fact that a much larger dose of naloxone was used (.01 as opposed to .003 of dl-cyclazocine).

In the squirrel monkey, there is evidence that for equivalent doses, naloxone is a much more potent antagonist of the suppressant effects of morphine than is cyclazocine (Stretch & Henry, Note 2). So for the present research, a combination of the small dose of dl-cyclazocine and a possible diminished degree of morphine dependence might have resulted in an increased tolerance to dl-cyclazocine injections in monkeys receiving chronic morphine pretreatment. It is clear that further research is necessary to investigate the effects of both an increased dose of morphine and increased doses of dl-cyclazocine.

That continued exposure to dl-cyclazocine resulted in increased tolerance of the drug in morphine-dependent squirrel monkeys is an additional indication that Hoffmeister and Wuttke's (1973) original results for cyclazocine in the naive rhesus monkey were not consistently applicable to the present observations. While dl-cyclazocine has been shown to be aversive in morphine-naive rhesus monkeys and was not self-administered, it appeared that its aversiveness was not as clear cut in the squirrel monkey. In comparison to the negative-reinforcing properties of naloxone, either a larger dose of dl-cyclazocine might be necessary to maintain equivalent escape/avoidance behavior and/or a higher-grade physiological dependence might result in sharpening the aversiveness of dl-cyclazocine.

To conclude, the research was designed to investigate the negative-reinforcing properties of dl-cyclazocine, a morphine-antagonist drug with mixed agonist-antagonist effects. Squirrel monkeys were trained on an FR 10 negative-reinforcement schedule to terminate (escape or avoid) electric-shock presentations which were then replaced with different drug and control-solution injections delivered through a chronic intravenous catheter. Injections of saline, naloxone (.01 mg/kg/inj), dl-cyclazocine vehicle and dl-cyclazocine (.005 mg/kg/inj) did not maintain responding to terminate drug delivery. Accumulation of dl-cyclazocine by repeated, tolerated injections resulted in severely debilitating direct effects that prevented further lever-pressing to terminate subsequent injections. Tolerance to

these agonist effects did not develop over four consecutive sessions. It was suggested that while higher doses of dl-cyclazocine would certainly not have initiated escape or avoidance responding, lower doses might have maintained responding without side effects. Experimental conditions were altered to study the effect of morphine dependence and post-dependence on the negative-reinforcing properties of dl-cyclazocine as compared to naloxone, a standard morphine antagonist. Monkeys consistently escaped or avoided non-contingent injections of naloxone (.01 mg/kg/inj) while they were morphine dependent (10 mg/kg i.m. daily). When morphine was withdrawn, naloxone was tolerated like saline. dl-Cyclazocine (.003 mg/kg/inj) was likewise tolerated by animals in the post-dependent state. For two determinations while morphine-dependent, monkeys terminated the stimulus-complex associated with dl-cyclazocine injections. During a final series, following sessions in which dl-cyclazocine was tolerated by post-dependent monkeys, drug injections were tolerated to a much greater degree. It was hypothesized that a combination of a reduced grade of physiological dependence as well as the small dose of dl-cyclazocine accounted for the increase in the number of dl-cyclazocine injections delivered when animals were receiving chronic morphine pretreatment. A species-specific effect might be responsible for the observation that while dl-cyclazocine was aversive in naive rhesus monkeys; present results indicated that it did not have strong negative-reinforcing properties in naive, or post-dependent squirrel



monkeys. These results must be interpreted with caution as dose-effect curves remain to be established for the negative-reinforcing properties of dl-cyclazocine in morphine-naive, morphine-dependent and post-dependent squirrel monkeys. dl-Cyclazocine did not appear to have intrinsic aversive properties for the squirrel monkey. Indeed, morphine-dependence had to be established before drug injections were consistently terminated.

2

#### Reference Notes

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Stretch, R., & Henry, M. Personal communication, November, 1978.

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APPENDIX I

Table 1

Mean Number of Injections Completed and  
Responses/Sec During Consecutive Experimental  
Conditions of the Main Experiment for Monkey 221.

| Condition | Injections Completed                        | Responses/Sec | N <sup>a</sup> |
|-----------|---------------------------------------------|---------------|----------------|
| A 1       | 20.0 ± 17.5 <sup>b</sup> ; 7.8 <sup>c</sup> | .6 ± .2; .1   | 5              |
| A 2       | 32.3 ± 8.9; 3.2                             | .5 ± .1; 0    | 8              |
| B 1       | 46.0 ± 37.1; 16.6                           | .4 ± .2; .1   | 5              |
| B 2       | 96.6 ± 6.1; 2.7                             | .2 ± .1; 0    | 5              |
| C 1       | 83.0 ± 17.2; 7.7                            | .2 ± .1; .1   | 5              |
| C 2       | 41.5 ± 33.5; 9.7                            | .6 ± .4; .1   | 12             |
| D 1       | 100.0 ± 0; 0                                | 0 ± 0; 0      | 5              |
| D 2       | 100.0 ± 0; 0                                | 0 ± 0; 0      | 5              |
| E 1       | 21.8 ± 10.7; 4.8                            | .6 ± .1; .1   | 5              |
| E 2       | 12.0 ± 1.9; .8                              | .6 ± .1; 0    | 5              |
| F 1       | 100.0 ± 0; 0                                | 0 ± 0; 0      | 5              |
| F 2       | 100.0 ± 0; 0                                | .1 ± 0; 0     | 5              |
| G 1       | 10.0 ± 2.3; 1.0                             | .7 ± .1; 0    | 5              |
| G 2       | 14.6 ± 2.7; 1.2                             | .6 ± 0; 0     | 5              |
| H 1       | 72.6 ± 42.3; 18.9                           | .3 ± .4; .2   | 5              |
| H 2       | 100.0 ± 0; 0                                | .1 ± 0; 0     | 5              |
| I 1       | 74.0 ± 13.7; 6.1                            | .3 ± 0; 0     | 5              |
| I 2       | 65.7 ± 18.4; 5.8                            | .3 ± .1; 0    | 10             |
| J 1       | 32.6 ± 10.4; 4.6                            | .5 ± .1; 0    | 5              |
| J 2       | 15.5 ± 4.9; 3.5                             | .8 ± .3; .1   | 2              |
| K 1       | 12.4 ± 8.4; 3.5                             | .9 ± .3; .1   | 5              |
| K 2       | 71.7 ± 34.9; 10.5                           | .3 ± .2; 1    | 11             |

<sup>a</sup> N refers to the number of sessions for each condition.

<sup>b</sup> denotes the standard deviation.

<sup>c</sup> denotes the standard error of the mean.

Table 2

Mean Number of Injections Completed and  
Responses/Sec During Consecutive Experimental  
Conditions of the Main Experiment for Monkey 222.

| Condition  | Injections Completed                         | Responses/Sec | N <sup>a</sup> |
|------------|----------------------------------------------|---------------|----------------|
| A 1        | 21.6 ± 29.9 <sup>b</sup> ; 13.4 <sup>c</sup> | .9 ± .4; .2   | 5              |
| 2          | 32.6 ± 20.3; 9.1                             | .7 ± .3; .1   | 5              |
| B 1        | 11.3 ± 13.5; 3.9                             | .9 ± .3; .1   | 12             |
| 2 (FR30)   | 60.9 ± 40.0; 15.1                            | .8 ± .7; .2   | 7              |
| 3          | 78.9 ± 29.6; 11.2                            | .5 ± .2; .1   | 7              |
| C 1        | 12.2 ± 6.8; 3.0                              | .9 ± .2; .1   | 5              |
| 2          | 8.2 ± 2.2; 1.0                               | 1.1 ± 0; 0    | 5              |
| D 1        | 98.5 ± 3.1; 1.4                              | .1 ± .1; 0    | 5              |
| 2          | 86.4 ± 16.3; 7.3                             | .2 ± .1; 0    | 5              |
| E 1        | 7.6 ± 2.4; 1.1                               | .9 ± .1; 0    | 5              |
| 2          | 9.2 ± 3.0; 1.4                               | .8 ± .1; 0    | 5              |
| F 1        | 97.8 ± 4.9; 2.2                              | .1 ± .1; 0    | 5              |
| 2          | 100.0 ± 0; 0                                 | .1 ± 0; 0     | 5              |
| G 1        | 18.2 ± 13.8; 6.2                             | .6 ± .1; .1   | 5              |
| 2          | 5.0 ± 2.6; 1.5                               | .8 ± .2; .1   | 3              |
| H 1        | 21.0 ± 17.4; 7.8                             | .8 ± .3; .1   | 5              |
| 2          | 44.7 ± 13.8; 3.4                             | .4 ± .1; 0    | 16             |
| 3 (FR30)   | 87.5 ± 16.2; 5.1                             | .6 ± .2; .1   | 10             |
| I 1 (FR30) | 42.3 ± 4.0; 2.3                              | 1.2 ± .1; 0   | 3              |

<sup>a</sup> N refers to the number of sessions for each condition.

<sup>b</sup> denotes the standard deviation.

<sup>c</sup> denotes the standard error of the mean.

Table 3

Mean Number of Injections Completed and  
Responses/Sec During Consecutive Experimental  
Conditions of the Main Experiment for Monkey 224.

| Condition | Injections Completed                         | Responses/Sec | N <sup>a</sup> |
|-----------|----------------------------------------------|---------------|----------------|
| A 1       | 47.8 ± 30.9 <sup>b</sup> ; 13.8 <sup>c</sup> | .2 ± .1; 0    | 5              |
| 2         | 27.3 ± 17.0; 6.0                             | .4 ± .2; .1   | 8              |
| B 1       | 54.4 ± 37.9; 17.0                            | .4 ± .3; .1   | 5              |
| 2         | 100.0 ± 0; 0                                 | 0 ± 0; 0      | 5              |
| C 1       | 83.8 ± 22.7; 10.1                            | .2 ± .1; .1   | 5              |
| 2         | 24.3 ± 16.0; 4.6                             | .6 ± .2; .1   | 12             |
| D 1       | 100.0 ± 0; 0                                 | .1 ± .1; 0    | 5              |
| 2         | 88.6 ± 16.3; 7.3                             | .1 ± .1; .1   | 5              |
| E 1       | 35.0 ± 40.7; 18.2                            | .5 ± .3; .1   | 5              |
| 2         | 36.8 ± 40.7; 14.4                            | .4 ± .3; .1   | 8              |
| F 1       | 97.4 ± 5.8; 2.6                              | .2 ± 0; 0     | 5              |
| 2         | 91.8 ± 9.9; 4.4                              | .2 ± 0; 0     | 5              |
| G 1       | 25.2 ± 39.1; 17.5                            | .1 ± .2; .1   | 5              |
| 2         | 54.0 ± 65.1; 46.0                            | .3 ± .4; .3   | 2              |
| H 1       | 94.8 ± 11.6; 5.2                             | .1 ± .1; 0    | 5              |
| 2         | 100.0 ± 0; 0                                 | 0 ± 0; 0      | 4              |
| I 1       | 100.0 ± 0; 0                                 | 0 ± 0; 0      | 5              |
| 2         | 56.2 ± 21.0; 4.8                             | .3 ± .1; 0    | 19             |
| J 1       | 41.2 ± 12.3; 5.5                             | .5 ± .1; 0    | 5              |
| 2         | 43.0 ± 14.1; 10.0                            | .5 ± .1; .1   | 2              |
| K 1       | 35.6 ± 31.9; 14.3                            | 1.0 ± .6; .3  | 5              |
| 2         | 96.3 ± 9.0; 3.7                              | .1 ± .1; 0    | 6              |

<sup>a</sup> N refers to the number of sessions for each condition.

<sup>b</sup> denotes the standard deviation.

<sup>c</sup> denotes the standard error of the mean.