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EFFECTS OF THE OPTICAL ISOMERS OF PENTAZOCINE AND CYCLAZOCINE UPON RESPONDING MAINTAINED BY SECOND-ORDER SCHEDULES OF INTRAVENOUS MORPHINE REINFORCEMENT IN SQUIRREL MONKEYS (SAIMIRI SCIUREUS)

by Margaret E. Henry

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CURRICULUM STUDORIUM

Margaret Elizabeth Henry, was born in Woking, England in 1943. She received her primary and secondary education in Red Deer, Alberta, graduating from Lindsay Thurber Composite High School in 1961. She attended the University of Alberta, School of Nursing in Edmonton where she received a Nursing Diploma in January, 1965. In 1974, she obtained a B.Sc. degree in Biology from the University of Ottawa and an Honours B.A. in Psychology from the University of Ottawa in 1976.

ABSTRACT

Effects of the optical isomers of pentazocine and cyclazocine upon responding maintained by second-order schedules of intravenous morphine reinforcement in squirrel monkeys (Saimiri sciureus).

Monkeys were trained trained under schedules in which either every 10th (FR 10) or 30th (FR 30) response during a fixed-interval of 50 min (FI 50 min) produced a brief presentation of an external signal (S), unaccompanied by an injection; the first ratio-requirement completed after expiry of the FI produced the signal (S) accompanied by an i.v. infusion of morphine. Morphine pretreatment (1-5.6 mg/kg i.m.) suppressed drug-seeking behaviour in a dose-dependent manner. Naloxone pretreatment (0.1 mg/kg) when given alone exerted no effect on response-rate; when given in combination with graded doses of morphine, morphine-induced suppression of drug-seeking behaviour was antagonized. l-Pentazocine (0.1-10 mg/kg i.m.) pretreatment suppressed responding more effectively than d-pentazocine at equivalent doses. l-Cyclazocine (0.01-1.0 mg/kg i.m.) suppressed responding whereas d-cyclazocine at equivalent doses did not. Pentazocine isomers failed to antagonize the effects of morphine pretreatment. l-Cyclazocine antagonized the effects of morphine pretreatment more effectively than pentazocine but d-cyclazocine was ineffective at equivalent doses. Cyclazocine and pentazocine differ in their capacity: (i) to suppress morphine-reinforced responding, and (ii) to antagonize

the effects of morphine pretreatment upon such patterns of drug-seeking behaviour. The stereoisomers of these drugs were found to be less potent than naloxone in reversing morphine-induced suppression of morphine-seeking behaviour.

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INTRODUCTION

Since the self-administration of dependence-producing drugs may result in adverse individual and/or public health and related social problems, it is important that chemical compounds possessing the capacity to induce dependence, should be identified as early as possible (Cameron, 1970). Sound biomedical techniques have been developed for the preclinical identification of substances possessing significant physical or physiological-dependence liability, but equal progress has not been made with regard to the definition and measurement of behavioural dependence upon psychoactive compounds (Dews, 1973; Schuster & Balster, 1973).

One of the approaches which appears to afford a necessary link in the preclinical assessment of the dependence-producing capacity of the major classes of drugs abused by man, is the utilization of operant procedures involving self-administration of drugs by infrahuman organisms (see Bulletin on Narcotics, 1977; WHO, 1975). Infrahuman subjects have been utilized in investigations dealing with drug abuse and dependence on psychoactive drugs for nearly fifty years. The biological and behavioural responses of the monkey to acute and chronic administration of psychoactive substances, in most respects, closely parallels their actions in man, and predictions for man, based on infrahuman data, have proved to be qualitatively accurate.

This finding has opened the way for studies on the mechanisms of tolerance, physiological dependence, and drug-taking and drug-seeking

behaviour in infrahuman subjects, and led to the more recent investigations on narcotic self-administration behaviour in rhesus and squirrel monkeys (see reviews by Schuster & Thompson, 1969; Schuster & Villarreal, 1968).

When monkeys are provided with indwelling intravenous catheters so that injections can be delivered directly into the animal's bloodstream, it has been found that a variety of drugs, known to engender problems of abuse in man, act as reinforcers for behaviour leading to self-injection by monkeys. Conversely, other drugs with negligible abuse liability in man, are not readily self-injected by monkeys.

These findings are significant because they indicate that the effects of drug injections as consequent events can be objectively analyzed in experimental animals under controlled conditions. Procedures in which the behaviour of infrahuman primates is maintained by drug injections are being applied as a part of preclinical screening programmes which attempt to assess the potential abuse liability of new drugs for man (Kelleher, 1975), that is, the identification of drugs with such strong reinforcing effects that, primarily because of their pharmacological properties, their intake leads eventually to physiological dependence in man.

The World Health Organization (1975) defined physical dependence as a state which is produced by chronic drug administration (usually opiates and their alternates) and is revealed by the occurrence of signs of physiological and behavioural dysfunction when the drug administration is sharply discontinued or when an opioid-antagonist (e.g.,

cyclazocine, naloxone) is administered. The abstinence or withdrawal syndrome is readily suppressed by further administration of an agonist. In addition to restoring the organism to its previous condition, continued administration of the drug leads to maintenance of physical dependence.

Although the reinforcing efficacy of opiates is markedly amplified when organisms are undergoing withdrawal, it is now generally recognized that these drugs can act as positive reinforcers independent of their ability to relieve the abstinence syndrome. That is, physiological dependence is a strong contributing factor to the strength and persistence of drug-seeking behaviour but is neither a necessary nor a sufficient antecedent condition for compulsive drug-taking behaviour (Deneau, Yanagita & Seevers, 1969; Pickens & Thompson, 1968; Spealman & Goldberg, 1978). In a review of the variables influencing the self administration of drugs, Schuster and Thompson (1969) established that in addition to pharmacological variables, other factors can influence an individual's propensity to become dependent on drugs. These include organismic variables such as antecedent conditions, current environmental circumstances, schedules of drug reinforcement and stimuli paired with drug administration.

These factors are also important in the relapse to opioid dependency by drug-dependent individuals. Wikler (1965, 1971) maintains that drug-taking behaviour and relapse are due to both classical and operant conditioning and unless drug-taking and drug-seeking behaviours are extinguished during treatment of opioid-dependence, relapse is

likely to occur. Drug-dependence programmes advocating the use of an opioid-antagonist in conjunction with an opioid-substitute (e.g., methadone) are based on the theory that the antagonist will block the pharmacological actions of the opioid resulting in the extinction of physiological dependence and drug-seeking behaviour, thereby decreasing the probability of future relapse. Contradictory results by Stretch (1977a, 1977b) suggest however that agonist-induced suppression of drug-seeking behaviour can be re-instated by appropriate doses of an opioid-antagonist.

One of the prime objectives of this paper was to extend the investigations of Stretch to a second-order schedule of morphine reinforcement. Under this schedule of morphine reinforcement, drug-injections occur only at the end of the session; behaviour is maintained throughout the session by stimuli paired with the drug-injection. As second-order schedules of drug-reinforced behaviour appear to be analogous to drug-seeking behaviour of drug-dependent humans it seemed profitable to extend the analogy to the problem of the suppression of self-administration of drugs. Thus morphine-pretreatment could be considered analogous to methadone substitution, and pre-session administration of an antagonist in conjunction with morphine similar to the programmes advocating administration of methadone in combination with narcotic antagonists.

Briefly, the problems under study in these experiments were: will morphine pretreatment suppress drug-seeking behaviour as distinct from drug-taking behaviour; and will drugs with morphine antagonist (naloxone), or mixed agonist-antagonist (cyclazocine, pentazocine)

properties reverse this agonist-induced suppression of drug-seeking behaviour? A more specific and detailed description of the objectives of these experiments follow the review of literature presented in Chapter I. The survey of the literature includes discussion of the main theoretical principles of operant conditioning, the variables determining the direction and extent of drug-induced changes in behaviour, an evaluation of second-order schedules as a preclinical tool in the assessment of drug-behaviour interactions and finally, an analysis of the behavioural effects of various narcotic and narcotic antagonist drugs. Chapter II provides a description of the experimental procedures used in these manipulations. The results are presented in Chapter III and discussed in Chapter IV.

CHAPTER I

REVIEW OF THE LITERATURE

A) Operant Conditioning: Drugs as Reinforcers

The search for more precise methods of behavioural control has led to the analysis of a set of variables which appear to contribute powerfully to the consequences of drug administration on behaviour. Broadly described, these variables may be identified as the relations between behaviour and its controlling environment, and the development of techniques that permit a high degree of experimental control over the behaviour of the individual has made it possible to explore and identify many of the contingencies that generate behavioural processes. These techniques have developed independently of pharmacological applications, but the precision, sensitivity and reproducibility in behavioural control which they provide have made it possible to extend the basic methodology. The conceptual framework for this animal experimental approach to the investigation of psychopharmacological relationship rests upon a simple principle: namely, the characteristics of an organism are to a considerable extent, at least, determined by what the environmental consequences of that behaviour have been in the past. The animal laboratory has provided an opportunity for the systematic analysis of orderly relations among behaviour segments within this framework and the term operant behaviour (Skinner, 1938) has been used to refer to behaviour which operates upon the environment in this fashion.

Operant conditioning techniques were early recognized as being extremely useful for studying the behavioural effects of drugs (Skinner & Heron, 1937) as these techniques provide a stable objective behavioural baseline that is reproducible and highly sensitive to the behavioural effects of drugs. This reproducibility of behavioural baselines is an essential requirement in the assessment of drug-behaviour interactions. Reproducibility among subjects within a given species, and between species, has been enhanced by selecting, for measurement and manipulation, a response whose topography is congenial to the organism, and one that the organism can perform and immediately be in a position to repeat; by selecting an environmental consequence or "reinforcement" that is appropriate to the particular individual, and by systematically limiting the experimental environment to permit stimulus control and specification (Brady, 1958; Sidman, 1959).

Operant behaviour is maintained or eliminated by its consequences. These consequences of behaviour are termed reinforcers. Reinforcers are the events that follow operant responses and determine whether the behaviour is maintained or eliminated. Reinforcers can be divided into two types, depending on the effects they produce. Positive reinforcers are events that maintain the responses that produce them, and negative reinforcers are events that decrease the probability of responses that produce them.

Reinforcers can be either presented or withdrawn depending upon an organisms behaviour. The process of presenting a positive

reinforcer and increasing the probability of occurrence of the behaviour immediately preceding it is called positive reinforcement. Withdrawal of a positive reinforcer produces a decrease in the probability of the behaviour that produced the withdrawal. The process of removing a positive reinforcer and decreasing the probability of responding is called punishment. An example of positive reinforcement is the response contingent presentation of food to a food-deprived rat; an example of withdrawing a positive reinforcer contingent upon a response (punishment) is the use of time-outs (TO's) whereby responses produce conditions under which positive reinforcers are not available. Likewise, a negative reinforcer can be presented or withdrawn contingent upon a response. Presentation of a negative reinforcer contingent upon a response, which thereby decreases the future probability of responding, is also punishment. The process of withdrawing a negative reinforcer contingent upon a response and thereby increasing the probability of responding is termed negative reinforcement. Thus both positive and negative reinforcement can produce increases in the probability of responding, while punishment, whether it is withdrawal of positive reinforcers or presentation of negative reinforcers, produces a decrease in responding (Skinner, 1953).

This paper is primarily concerned with events that increase the probability of a response occurring, that is, with positive reinforcers. Events as diverse as the presentation of food or water (e.g., Skinner, 1938), the electrical stimulation of the brain (e.g., Olds

& Milner, 1954), and the delivery of electric shock (e.g., Stretch, Orloff & Dalrymple, 1968) can similarly act in reinforcing operant behaviour under suitable conditions (Morse & Kelleher, 1970; Spealman & Goldberg, 1978). Good evidence is now available to show that the establishment and maintenance of operant responding reinforced by drug injections is comparable in principle, to the establishment of responding maintained by these other non-drug events. The earliest evidence that drugs might serve as reinforcers was a report that physically-dependent chimpanzees would engage in behaviour which led to the experimenter's administration of morphine (Spragg, 1940). With the advent of techniques permitting experimental animals to self-inject drugs intravenously, a large number of drugs from several pharmacologic classes has been shown to reinforce behaviour in experimental animals. For instance, the reinforcing efficacy of morphine, over a considerable dosage range, has been demonstrated in rats (e.g., Weeks, 1960, 1962; Weeks & Collins, 1964) rhesus monkeys (e.g., Deneau, Yanagita & Seevers, 1969; Goldberg, Hoffmeister, Schlichting & Wuttke, 1971, 1972; Goldberg, Morse & Goldberg, 1974), and squirrel monkeys (e.g., Stretch, 1977b; Stretch & Gerber, 1977). In a review on the self-administration of drugs, Schuster and Thompson (1969) note that both rats and monkeys have been shown to self-administer representative compounds from several of the major classes of psychotropic drugs that are illicitly self-administered by man including opioids such as morphine, methadone and codeine; sedative-hypnotics, such as barbiturates and alcohol; and psychomotor stimulants

such as cocaine, nicotine and the amphetamines. Conversely, other drugs, with negligible abuse liability in man, are not readily self-administered by laboratory animals; indeed, some psychoactive drugs such as chlorpromazine, will maintain responding that averts or terminates their delivery, indicating that such drugs may exert negative reinforcing properties (e.g., Hoffmeister, 1975; Hoffmeister & Goldberg, 1973).

In their review of variables influencing the self-administration of drugs, Schuster and Thompson (1969) established that, in addition to the pharmacological variables including reinforcing properties, the magnitude of reinforcement and drug interaction; other factors can influence an organisms propensity to self-administer drugs. These include organismic variables such as antecedent conditions, stimuli paired with the administration of drugs and schedules of reinforcement. The primary variables determining the direction and extent of drug-induced changes in behaviour that will be dealt with in the next two sections of this paper are stimuli paired with drug injections and schedules of reinforcement.

B) Stimuli Associated with Drug Injections Acting as Reinforcers

Behaviour is maintained, not only by the terminal reinforcer (such as a drug injection) which follows a response sequence, but also by stimuli which precede the terminal reinforcer. That is, stimuli which signal the availability of a reinforcer, thus acting as discriminative stimuli, acquire conditioned reinforcing properties

(Schuster, 1973). These conditioned reinforcers are powerful influences in controlling sustained behaviours where long periods elapse between successive terminal reinforcers such as occurs in the procurement, preparation and administration of a drug by human addicts (Kelleher, 1966; Schuster & Thompson, 1969; Goldberg, 1976b). Goldberg (1976b) reports that long sequences of drug-seeking and drug-taking behaviour are maintained by a combination of the intrinsic pharmacological properties of the abused drugs with environmental factors. A fundamental component in this interaction is the regular and predictable occurrence of environmental stimuli associated with the maintenance of drug-seeking and drug-taking behaviour.

The importance of the role of environmental stimuli in the maintenance of human drug-seeking and drug-taking behaviour was recognized as early as 1927 when Kleitman and Crisler investigated the effects of stimuli associated with injections of morphine. In their experiments with dogs, each daily morphine injection was preceded by the sound of a bell. After several pairings of the bell with the injection, the dogs salivated not only after the morphine injection, but also when the bell sounded prior to the injection. Repeated exposure to the sound of the bell without the morphine injections resulted in the gradual loss of this response, however the response was quickly re-established after further pairings of the sound of the bell and injections of morphine. In a review of experimental studies illustrating behavioural control by environmental stimuli associated with drug injections, Goldberg (1976b) reports that environmental stimuli

associated with injections of morphine can actually elicit the physiological effects of morphine originally elicited by the morphine itself. He gives as an example a study by Bykov (1957) in which the conditioned stimuli produce electrocardiogram and blood pressure changes initially produced by injections of morphine.

Several investigators have also demonstrated that stimuli associated with morphine injections can attenuate withdrawal symptoms in morphine-dependent organisms. For instance, Thompson and Schuster (1964) studied behaviour of morphine-dependent rhesus monkeys. Monkeys were conditioned on a complex multiple reinforcement schedule (FI-FR chain) to obtain food and avoid shocks. In addition, the animals self-administered 1 mg/kg of morphine every six hours. During a period when the opportunity to self-administer morphine was removed, the food-reinforced and shock-avoidance behaviours progressively deteriorated. A single morphine self-administration reinstated these behaviours. In a replication of this procedure, the animals were allowed to self-administer saline accompanied by a light which had previously been paired with morphine infusion. There was a temporary recovery of the food-reinforced and shock-avoidance behaviours indicating that the ameliorative effects of morphine had become conditioned to the light paired with morphine infusion.

Schuster and Woods (1968) examined the reinforcing properties of a light paired with morphine infusion in monkeys, which had previously self-administered morphine on a variable-interval schedule. A series of 24-hour extinction tests were conducted, in which responses

produced the light, previously paired with morphine, on a variable-interval schedule on one day, while on alternate days responses produced no consequence. On the days on which the light was presented, response rates were significantly higher than on the days when responding had no programmed consequence. Schuster and Woods (1968) concluded that the increases in response rate during the extinction conditions in the presence of the stimuli previously associated with morphine reinforcement were attributable to the conditioned reinforcing efficacy of these stimuli. Their reinforcing strength was assumed to be acquired through classical conditioning. Other investigators have reported similar evidence that the reinforcing effectiveness of a stimulus paired with a primary reinforcer, such as morphine infusion, is, in large part, the result of respondent or classical conditioning (e.g., Kelleher & Gollub, 1962; Kelleher, 1966b).

In the majority of experiments dealing with the control of behaviour by stimuli associated with the administration of morphine, the stimuli were paired either in association with morphine administration or during extinction, that is, once morphine administration had been discontinued. Therefore, the role of these stimuli in the control of behaviour could be assessed directly only during extinction. However, this can be circumvented with the use of second-order schedules which provide a means of analyzing the control of drug-seeking behaviour by scheduled brief presentations of stimuli associated with drug injections. Long, complex sequences of behaviour are

controlled throughout the experimental sessions by scheduled presentations of an exteroceptive stimulus that has been associated with drug injection; actual drug injection occurs (in the presence of the stimulus) only at the end of each session. Investigations utilizing second-order schedules will be discussed in the following section on schedules of reinforcement.

In addition to the role that environmental stimuli, associated with morphine injections, play in the control and maintenance of drug-taking and drug-seeking behaviour, it has been amply demonstrated that stimuli associated with the withdrawal syndrome may come to elicit withdrawal symptoms when presented alone. For instance, Wikler and Pescor (1967) placed rats in an environment in which they had previously experienced morphine-withdrawal symptoms, and observed abstinence signs. The number of "wet dog" shakes (a sign of acute withdrawal distress in rats) was significantly higher in rats that had experienced withdrawal in the environment than it was in controls. The cages associated with the withdrawal syndrome continued to elicit withdrawal symptoms in rats for 1-5 months after complete termination of morphine treatment. From these and other studies (e.g., Wikler, 1965) Wikler has developed a two-factor theory of relapse to opioid dependence. Briefly stated, Wikler has suggested (1965, 1971) relapse occurs due to (a) classical conditioning of physical dependence through repeated pairing of environmental stimuli and the occurrence of the withdrawal syndrome, and (b) reinforcement of operant behaviour (drug-seeking and drug-taking) through repeated reductions by

the drug of such withdrawal symptoms as developed during drug-taking intervals. He argues that relapse to drug-taking behaviour is generated by the failure of drug-treatment programmes to extinguish conditioned environmental stimuli associated with previous occasions of withdrawal and their relief by opioid self-administration. When post-dependent individuals return to their home environments, these conditioned stimuli could precipitate abstinence changes previously relieved by drug-taking behaviour. If this drug-taking behaviour had not been extinguished during treatment, the post-dependent individual may then respond to these abstinence changes, as he had during dependence, that is by self-administering the drug.

This theory is further supported by investigations of the behavioural and physiological effects of environmental stimuli paired with injections of narcotic antagonists in opioid-dependent subjects. In opioid-dependent subjects, but not non-dependent subjects, administration of an opioid-antagonist precipitates the withdrawal syndrome characteristic of abrupt termination of chronic morphine treatment. Irwin and Seevers (1956) were the first to provide experimental evidence that the morphine withdrawal syndrome could be elicited by a stimulus associated with injections of a narcotic antagonist, in this instance, nalorphine. In their studies, rhesus monkeys, physiologically dependent on morphine-like drugs, such as methodone, were subjected to a series of nalorphine-induced withdrawal episodes. Then the administration of the narcotic drugs was completely terminated. After one to two months of abstinence from the drug, about

25 percent of the animals continued to demonstrate withdrawal symptoms after subcutaneous injection of nalorphine. The abstinence-like response to nalorphine was also elicited when nalorphine was substituted by saline injections in these monkeys.

Investigations of this effect were conducted more recently by Goldberg and Schuster (1967). They demonstrated that a stimulus paired with an intravenous injection of a small nalorphine dose in physiologically-dependent monkeys, elicited withdrawal symptoms. Rhesus monkeys working for food on a fixed-ratio schedule were presented with a 5-minute tone followed by an infusion of nalorphine. After several sessions of pairings, the onset of the previously neutral stimulus (tone) was followed by complete suppression of the operant responding. In addition, the tone acquired the ability to produce signs of acute withdrawal distress, including salivation and vomiting. In an extension of these experiments, Goldberg and Schuster (1970) paired a stimulus (red light) with nalorphine injections. The chronic morphine treatment of monkeys in the preceding study was abruptly discontinued and the monkeys were tested monthly for persistence of the conditioned response. The presence of the light continued to suppress food-maintained responding and to produce conditioned heart rate decreases for two to four months. Persistent physiological changes have been found in both animals and humans after many months of abstinence from opioids (Martin, 1967). These findings agree with results obtained by Wikler (1965) and Wikler and Pescor (1967) and illustrate the long-lasting effect of environmental stimuli on behavioural and physiological responses in post-dependent subjects.

Conditions have also been described under which schedule-controlled behaviour can be maintained over long periods of time in morphine-dependent rhesus monkeys, when responses terminate a stimulus associated with intermittent schedules of brief presentations of a narcotic antagonist. Goldberg et al. (1971) showed that rhesus monkeys dependent on morphine would press a lever under a fixed-ratio schedule of termination of a stimulus light which had been associated with periodic intravenous injections of the narcotic antagonists, nalorphine and naloxone. Hoffmeister and Wuttke (1973) subsequently reported other conditions under which responses terminating a stimulus associated with injections of narcotic antagonists can function to maintain behaviour. Morphine-naive rhesus monkeys which had a history of terminating a stimulus associated with electric shock also terminated a stimulus light associated with intravenous infusions of nalorphine and cyclazocine, but responding that terminated a stimulus associated with intravenous infusions of naloxone did not differ from responding that terminated a stimulus associated with the injection of saline. Caution is needed in the interpretation of these results, however, since Pink and Stretch (1978) were unable to demonstrate cyclazocine-avoidance in post morphine-dependent squirrel monkeys. Goldberg (1975) reported that the critical factor maintaining behaviour leading to termination of a stimulus associated with the injection of narcotic antagonists is the presence or absence of physiological dependence on morphine. In the absence of physiological dependence on morphine,

negative reinforcing effects are not consistent among different narcotic antagonists. Narcotic antagonists such as pentazocine and propiram, which have weak antagonistic properties, have been repeatedly shown to maintain behaviour leading to self-injection (e.g., Hoffmeister & Schlichting, 1972; Goldberg et al., 1972; Woods & Villarreal, 1970), whereas narcotic antagonists such as nalorphine and cyclazocine, which exert more powerful antagonistic effects, generally fail to maintain behaviour leading to their injection (e.g., Deneau et al., 1969; Goldberg et al., 1972). In the presence of physiological dependence on morphine, the reinforcing effects of narcotic antagonists have been more consistent. Both narcotic antagonists with weak antagonistic properties and those with more potent antagonist-effects have been reported to maintain escape or avoidance behaviour. Goldberg et al. (1972) found that responding by morphine-dependent rhesus monkeys was maintained when it resulted in the termination of a stimulus associated with injections of either nalorphine, naloxone, pentazocine, or propiram, but was not maintained when it resulted in termination of a stimulus associated with injections of saline.

Downs and Woods (1976) have also shown that responding can be maintained by termination of naloxone infusion on a stimulus preceding an infusion. Responding was maintained in both morphine-dependent and non-dependent monkeys. However, the dose of naloxone required for response-maintenance was approximately 1000 times greater in the non-dependent monkey. Furthermore, smaller doses of naloxone

maintained higher rates of responding after previous exposure to a larger dose. These results emphasize both the importance of dose in maintaining responding and the history of the subject. Tang and Morse (1976) investigated the factors controlling termination of stimuli associated with injections of narcotic antagonists in morphine-dependent rhesus monkeys and concluded that a complex of interrelations between association of the stimulus with narcotic-antagonist injections, termination of the stimulus, the dose of narcotic antagonist, and the degree of morphine dependence could be demonstrated.

This section reviewed some of the ways in which environmental stimuli that have been associated with injections of narcotics or narcotic antagonists can come to modify and control behaviour. Many of the effects described here have been demonstrated with drugs from other pharmacological classes (Goldberg, 1976b). Environmental stimuli that occur in association with human drug-seeking and drug-taking behaviour play an important role in the development, control, and perpetuation of this behaviour.

C) Schedules of Reinforcement: Second-Order Schedules

One of the major theoretical concepts that has emerged in behavioural pharmacology to account for the behavioural effects of drugs is schedule-drug interaction. That is, an important variable influencing the effects of pharmacological agents upon operant behaviour is the schedule of reinforcement. The action of drugs, in fact,

seems to depend more upon the schedule-controlled pattern of responding than upon any other environmental influence (Goldberg, 1976a; Morse & Kelleher, 1966). There has been a substantial volume of research in this area in the past twenty years and several exhaustive reviews have been published (e.g., Kelleher & Morse, 1966; Spealman & Goldberg, 1978). An attempt will be made in this paper to review some of the major research that contributed to the generalization that ongoing patterns of responding engendered by different schedule contingencies are a fundamental determinant of drug action. Particular emphasis will then be given to the schedule of interest here, namely the second-order schedule.

Schedules of reinforcement are specifically those rules which govern the temporal and sequential relations between responses and reinforcers. These are many possible schedules of reinforcement, each engendering characteristic rates and patterns of behaviour which have been found to be highly reproducible across a wide range of species, response topographies, and consequent events. Although many pharmacological experiments have utilized the continuous reinforcement schedule (e.g., Deneau, Yanagita & Seevers, 1969; Goldberg, Hoffmeister, Schlichting & Wuttke, 1971), that is, each response results in an injection of a drug, many of the most interesting and important characteristics of operant behaviour are revealed when reinforcers are delivered intermittently (Morse, 1975; Spealman & Goldberg, 1978). Formal classification of intermittent schedules

is usually made on the basis of whether the reinforcer follows a given number of responses (ratio schedules) or follows a response after a given period of time has elapsed (interval schedules).

Studies of behaviour maintained by drug reinforcement have widely utilized a fixed-ratio (FR) schedule, in which reinforcement follows the occurrence of a constant number of responses (Goldberg, 1976b). Responding under this schedule is characterized by a pause before each initial response in the ratio, followed by a high sustained rate of responding until the ratio is completed. Characteristic fixed-ratio rates and patterns of responding can be maintained by a variety of events, including presentation of food (Ferster & Skinner, 1957; Holtzman & Villarreal, 1973; Thompson, Trombley, Luke & Lott, 1970), electric-shock (McKearney, 1970), and termination of a stimulus associated with aversive stimuli (Kelleher & Morse, 1964; Morse & Kelleher, 1966). Characteristic FR patterns of responding have also been maintained in rats and monkeys by intravenous infusion of a wide variety of pharmacological agents including psychomotor stimulants (e.g., Downs & Woods, 1974; Goldberg, 1973; Goldberg et al., 1971; Hoffmeister & Schlichting, 1972; Pickens & Thompson, 1968), opioids (e.g., Deneau, Yanagita & Seevers, 1969; Hoffmeister & Goldberg, 1973; Hoffmeister & Schlichting, 1972; Weeks, 1962; Weeks & Collins, 1964), narcotic antagonists (e.g., Hoffmeister & Schlichting, 1972; Schuster & Balster, 1973), and sedative-hypnotics (e.g., Deneau et al., 1969; Goldberg, Hoffmeister & Schlichting, 1971; Kelleher, 1975). Although characteristic fixed-ratio patterns of

responding have been maintained by drug injections in these studies, very often pauses in responding at the start of each ratio component have been longer and mean-response rates have been lower than those that characteristically develop under similar schedules of food presentation or termination of a stimulus associated with electric shocks. In one study, for example Hoffmeister & Schlichting (1972), responding by rhesus monkeys was maintained under a 10-response fixed-ratio schedule by infusions of several drugs, including morphine and cocaine. The maximal rate of responding maintained by morphine was approximately 0.05 responses per second; while that maintained by cocaine was about 0.12 responses per second. These low rates of responding most likely resulted from the 'generalized rate-decreasing effects' (Spealman & Goldberg, 1978) of the self-administered drugs which cumulated over the course of each three hour experimental session; rates of responding generally declined as the sessions progressed. Also cumulation of the rate-decreasing effects of the drugs appeared to have been directly related to their durations of action. The shorter-acting psychomotor stimulant, cocaine, maintained higher rates of responding than the longer-acting narcotic. This inverse relation of rate of response and duration of action was also observed in a study comparing rates of responding maintained under a continuous reinforcement schedule by infusions of several barbiturates with varying durations of action (Winger, Stitzer & Woods, 1975).

Under a second type of frequently studied schedule, termed an interval schedule, reinforcement follows the first response that

occurs after a constant minimum interval of time has elapsed (fixed-interval schedules) or after intervals of time have elapsed that vary from reinforcement to reinforcement around a given mean with a specified range (variable-interval schedules). Under variable-interval (VI) schedules, behaviour maintained by a variety of reinforcers is characterized by relatively constant responding at moderate rates (Ferster & Skinner, 1957; McKearney, 1972; Morse, 1966; Schoenfeld, 1970; Spealman & Goldberg, 1978). Although variable-interval schedules of drug infusion have not been studied extensively, responding has been maintained under these schedules by intravenous infusions of morphine (e.g., Schuster & Woods, 1968; Woods & Schuster, 1968) codeine (Carney, Llewellyn & Woods, 1977), cocaine (Pickens & Thompson, 1971, 1972), and ethanol (Carney, Llewellyn & Woods, 1977). Responding usually occurred at relatively constant rates between successive injections, but rates of responding often declined during the experimental session and, in some cases, ceased by the end of the session. It is again probable that generalized rate-decreasing effects of cumulative drug intake were responsible, to a great degree, for the progressive decline in responding over the course of the session.

In contrast to the relatively constant rates of responding characteristic of VI schedules, performance under fixed-interval schedules is characterized by a period of no responding at the beginning of each interval, followed by progressively-increased responding until the interval elapses. This characteristic pattern of positively-accelerated responding can be maintained in different species by a

variety of events, including reinforcement by food or water (e.g., Ferster & Skinner, 1957; Schoenfeld, 1970), presentation of electric-shock (e.g., Byrd, 1976; McKearney, 1974, 1975), and termination of a stimulus associated with electric shocks (e.g., Kelleher & Morse, 1964; Morse & Kelleher, 1966). It is interesting to note that responding under fixed-interval schedules is highly sensitive to both rate increasing and rate-decreasing effects of presession drug treatments (Iversen & Iversen, 1975; Kelleher & Morse, 1968; Spealman & Goldberg, 1978).

Although responding can be maintained under FI schedules by injections of morphine (Thompson & Schuster, 1964) and methohexital (Kelleher, 1975) or by presentations of ethanol solutions (Anderson & Thompson, 1974), only fixed-interval schedules of intravenous cocaine infusions have been studied extensively (e.g., Balster & Schuster, 1973; Goldberg & Kelleher, 1976, 1977; Pickens & Thompson, 1971, 1972; Spealman & Goldberg, 1978). It has been demonstrated that doses of cocaine below that which would disrupt the responding characteristic of fixed-interval schedules, will engender and maintain that characteristic pattern of responding despite a marked tendency to increase low rates of responding through its direct effects (see Kelleher, 1975).

Characteristic responding can be maintained under fixed-interval schedules of drug injection by doses that disrupt performances under fixed-ratio schedules (Spealman & Goldberg, 1978). This differential effect of drugs upon schedule-controlled behaviour was first reported Dews.

In 1955, Dews studied the effects of pentobarbital on fixed-ratio and fixed-interval performance in pigeons. For both schedules, response rate was increased by low drug doses and decreased by intermediate and high drug doses. However, at one dose level (1 mg), performance was differentially affected by the two schedule conditions. At this dose, response rate on the fixed-ratio schedule was increased by the drug, while being decreased on the fixed-interval schedule, both relative to saline controls. Thus, the same dose of a drug was shown to either increase or decrease operant responding, depending on whether the performance was maintained by fixed-ratio or fixed-interval reinforcement schedules. After showing that the effects of pentobarbital were dependent on the reinforcement schedule maintaining responding, Dews (1958a) investigated the effects of methamphetamine on fixed-interval, variable-interval, and fixed-ratio reinforcement schedules in pigeons. While the drug effect was again found to be dependent on the reinforcement schedule employed, Dews revealed an alternative and more basic interpretation of the results, namely that the drug selectively functioned to increase low rates of responding and to decrease high rates of responding.

A number of subsequent studies have confirmed Dews' (1958b) hypothesis that a drug's behavioural effects are controlled by the response rate generated by a given schedule. Many of these studies utilized multiple FI-FR schedules in which FI and FR components alternate, that is multiple FI-FR schedules juxtapose low and high rates

of responding. The results of many of these studies suggest that the effects of drugs, in addition to amphetamines and barbiturates, are at least partially dependent on the rates of responding engendered by the schedules of reinforcement (Kelleher & Morse, 1968). Other drugs shown to be differentially sensitive to ongoing rates of behaviour include meprobamate (e.g., Cook & Catania, 1964; Cook & Kelleher, 1962; Kelleher, 1961), chlordiazepoxide (e.g., Cook & Catania, 1964; Richelle & Djahanguiri, 1964), cocaine (Balster & Schuster, 1973; Smith, 1964), imipramine (Smith, 1964), narcotic analgesics (e.g., Byrd, 1975; McMillan, 1973; Thompson et al., 1970), and hallucinogens (e.g., Appel, Freedman & Filby, 1967; McMillan, 1973). These laboratory findings parallel human clinical findings that certain pharmacological agents exert differential effects upon ongoing behaviour (Freedman, Kaplan & Sadock, 1975). For example, the tricyclic antidepressant drugs do not markedly influence normal human behaviours but in severely depressed psychotic individuals, they produce a striking improvement in the clinical syndrome (Freedman et al., 1976).

There are major disadvantages in utilizing simple ratio and interval schedules of drug reinforcement in which drug reinforcement occurs after completion of a given number of responses or follows a response after a period of time has elapsed. These disadvantages include direct pharmacological and behavioural effects of the drugs such as toxicity, satiation, suppression of responding due to cumulative effects and nonspecific rate-modifying effects of the drug. Since the capacity of a drug infusion to serve as a reinforcing event

is confounded with other pharmacological effects of the drug under simple schedules of drug-taking behaviour, other procedures have been devised to circumvent this problem. Second-order schedules, drug choice procedures and appropriate spacing of discrete trials have been used to avoid the influence of rate-modifying drugs (Balster & Schuster, 1973; Goldberg, 1973b; Goldberg, Kelleher & Morse, 1975; Goldberg, Morse & Goldberg, 1976b; Johanson & Schuster, 1975; Sanchez-Ramos & Schuster, 1977). In this study, a second-order schedule of drug reinforcement was chosen to separate the response-maintaining actions of morphine from its many other pharmacological actions which tend to suppress or interfere with lever-pressing that follows each drug infusion (Goldberg, 1973b; Goldberg et al., 1976; Sanchez-Ramos & Schuster, 1977). In addition, it is believed that a second-order schedule more closely approximates the drug-taking and drug-seeking behaviour of drug-dependent humans (Goldberg, 1973b). In the life of a drug-dependent individual, the actual taking of drugs is highly intermittent and irregular and much more complex than either FR or FI schedules. Each drug injection is preceded by a set sequence of behaviour, for example, obtaining money, purchasing the drug, and preparing to inject the drug. The environmental stimuli associated with this set sequence of behaviour such as locations, injection rituals and the presence of friends, probably come to play an important role in the maintenance of drug-seeking behaviour (Goldberg, 1976a; Wikler, 1965). As discussed in the previous section, analogous laboratory studies with animals have

demonstrated that exteroceptive stimuli associated with drug reinforcement will markedly increase the drug-seeking behaviour (Thompson & Schuster, 1968) and these stimuli will maintain long complex sequences of responding (Goldberg, 1976a, 1976b; Kelleher, 1966a, 1966b; Kelleher & Goldberg, 1976).

The schedule of presentations of stimuli which are only intermittently associated primary reinforcement (such as a drug injection) is a second-order schedule (Kelleher, 1966a; 1966b). Under second-order schedules, the behavioural requirements specified by one schedule is treated as a unit of responding that is itself reinforced according to a second schedule (Kelleher, 1966a; 1966b). An example of a second-order schedule is the procedure in which primary reinforcement is contingent upon the completion of three successive FI 2 min schedules; this would be referred to as FR3 (FI 2:S). Note that the schedule contingency that is being treated as a unitary response is enclosed in parentheses; S, a briefly presented exteroceptive stimulus (such as a light) would occur at the termination of each FI component. The schedule of primary reinforcement for this unitary response precedes the parentheses. The brief presentation of light becomes an effective conditioned reinforcer because it is intermittently-paired with a primary reinforcer (Kelleher, 1975).

In one series of experiments utilizing second-order schedules of drug reinforcement, squirrel monkeys, prepared with chronic intravenous catheters, were studied during daily sessions lasting approximately two hours (Goldberg, 1973a). Initially each lever-press

response by the monkey produced a yellow light for two seconds accompanied by an intravenous injection of 100 µg/kg of cocaine. Once the monkey started responding the schedule was changed so that 30 responses were required to produce the yellow light and cocaine injection.

When behaviour was stabilized, the parameters were again changed. Under the final schedule, FI 5 (FR 30:S), every thirtieth response during a five-minute interval produced the 2-second yellow light but had no other programmed consequences. The first 30 response component completed by the monkey after the 5 minute interval elapsed produced both the yellow light and the cocaine infusion.

Although cocaine injections were highly intermittent relative to responses, repeated sequences of rapid responding occurred throughout experimental sessions. Short pauses in responding occurred after each light presentation and were followed by a high response rate until the light was again produced; this pattern of responding is characteristic of simple fixed-ratio schedules. The pauses in responding were longest at the start of the fixed-interval and became progressively shorter as time elapsed in the interval. This overall pattern of positively-accelerated responding is characteristic of fixed-interval schedules. Thus a FI (FR :S) second-order schedule engendered patterns of responding characteristic of both schedules. Goldberg (1973a) demonstrated that the brief visual stimuli were important in maintaining the behaviour since responding markedly decreased when the brief visual stimuli were discontinued (extinction).

In another series of experiments (Goldberg, Kelleher & Morse, 1975) squirrel monkeys were studied under a second-order schedule with fixed-interval components such as was described earlier. Completion of each 5-min fixed-interval component produced the injection signal alone; completion of every tenth fixed-interval component produced the injection signal in conjunction with an intravenous infusion of cocaine. Under this second-order schedule (FR 10 (FI 5: S)), repeated sequences of positively-accelerated responding, characteristic of fixed-interval schedules, were maintained throughout each daily session.

Under second-order schedules, drug injections occur only when the experimental animal has completed a sequence of schedule components. These schedules extend the range of conditions and the parameters under which drug-maintained behaviour can be studied. With the high degree of intermittency possible under second-order schedules, long and orderly sequences of behaviour can be maintained, and powerful moment-to-moment control can be exerted over rates and patterns of responding at times when the direct effects are minimal or absent. It is, for example, possible to arrange the parameter values of the second-order schedules so that drug injection occurs only at the end of the experimental session (Goldberg, 1976a).

An example of this extended second-order schedule was demonstrated in a series of experiments conducted by Goldberg, Morse and Goldberg (1976b). In the second-order schedule used FI 60 (FR 10:S), rhesus monkeys received either intramuscular injections of cocaine,

or morphine or were on a food reinforcement schedule. The reinforcers were delivered after a 60-min interval elapsed in the presence of a light. During the session, the light stimulus was presented alone after every tenth response. Responding was consistently maintained in sessions conducted over periods of time as long as 6 to 9 months by all three reinforcers. Again the patterns of responding were characteristic of both fixed-ratio and fixed-interval responding. Goldberg et al. (1976b) observed that behaviour maintained under the second-order schedules of intramuscular cocaine or morphine injection was relatively insensitive to changes in the dose of drug maintaining the behaviour, compared to behaviour maintained under simple fixed-ratio or fixed-interval schedules of cocaine or morphine injection.

Under second-order schedules of responding the brief exteroceptive stimuli controlled characteristic patterns of responding that were strikingly similar to those initially maintained by the reinforcers with which the stimuli were paired. Second-order schedules of drug injections thus provide a convenient means of analyzing complex sequences of drug-seeking behaviour as it is possible to analyze the ways in which stimuli associated with drug injections can control responding in the sequence, without changing the frequency of drug injection (Goldberg, 1976a). As responding engendered by second-order schedules of drug injection in laboratory animals seems analogous to that operating in the drug-seeking behaviour displayed by human addicts, it seems profitable to extend these findings to the problem

of suppression of self-administration of drugs. In efforts to reverse the pathophysiology of drug dependence, several authors support the use of opiate substitutive programmes (e.g., methadone maintenance) in conjunction with a drug displaying opioid-antagonistic properties (Fink, 1970; Fink, Freedman, Resnick & Zaks, 1973; Fink, Zaks, Sharoff, Mora, Bruner, Levitt & Freedman, 1968; Martin, Gorodetzky & McClane, 1966; Nutt & Jasinski, 1973). These substitutive programmes provide legal delivery of agonists (usually methadone) to sustain drug-dependent individuals and relieve them of the necessity to engage in drug-seeking behaviour. However, these substitution approaches are based upon the sustained dependence of the subjects on opioids (Dole & Nyswander, 1965). The rationale for administering a narcotic antagonist in conjunction with methadone is the theory that the antagonist will block the pharmacological actions of the opioid and thus extinction of physiological dependence and drug-seeking behaviour will occur.

The results of Stretch (1977a) however, suggest that agonist-induced suppression of drug-seeking behaviour can be reinstated by appropriate doses of the opioid-antagonist, naloxone. Thus, the supposition underlying the aforementioned programmes using opioid-antagonists in conjunction with methadone must be re-examined. That is, is there reinstatement of the drug-seeking behaviour as determined by Stretch, or is there extinction of drug-seeking behaviour as postulated by the other authors mentioned in this context?

The basic schedule in the experiments by Stretch (1977a) was a discrete-trials schedule of cocaine reinforcement. Daily sessions consisted of two sets of 40 discrete-trials, separated by a 5-min time-out period; the intertrial interval during each segment was equal to 50 sec. In the first part of the study, cocaine self-injection behaviour was suppressed by morphine pretreatment in a dose-dependent manner. In the second phase, it was determined that the morphine-antagonist, naloxone, was capable of reinstating cocaine self-injection responding suppressed by morphine pretreatment. The degree of reinstatement was dependent upon the dose of naloxone given, in relation to the degree of suppression produced by morphine pretreatment. The reversal of morphine-suppressed responding was more apparent during the first segment of the session with only a partial reversal of the suppressive effects of morphine pretreatment in the second segment. The fact that naloxone has a shorter duration of action than does morphine appeared to account for these results. These findings were duplicated in a later series of experiments using a discrete-trial procedure of self-administration of morphine (Stretch, 1977b). The purpose of the present experiments was to extend the discrete-trial schedule of self-administration of morphine to that of a second-order schedule of morphine reinforcement utilizing techniques similar to those of Goldberg (1973b, 1976b).

D) Pharmacological and Behavioural Properties of Morphine

The group of drugs known as narcotic analgesics includes naturally-occurring alkaloids of opium, of which morphine is the main

example, and various semi-synthetic or synthetic drugs with similar actions. Included in this class in addition to morphine are heroin, the diacetyl derivative of morphine, and the synthetic compounds levorphanol, meperidine, and methadone.

The narcotic analgesics have a complex neuropharmacological action and are used clinically for the alleviation of pain (analgesia). Their analgesic action, however, is also associated with complex behavioural effects, of which the ability to induce a subjective state of euphoria is the primary reason for their importance as drugs of abuse. Other side effects of opiate administration include physiological dependence and tolerance. Physiological dependence, as discussed in the Introduction, is a latent hyperexcitable state induced by prolonged administration and becomes evident only upon withdrawal of the drug or upon administration of a narcotic antagonist. While tolerance and physical dependence usually develop simultaneously, Seevers and Deneau (1963) point out they are not synonymous. Tolerance implies decreased responsiveness to the pharmacological effects of a drug, which follows previous experience with that drug, with a concomitant decrease in its reinforcing efficacy. The degree of tolerance may vary from partial tolerance, involving a slight decrease in the drug's effectiveness, to complete tolerance, where the drug no longer elicits a measurable effect (Seevers & Deneau, 1963).

There have been few reports dealing with the effects of chronic morphine administration upon operant behaviour, however tolerance to

the effects of morphine on schedule-controlled behaviour have been reported to occur in the cat (Djahanguiri, Richelle & Fontaine, 1966), pigeon (Heifetz & McMillan, 1971; McMillan & Morse, 1967), rhesus monkeys (Holtzman & Villarreal, 1973) and the rat (Babbini, Gaiardi & Bartoletti, 1976; Ford & Balster, 1976). The development of tolerance to the behavioural effects of morphine does not appear to result simply in a shift of the dose-effect curve to larger doses but is also evident in the reduction of the initial rate-decreasing effects of morphine. McMillan and Morse (1967) for example reported tolerance to morphine-induced behavioural suppression of responding which was manifested by an increase in response rates maintained under the FI component of multiple FI-FR schedule. Response rates under the FR component did not increase significantly. These data were confirmed in the pigeon by Heifetz and McMillan (1971), McMillan et al. (1970) and Woods (1969). Increases in rates of responding after chronic morphine treatment have been demonstrated in rats working under VR and FR schedules (Thompson et al., 1970). Increases in the rate of responding under FI schedules have also been observed during chronic administration of morphine in cats (Djahanguiri et al., 1966) and rats (Tsou, 1963). Under an FI 2 min schedule of food presentation in rats Babbini et al. (1976) reported an actual increase over control rates of responding. In a series of experiments using a DRL schedule (differential reinforcement of low rates of responding), Ford and Balster (1976) reported that the variability and generally decreased

rates of responding found after initial morphine pretreatment was nearly or completely reversed after two weeks of morphine administration. Mean response rates were near or within the control baselines. Acute tolerance to the rate-decreasing effects of morphine has been reported to occur after only one or two injections of morphine (Heifetz & McMillan, 1971; Rhodus, Elsmore & Manning, 1974). All studies mentioned indicated considerable individual variation in the degree of tolerance. For instance, McMillan et al. (1970) demonstrated tolerance in less than half the pigeons studied; Heifetz and McMillan (1971) were able to demonstrate tolerance in only two-thirds of the subjects studied. Thus, the development of tolerance to morphine appears to be a function of the individual as well as a function of the drug and of the schedule maintaining behaviour.

The acute effects of single doses of morphine upon schedule-controlled responding have been somewhat more widely investigated than the effects of chronic administration discussed above. Most frequently the studies were performed with pigeons working under a multiple FI-FR schedule of food reinforcement (Dykstra et al., 1974; McMillan & Harris, 1972; McMillan & Morse, 1967; McMillan et al., 1970); with rats working under a shock-avoidance schedule (Holtzman, 1974a, 1974b; Holtzman & Jewett, 1972a, 1972b, 1973); and in the monkey working under food-reinforced and/or shock-avoidance schedules (Downs & Woods, 1976; Goldberg et al., 1976a; Holtsman, 1976a; McKearney, 1974). In the studies using a multiple

FI-FR schedule of food reinforcement (Downs & Woods, 1976; Goldberg et al., 1976a; McMillan & Morse, 1967), it was generally found that acutely-administered morphine exerts dose-related decreases in responding under both the fixed-interval and fixed-ratio components and in the fixed-interval quarter-life value (that is, the percentage of interval in which the first one-quarter of responses occur). Statistically insignificant and inconsistent increases in responding following small doses of morphine occurred occasionally. Comparable results were obtained with rats trained under a variety of operant schedules of food reinforcement (Ford & Balster, 1976; Thompson et al., 1970; Tsou, 1963). Ford and Balster (1976), for instance, reported that acute administration of morphine produced small statistically non-significant increments in DRL responding at small doses (1.8-5.6 mg/kg) and decrease in frequency of emitted responses at larger dose levels (10-30 mg/kg).

In another study examining the effects of morphine in rats responding under a continuous avoidance schedule, morphine generated a dose-effect curve similar to that of a psychomotor stimulant (Holtzman & Jewett, 1972a). Following acute morphine treatment, large dose-related increments in avoidance behaviour were observed at doses of 0.3 mg/kg to 8.0 mg/kg. A larger dose disrupted avoidance responding as manifested by a change in the temporal patterning of responses and by the increased number of shocks received. Studies conducted with the squirrel monkey using similar schedule parameters yielded qualitatively analogous results (Holtzman, 1976a). The apparent

divergence in morphine action upon shock-maintained behaviour compared to food-reinforced performance have led researchers to investigate the extent to which the nature of the maintaining event may be important in determining the behavioural actions of morphine.

In a series of experiments, McKearney (1974) compared the effects of morphine, d-amphetamine, and chlorpromazine on responding under fixed-interval schedules of food presentation or electric shock presentation. McKearney's results indicated that the effects of d-amphetamine and to a lesser degree, chlorpromazine, were relatively independent of the event maintaining the behaviour. In contrast, morphine was reported to increase responding under the FI schedules of shock presentation but only decreased responding under the FI schedules of food presentation. McKearney (1974) concluded that the differential effects of morphine upon behaviour maintained by different environmental events indicated a dependence of morphine on the nature of the event maintaining responding.

A more recent study by Byrd (1976) using similar schedule parameters and animal species failed to reproduce the consistent rate increases above control levels of responding in shock-maintained behaviours as observed by McKearney (1974) following acute morphine administration. As these two studies were comparable in most respects: ongoing rates, and patterns of behaviour, shock intensity and duration, species, and doses tested, it is difficult to explain the contradictory results. Byrd (1976) suggested the differences in results obtained

may be due to some procedural variation or prior experimental histories of the subjects. However, further research is needed before more conclusive statements can be made regarding the interaction between morphine and the reinforcing stimuli.

Although it is well-established that morphine will function as a positive reinforcer and maintain behaviour under conditions when physiological dependence and withdrawal symptoms are absent (see reviews by Goldberg, 1976; Seevers, Schuster & Thompson, 1969; Seevers & Deneau, 1963), once dependence develops it may be an important condition in the control of drug-seeking and drug-taking behaviour. Experimental studies of the role of physiological dependence in the control of drug-seeking and drug-taking behaviour have almost exclusively focused on morphine dependence (Goldberg, 1976b). As mentioned previously, withdrawal signs and symptoms in morphine-dependent subjects can be precipitated either by discontinuing morphine or by giving naloxone. Studies attempting to characterize the effects of withdrawal by morphine deprivation upon operant responding will be discussed here; studies of the effects of administration of morphine-antagonists upon operant behaviour of morphine-dependent subjects will be reviewed later.

In a series of experiments by Woods and Schuster (1968) responding by rhesus monkeys was maintained either by a small injection dose of morphine (10 µg/kg), which did not result in physiological dependence, or by a large injection dose of morphine (1000 µg/kg), which resulted in the development of physiological dependence, the effects of discontinuing the opportunity for response-produced injections of morphine

were studied. When saline was substituted for morphine after 15 days at the small dose, response rates rapidly declined. In contrast, when saline was substituted for morphine after 15 days at the larger dose, response rates increased markedly for 3 to 5 days followed by a progressive decline. These increases in responding previously reinforced by morphine were not a result of a nonspecific generalized rate-increase in all behaviours. These monkeys also responded under schedules of food or water presentation; it was found after 24 to 72 hours of saline substitution, when responding previously reinforced by morphine injection had increased significantly, response rates reinforced by food and water were significantly decreased.

Numerous other studies have also indicated that drug-seeking behaviour may be enhanced in subjects undergoing withdrawal. Thompson and Schuster (1964) examined the effects of morphine deprivation on lever-press responding maintained by intravenous morphine injection in rhesus monkeys physiologically dependent on morphine. The monkeys responded under a FI-FR schedule for a single injection of 3.0 mg/kg morphine, once every 6 hours. When deprived of morphine the number of responses in the fixed interval were 'dramatically' increased as compared with the baseline condition; the latency to completion of the ratio requirement in the FR was also reduced. Following 48 hours of morphine deprivation, a single morphine infusion restored behaviour to baseline levels. It is interesting to note that when saline was given in conjunction with the stimulus previously paired with morphine, a transitory placebo effect was noted. That is, following 48 hours of

morphine deprivation, the same immediate return to baseline behavioural levels was observed when saline was substituted for morphine. Although responding previously reinforced by morphine increased in this study, other behaviours reinforced by either the presentation of food or by the termination of electric shock were suppressed by morphine deprivation.

Ford and Balster (1976) reported that cessation of morphine injections in morphine-dependent rats maintained under a DRL schedule of food reinforcement produced a biphasic effect on mean response rate. There was a marked decrease in responding early in withdrawal, followed by a marked and more prolonged response rate increase. These authors suggested that the period of high response rates may have corresponded to the "increased excitability and increased activity" reported by Lorenzetti and Sancilio (1970). Holtzman and Villarreal (1973) observed that punished responding emitted at high baseline rates were decreased by morphine withdrawal, whereas punished responding emitted at low rates was increased. Holtzman and Villarreal (1973) suggested that withdrawal effects are dependent on the baseline rate of responding maintained prior to withdrawal. This conclusion appears to be confirmed by the results obtained by Babbini, et al. (1972, 1975). A decrease in lever-pressing behaviour was obtained during the first day of withdrawal of morphine in morphine-dependent rats working under a fixed-ratio schedule of food-reinforcement (1972); however, morphine-dependent rats working under a fixed-interval schedule of food-

reinforcement showed a substantial increase in rate of responding when deprived of morphine injections (1975).

Heifetz and McMillan (1971) reported that morphine-dependent pigeons on a multiple FI-FR schedule of food-reinforcement, showed a decrease in rates of responding under the FR component and an increase in response rate under the FI component. Since FR schedules engender higher rates of responding than FI schedules, it appears that at least the early effects of morphine withdrawal upon operant behaviour are rate-dependent. Thus, the effects of morphine withdrawal are a function of the event maintaining the behaviour, the schedule of reinforcement and the size of the injection dose.

E) Pharmacological and Behavioural Properties of Naloxone, Pentazocine and Cyclazocine

The narcotic antagonists, that is, drugs that suppress the effects of agonists such as morphine, differ only slightly in chemical structure from the narcotic analgesics. Some narcotic antagonists produce many of the same effects as the narcotic analgesics, including respiratory depression and analgesia. Other narcotic antagonists show marked antagonist activity with few morphine-like effects. Cyclazocine and pentazocine are examples of the first type of narcotic antagonist, while naloxone is the prototype of the relatively "pure"antagonists.

The narcotic antagonists are believed to compete for the same enzymes and neuronal receptor sites where narcotic drugs such as

morphine would normally attach themselves. By occupying these sites, the narcotic antagonists are actually attracted to the morphine receptor sites (found primarily, though not exclusively in the mesolimbic system) more strongly than is morphine itself (Criswell & Levitt, 1975). Thus, they will displace morphine molecules already bound to the morphine receptor site rendering them ineffective. In order to be attracted to the morphine receptor site on the neuron, the narcotic antagonist must be similar in structure to the active part of the morphine molecule. Most of the narotic antagonists are, therefore, similar in form to the narcotic drugs.

The use of operant baseline performances as a means to assess the individual effects of various narcotic antagonists has generated data that are qualitatively similar to those described for acute administration of morphine. That narcotic antagonists affect schedule-controlled behaviour was demonstrated by Weiss (1956), who found that nalorphine decreased the rate of schedule-controlled response in the rat. Subsequently, McMillan and Morse (1967) compared the effects of several narcotic antagonists with the effects of morphine on schedule-controlled behaviour, and Weiss and Laties (1964) studied morphine and narcotic antagonists on the behaviour maintaining the intensity of an electric-shock at nonaversive levels in monkeys.

Schedule-controlled behaviour also has been used to study the antagonism between narcotics and narcotic antagonists. For example, Cook and Catania (1964) were able to reverse some of the effects of

morphine on behaviour maintained by an avoidance schedule, whereas Woods (1969) and McMillan (1974) both reported that the narcotic antagonist, naloxone, could reverse morphine-induced decreases in the rate of food-reinforced responding in the pigeon. In this section, the individual effects of naloxone, cyclazocine and pentazocine on operant behaviour will be discussed; the following section will deal primarily with the effects of these narcotic antagonists upon schedule-controlled behaviour when given in conjunction with morphine.

Naloxone or N-allylnoroxymorphone, was first synthesized in 1960 and subsequently proved to be a potent narcotic antagonist that was non-addicting and which manifested little detectable agonist activity of its own (Blumberg & Dayton, 1973). At very large doses, naloxone does exhibit some agonist activity but at or well above, antagonist doses, naloxone appears to manifest few or no side-effects in animals or man. It is effective in counteracting the effects of narcotic antagonists which exhibit agonist activity (the so-called mixed agonist-antagonists such as cyclazocine and pentazocine) in addition to counteracting the effects of narcotic analgesics (Goodman & Gilman, 1970; Villarreal, 1973). It is apparently ineffective against non-narcotic depressants such as barbiturates.

Compared with the many studies on the effects of morphine on operant behaviour, relatively few have been reported on the individual effects of narcotic antagonists and even fewer on the individual effects of naloxone. The effect of naloxone on food-reinforced behaviour maintained by multiple FI-FR schedules has been investigated in the

pigeon (Downs & Woods, 1976; Goldberg, Morse & Goldberg, 1976a; McMillan, Wolfe & Carchman, 1970), rhesus monkeys (Downs & Woods, 1976) and squirrel monkeys (Goldberg et al., 1976). McMillan et al. (1970) found that naloxone exhibited effects similar to acute morphine injections, that is, FI rate increases were observed at small doses (3-16 mg/kg) while larger dose levels (32 and 64 mg/kg) decreased responding under both FI and FR components of the schedule. Confirmation of these results was obtained in a study by Downs and Woods (1976) in which the effects of morphine, pentazocine and naloxone upon responding under a multiple FI-FR schedule of food reinforcement were examined in both rhesus monkeys and pigeons. The order of potency in decreasing response rates in both species was morphine > pentazocine > naloxone. Compared to monkeys, pigeons were less sensitive to morphine and pentazocine but more sensitive to naloxone, however the order of the potency relationships remained the same for both species. Goldberg (1970) failed to replicate the rate-enhancing effects of small doses of naloxone in either FI or FR responding in squirrel monkeys but did find this effect in pigeons. In addition, his results indicated that squirrel monkeys were approximately three times more sensitive to the rate-decreasing effects of larger doses of naloxone when compared with pigeons.

Ambiguity exists in the literature regarding the rate-modifying effects of naloxone alone upon responding maintained by schedules of electric-shock presentation or postponement in monkeys. McKearney

(1975) reported that naloxone increased responding at certain doses under schedules of either shock presentation or shock termination. Stretch and Sanchez-Ramos (1978) also found naloxone exerted slight rate-increasing effects on shock-postponement responding at small doses (0.1-3 mg/kg) in comparison with saline pretreatment and induced a substantial (56.8%) increase at a dose of 10 mg/kg. Byrd (1976) reported that naloxone when administered alone had no systematic effect on rates or patterns of responding maintained by a fixed-interval schedule of shock delivery. Holtzman (1973, 1976a) found no alteration in the rate of shock-avoidance responding when naloxone was administered at doses of 0.1 - 56 mg/kg.

In an escape/avoidance paradigm Hoffmeister and Wuttke (1973) trained naive rhesus monkeys to press a lever to extinguish a light associated with a drug infusion. Infusions of naloxone (100-5mcg/kg/infusion) were tolerated by the monkeys and did not generate and maintain avoidance/escape behaviour. In contrast, experiments using morphine-dependent rhesus monkeys (Goldberg, Hoffmeister, Schlichting & Wuttke, 1971) demonstrated that high rates of avoidance and escape responding were maintained with naloxone injections but not with saline injections.

Pentazocine and cyclazocine are mixed agonist-antagonists of the N-substituted 6, 7-benzomorphan series. As mentioned earlier they are termed mixed agonist-antagonists as they exhibit both agonist and antagonist properties. Pentazocine exerts its major effects on the

central nervous system and smooth muscle and is an effective clinical analgesic. Psychotomimetic side-effects are sometimes seen following its administration and it is capable of producing physiological and behavioural effects similar to those of narcotics. Cyclazocine has morphine-antagonistic and analgesic potencies about two orders of magnitude greater than those of pentazocine in both the rat (Blumberg, Wolf & Dayton, 1965) and in man (Eddy & Martin, 1970). Cyclazocine produces a marked depression of the central nervous system which differs from the depression caused by narcotic analgesics. The occurrence of behavioural depression in monkeys contains elements such as loose grip and inability to climb, suggestive of strong central muscle-relaxant effects (Villarreal, 1973).

Many experiments on the effects of pentazocine and cyclazocine upon operant behaviour have used the pigeon to study the effects of these drugs on performance maintained under a multiple FI-FR schedule of food presentation (e.g., Downs & Woods, 1976; McMillan, 1974; McMillan & Harris, 1972; McMillan & Morse, 1967; McMillan, Wolf & Carchman, 1970). Both pentazocine and cyclazocine increased FI rates of responding at small doses and decreased rates at larger doses. McMillan and Morse (1967) for example, found that a dose of 1.0 mg/kg of dl-cyclazocine and a dose of 10 mg/kg of dl-pentazocine increased the rate of responding under the FI component of the multiple schedule. Most of the increase in the mean rates of responding occurred during the early part of the FI component where rate of responding were very low. At larger doses, both dl-cyclazocine (3 mg/kg) and, dl-pentazocine (10-

30 mg/kg) decreased the rate of responding under both schedule components. Neither drug increased the high rates of responding under the FR component at any of the doses studied.

Utilizing the same schedule contingencies, Downs and Woods (1976) observed comparable results for dl-pentazocine in rhesus monkeys. Increases in responding with small doses of dl-cyclazocine and substantial decrease in responding to larger doses, were also obtained by Adam-Carrière, Merali and Stretch (1978) with rats responding under a DRL schedule of food-reinforcement. Thus in these experiments cyclazocine and pentazocine manifested rate-dependent sensitivity similar to that shown in the acute morphine studies discussed in the preceding section, with cyclazocine exhibiting a potency about ten times that of pentazocine.

Whereas most experiments examining the effects of pentazocine and cyclazocine upon operant behaviour have utilized the racemates of these drugs, McMillan and Harris (1972) compared the effects of the optical isomers on responding in pigeons maintained by a multiple FI-FR schedule of food presentation. In these experiments, both isomers of cyclazocine and pentazocine increased response rate under the fixed-interval schedule and at larger doses decreased key-pecking under both components of the multiple schedule. The rate-increasing effects of pentazocine and cyclazocine, under the FI component, were slightly more pronounced with the d-isomers than with the l-isomers. l-Cyclazocine and l-pentazocine were two to three times as potent as their

respective d-isomers in decreasing the rates of responding at the larger doses. This separation of the isomers with respect to potency is small relative to the separation obtained by Pearl, Aceto and Harris (1968) who found the l-isomers of benzomorphans to be more potent than the d-isomers by a factor of 10 to 70 times in the writhing test, 4 to 100 times in the rotorod test and 6 to 3800 times in increasing locomotion. However, Harris, Dewey, Howes, Kennedy and Pars (1969) reported l-pentazocine to be only 4 times as potent as d-pentazocine in inhibiting the contraction of the coaxially stimulated guinea-pig ileum. Although Harris et al. (1969) found a wide separation between l- and d-cyclazocine in this system, they reported the racemic mixture to be more potent than either optical isomer.

There have been several experiments on the effects of these benzomorphan antagonists on avoidance responding. Holtzman and Jewett studied the effects of dl-pentazocine (1972) and dl-cyclazocine (1973b) on the operant behaviour of the rat. In these experiments, the rats were trained to press a lever under a continuous shock avoidance schedule. Under this schedule, rats lever pressed at a rate of less than 0.1 response per second and avoided more than 90% of the shocks. dl-Pentazocine at dose levels of 2-16 mg/kg, increased the rate of avoidance responding. A larger dose of 3.2 mg/kg of dl-pentazocine decreased the rate of avoidance responding. Similar effects were obtained with dl-cyclazocine but at smaller doses, that is, increases in avoidance response rate were found at 0.125 - 2.0 mg/kg while decreases in response rate were obtained at a dose of 4-8 mg/kg.

The inverted U-shaped dose-response curve or biphasic effect of cyclazocine and pentazocine on food-reinforced and shock-maintained responding was not found in responding maintained by intracranial electrical self-stimulation in rats (Holtzman, 1976); rather, dose-dependent decreases in responding were observed for both dl-cyclazocine (0.3-3 mg/kg) and dl-pentazocine (1.0-30 mg/kg). As food-reinforced responding and responding maintained by a schedule of shock-avoidance appear to be rate-dependent and non-species specific, further study is needed to determine whether the conflicting results obtained by Holtzman (1976) were dependent on the nature of the reinforcing event maintaining behaviour or dependent on baseline rates of responding.

Before leaving this section on antagonist-induced changes in operant behaviour, it should be mentioned that according to several authors (e.g., Goldberg, 1976; Woods, Downs & Villarreal, 1973) a critical factor in studying the effects of antagonists upon schedule-controlled behaviour is the presence or absence of physiological dependence on morphine. In animals without morphine histories, effects of antagonists such as naloxone, are minimal and only observed well above the effect range for precipitating withdrawal in dependent animals. For example, in monkeys maintained on totals of 12 to 42 mg/kg of morphine each day for up to 18 months, an injection of the antagonist nalorphine (2 mg/kg) completely suppressed food-reinforced responding for the remainder of each two-hour session in which nalorphine was administered. In monkeys not dependent on morphine, however, comparable

doses of nalorphine had no effect on food-reinforced responding under identical conditions (Goldberg & Schuster, 1967). Thus, antagonists are comparable to narcotic deprivation in terms of disrupting behaviour maintained by reinforcers other than morphine.

As mentioned previously, the withdrawal signs elicited by antagonists are essentially identical to those produced by morphine-deprivation. As with deprivation-induced changes, antagonists also increase responding previously reinforced by narcotics under conditions in which such increases in responding do not result in increased morphine intake (see Thompson & Schuster, 1964).

Woods, Downs and Villarreal (1973) demonstrated that morphine deprivation had little effect on morphine intake in rhesus monkeys. In contrast, the administration of narcotic antagonists has typically been found to have profound effects on drug intake. For example, Weeks (1962) found that nalorphine administration in rats caused approximately 8- to 20-fold increases above the mean hourly rate in morphine intake over the hour following nalorphine injection. In a subsequent experiment (Weeks & Collins, 1964), a continuous infusion of nalorphine was administered to rats with the unlimited opportunity to self-administer morphine. Under these conditions, the total daily intake of morphine increased as the amount of antagonist was increased. Similar effects of antagonists on morphine-reinforced responding have been observed in rhesus monkeys. Goldberg, Woods and Schuster (1971) administered nalorphine over a wide range of doses to morphine-

dependent monkeys in which each response delivered an injection of morphine. The rate of drug-taking responses increased as the dose of antagonist increased.

F) Naloxone, Cyclazocine and Pentazocine as Morphine-Antagonists

Schedule-controlled behaviour has also been used to investigate the interactions between narcotic analgesics and narcotic antagonists. This section will deal with the interactive effects of the agonist, morphine and the antagonists, naloxone, pentazocine and cyclazocine, upon operant responding.

Many of the investigations of the interaction between morphine and narcotic antagonists on operant behaviour have utilized the pigeon working under a multiple FI-FR schedule of food reinforcement. Typically just prior to a session a narcotic antagonist is injected intramuscularly, followed immediately by an injection of morphine. In a study by McMillan et al. (1970) several antagonists were given in conjunction with either morphine or methadone. It was determined that the narcotic antagonists, with the exception of pentazocine, 'blocked' both the rate-increasing and rate-decreasing effects of the narcotics on schedule-controlled behaviour. The order of potency of the narcotic antagonists for reversing the rate-decreasing effects of morphine was: naloxone = dl-cyclazocine>nalorphine>dl-pentazocine. Morphine antagonism by dl-pentazocine could not be demonstrated at the doses studied (1.0-10 mg/kg). This antagonism of the rate-decreasing effects of morphine seemed to be specific for narcotic analgesics,

since naloxone and dl-cyclazocine reversed the effects of methadone as well as morphine, but naloxone did not reverse the rate-decreasing effects of chlorpromazine and dl-cyclazocine. In a similar study using rhesus monkeys and pigeons, Downs and Woods (1976) determined that the suppressive of morphine was effectively antagonized by naloxone in monkeys. In pigeons, however, the response rate decreases by naloxone alone appeared to prevent complete antagonism of morphine suppression of responding. dl-Pentazocine generally failed to antagonize morphine in monkeys and pigeons. In these experiments naloxone was also given in conjunction with dl-pentazocine. Antagonism of dl-pentazocine by naloxone was greatest at the lowest dl-pentazocine dose tested (1 mg/kg) in both species. At higher dl-pentazocine doses, antagonism was minimal or absent and the amount of antagonism typically did not increase as the naloxone increased. Goldberg et al. (1976a) compared morphine-antagonism by naloxone in both squirrel monkeys and pigeons. In the pigeons, antagonism of the rate-decreasing effects of 10 mg/kg of morphine occurred first at a dose of 0.1 mg/kg of naloxone; doses of 1 and 10 mg/kg of naloxone almost completely antagonized the rate-decreasing effects of 10 mg/kg of morphine on FI and FR responding. In the squirrel monkey, naloxone antagonized the rate-decreasing effects of morphine at a dose of 0.01 mg/kg; doses of 0.1 and 1 mg/kg of naloxone restored rates of FI and FR responding to control levels. From these data it was apparent that monkeys were approximately 10 times more sensitive to the antagonistic effects of naloxone when combined with morphine.

In a characteristic study of morphine and narcotic antagonist interactions upon shock-maintained behaviour in squirrel monkeys, Byrd (1976) reported reversal of morphine rate-suppression and a shift of the morphine dose-effect curve to the right when naloxone was administered concomitantly with morphine. The amount of shift in the morphine curve was quantitatively similar to the shift obtained in the Goldberg et al. (1976a) experiment, and was a function of the dose of naloxone. At some combinations, fixed-interval responding was above control rates, for example, response rates were 138% of control when 1.0 mg/kg naloxone and 10.0 mg/kg morphine were administered together. This increase above control rates of avoidance-responding when naloxone and morphine were administered concomitantly was also reported by Holtzman (1976a). Holtzman stated that these results were in accord with the "dual action" hypothesis first postulated by Tatum and Seevers (1929) that morphine exerts both a stimulant and a depressant component of action in most species. In species such as the monkey in which the depressant effects of morphine predominate, the stimulant activity of morphine can be "unmasked" by narcotic antagonists which block only the depressant component of the drugs activity (Seevers & Deneau, 1963). A more recent experiment (Stretch & Sanchez-Ramos, 1978) replicated these results in naive and morphine-tolerant squirrel monkeys. Naloxone (0.1-3mg/kg i.m.), given in conjunction with morphine, in morphine-tolerant monkeys produced dose-dependent increases in responding that greatly exceeded overall rates seen during reversal of the acute effects of morphine by naloxone

tested prior to the induction of tolerance at identical doses. For example at 10 mg/kg morphine and 1 mg/kg naloxone mean rate of responding in non-tolerant monkeys was approximately 0.4 responses per second; in tolerant monkeys, this same combination of drugs resulted in a mean response rate above 1 response per second. Antagonism of morphine-induced suppression of responding by concomitant injections of naloxone has also been demonstrated in DRL-schedules of food presentation in rats (Adam-Carrière et al. 1978) discrete-trials schedule of cocaine reinforcement in squirrel monkeys (Stretch, 1977a), and discrete-trials schedule of morphine reinforcement in squirrel monkeys (Stretch, 1977b).

McMillan and Harris (1972) studied the effectiveness of the isomers of cyclazocine and pentazocine to antagonize the rate-decreasing effects of morphine on behaviour controlled under multiple fixed-ratio fixed-interval schedule of food reinforcement in pigeons. Both d- and l-cyclazocine antagonized morphine-suppressed responding, but l-cyclazocine was more than 30 times as potent as d-cyclazocine. Neither d- nor l-pentazocine antagonized the rate decreasing effects of morphine, in fact, 10 mg/kg of both d- and l-pentazocine appeared to enhance the rate decreasing effects of morphine.

As discussed in the previous section, mixed agonist-antagonists such as cyclazocine and pentazocine exert morphine-like effects upon schedule-controlled behaviour; these morphine-like effects can be reversed if given in conjunction with an antagonist such as naloxone. In contrast to the results obtained in pigeons by McMillan et al (1970)

in which cyclazocine-suppressed behaviour was not antagonized by naloxone, naloxone appears to reverse cyclazocine-induced suppression in rats (Holtzman, 1974, 1976b; Holtzman & Jewett, 1974), monkeys (Holtzman, 1976a) and cyclazocine-induced euphoria and hallucinations in man (Jasinski, Martin & Haertzen, 1967). Although naloxone can antagonize various actions of pentazocine such as respiratory depression in humans (Kallos & Smith, 1968), rodents (Blumberg, Dayton & Wolf, 1966), rhesus monkeys (Downs & Woods, 1976); such antagonism typically requires higher doses or concentrations of naloxone than are necessary to antagonize equivalent effects of morphine (Kosterlitz & Watt, 1968).

From the experimental results discussed thus far, it is apparent that effective narcotic antagonists can antagonize the rate-decreasing effects of morphine on operant behaviour; however, it has not yet been made clear whether or not narcotic antagonists can affect morphine rate-enhancement. McMillan et al. (1970) selected pigeons whose response rates were increased by approximately 50% during the FI component of a multiple FI-FR schedule, after small doses of morphine and administered naloxone in conjunction with morphine. A dose of 0.1 mg/kg of naloxone 'blocked' the rate-increasing effect of morphine almost completely. Thus, naloxone has been demonstrated to antagonize both the rate-enhancing and rate-suppressing effects of morphine on schedule-controlled behaviour.

To summarize this section, the stimulatory and depressive effects of morphine on operant behaviour can be antagonized by the narcotic

antagonists. However, the degree of antagonism depends on the dose of morphine, the antagonist utilized and to some extent at least, the species studied.

G) Summary and Statement of Problem

The review of the literature began by stressing the importance of operant conditioning techniques in the preclinical assessment of pharmacological compounds upon behaviour, particular emphasis was given to those variables determining the direction and extent of drug-induced changes in behaviour. Second-order schedules were then discussed as a means of circumventing direct pharmacological and behavioural effects of drugs. It was suggested that second-order schedules more closely approximate the drug-taking and drug-seeking behaviour of drug-dependent humans. The final sections of the review dealt with the individual and interactive effects of morphine, naloxone, pentazocine and cyclazocine on schedule-controlled behaviour. To recapitulate, the review considered the following factors:

1. Operant conditioning techniques provide a stable objective behavioural baseline that is reproducible and highly sensitive to the behavioural effects of drugs.
2. The establishment of responding reinforced by drug injections is comparable to the establishment of responding maintained by non-drug events.
3. Experimental animals self-administer representative compounds from several of the major classes of psychotropic drugs that are illicitly self-administered by man. Conversely, drugs

with negligible abuse liability in man, are not readily self-administered by infra-human subjects.

4. The behavioural effects of drugs are dependent on organismic variables such as antecedent conditions, stimuli paired with the administration of drugs and schedules of reinforcement.
5. Stimuli paired with drug injections acquire conditioned reinforcing properties and are powerful influences in maintaining long sequences of drug-taking and drug-seeking behaviours.
6. Each schedule of reinforcement engenders characteristic rates and patterns of behaviour. The behavioural effects of drugs are controlled by the response rate generated by a given schedule.
7. Second-order schedules circumvent disadvantages of simple reinforcement schedules and provide a convenient means of analyzing complex sequences of drug-seeking behaviour without changing the frequency of drug injection.
8. Morphine, a powerful narcotic analgesic, can exert both stimulatory and depressant effects on schedule-controlled behaviour. Morphine tolerance and withdrawal are readily detected by schedule-controlled behavioural baselines.
9. Naloxone, an effective narcotic antagonist, exerts few agonist effects on schedule-controlled behaviour at doses at or below antagonist doses. Cyclazocine and pentazocine exert morphine-like biphasic effects upon schedule-controlled responding. Cyclazocine being about ten times more potent than pentazocine.

10. Both isomers of cyclazocine and pentazocine exerted biphasic effects on food-reinforced responding in pigeons. The l-isomers were 2-3 times more potent than their respective d-isomers.
11. Naloxone, when given in conjunction with morphine antagonizes both the stimulatory and depressant effects of morphine on schedule-controlled behaviour. Naloxone appears to antagonize cyclazocine-induced suppression in rats and monkeys but not in pigeons.
12. Both isomers of cyclazocine are effective in antagonizing the rate-decreasing effect of morphine on food-reinforced behaviour in pigeons but the l-isomer has much greater potency.
13. Both isomers of pentazocine are ineffective in antagonizing the rate-decreasing effects of morphine.

These concepts and experimental findings serve as a framework for this dissertation. A statement of the problems to be investigated will now be presented.

The purpose of the present series of experiments was to extend the discrete-trials schedule of morphine-reinforcement to that of a second-order schedule of morphine reinforcement, utilizing techniques similar to those of Goldberg (1973b, 1976b). The objectives were to study the effects of various drugs, individually and in combination, upon operant behaviour maintained by the second-order schedule of morphine-reinforcement. The first objective was to study the capacity

of various doses of morphine (1.0-5.6 mg/kg), given intramuscularly preceding experimental sessions, to suppress morphine-seeking behaviour. As food-reinforced responding (e.g., Downs & Woods, 1976; Goldberg et al., 1976b; McMillan & Morse, 1967) and responding for drug reinforcement (Stretch, 1977a, 1977b) are suppressed by morphine pretreatment in a dose-dependent manner, it was postulated that responding maintained by stimuli paired with morphine would be suppressed also in a dose-dependent manner by morphine pretreatment.

The second objective was to assess the capacity of a reference antagonist, naloxone, to reverse morphine-induced suppression of drug-seeking behaviour. Naloxone given in conjunction with morphine preceding experimental sessions has been demonstrated to antagonize the suppressive effects of morphine on schedule-controlled responding in food-reinforced behaviour (e.g., Downs & Woods, 1976; Goldberg et al., 1976b; McMillan et al, 1970), shock-maintained behaviour (e.g., Byrd, 1976; Holtzman, 1976; Stretch & Sanchez-Ramos, 1979) and drug-reinforced behaviour (Stretch, 1977a, 1977b). It was hypothesized that drug-seeking behaviour suppressed by morphine pretreatment would be reinstated when naloxone was combined with morphine preceding a session.

The third objective was to assess the relative capacities of the optical isomers of cyclazocine and pentazocine to effect drug-seeking behaviour when given individually prior to experimental sessions and to assess their abilities to antagonize the suppressive effects of

morphine when given in conjunction with morphine prior to experimental sessions. Most experiments studying the effects of the isomers of these benzomorphan antagonists have ranked their potency on the basis of non-operant measures such as the writhing test, the rotorod test or contractions of guinea-pig ileum (Harris et al., 1969; Pearl et al., 1968). One study reported by McMillan and Harris (1972) did compare the effects of the optical isomers on responding in pigeons maintained by a multiple FI-FR schedule of food presentation. It was suggested previously, however, that the sensitivity of pigeons to narcotic antagonists differs from that of other organisms (see Goldberg et al., 1976b). Thus one of the intents in this study was to rank the effects of the optical isomers of these mixed agonist-antagonists on schedule-controlled behaviour in an organism other than the pigeon. The effectiveness of the isomers of these drugs to antagonize morphine-induced suppression of operant responding has similarly been reported only by McMillan and Harris (1972). Therefore another intention here was to compare the antagonistic potencies of the optical isomers of cyclazocine and pentazocine with the reference antagonist naloxone.

As second-order schedules of drug-reinforced behaviour appear to be analogous to drug-seeking behaviour of drug-dependent humans it seemed profitable to extend the analogy to the problem of suppression of self administration of drugs. Thus, morphine pretreatment could be considered analogous to methadone substitution, and administration naloxone or other antagonist in conjunction with morphine

prior to experimental sessions appeared similar to the programmes supported by Fink et al. (1973), Freedman (1968), Martin et al. (1966), and Nutt and Jasinski (1973) in which methadone is given in combination with a narcotic antagonist. The rationale for these programmes is the theory that extinction of physiological dependence and drug-seeking behaviour will occur. It was hypothesized here that contrary to extinction of drug-seeking behaviour, conjunctive administration of an antagonist and an agonist would in fact reinstate drug-seeking behaviour.

CHAPTER II

METHODS

Animals

Five adult male squirrel monkeys (Saimiri sciureus) designated 195, 202, 226, 230 and 233 and weighing between 650-800 g, were used; none had been exposed to experimentation beforehand although in all instances, intravenous drug self-injection responding was established initially by cocaine injections. Using procedures described by Stretch and Gerber (1970), an intravenous catheter of PVC tubing (0.38 mm ID; 0.76 mm OD) was inserted into the external jugular or femoral vein before experimentation; monkeys wore leather vests at all times to protect their catheters. Each catheter was sealed with stylet wire and rested in a pouch on the animal's vest when not in use.

Apparatus

Each monkey, after recovery from surgery, was tested daily in a small primate restraining chair (BRS/LVE). The response lever was located above the waist lock, 8-10 cm in front of the seated monkey; each lever-press response closed a microswitch constituting the operant for recording purposes. A red cue lamp (BRS/LVE 111-05) was situated above the response lever: provision also was made to control presentation of a 28 v dc houselight and masking noise (75 dB) within

the ventilated test cubicle. Experimental conditions were controlled by standard relay, timing and counting equipment; responses and stimulus presentations were tabulated by digital (Sodeco) counters and plotted by a Gerbrands cumulative-response recorder.

The intravenous infusion of morphine was achieved by means of a Sage model 341 syringe driver; each i.v. infusion lasted 3 min and the volume per injection equalled 1 cm^3/min.

Drug Preparation

Cocaine hydrochloride, morphine sulphate and naloxone hydrochloride were dissolved and diluted with 0.9% saline solution, using sterile procedures; doses are expressed in terms of the salts. The stereoisomers of pentazocine and cyclazocine were dissolved in a solution containing 3 parts of 8.5% lactic acid and 2 parts of 1.0 N sodium hydroxide (vehicle): pH of the drug solution was 4 to 5. The doses of the benzomorphan isomers are expressed in terms of free base. Drug solutions were diluted to a concentration that allowed each dose studied to be injected in a volume of 0.1 ml/100 g. body weight. Equivalent volumes of 0.9% saline solution, and/or vehicle for pentazocine and cyclazocine doses, served as control injections. Saline, vehicle and drug solutions were injected intramuscularly into the calf or thigh muscle. When combinations of two drugs were studied, one injection was delivered into the calf or thigh muscle of one leg and the other injection immediately delivered into the calf or thigh

muscle of the other leg. All injections were given 5 minutes before the experimental sessions began. Animals were tested at the same time each day, seven days per week. Unless otherwise stated, at least two non-drug days, of which one chosen at random was preceded by a control (saline) injection, intervened between individual drug test sessions.

Procedure

Experimental sessions were conducted daily, seven days per week. Initially, each monkey was permitted to obtain intravenous injections of cocaine at a unit injection dose of 50 µg/kg delivered over 10 sec (volume equaled 0.25 cm^3/10 sec) by making a single lever-press response; during each response-produced injection, masking noise and the houselight were switched off, a red cue light accompanied each injection and responses emitted during each injection were without any programmed consequences. Each session lasted 50 min. After drug-taking behaviour was established (no specific shaping of the lever-press response was necessary), morphine at a unit injection dose of 50 µg/kg/inj, delivered over 10 sec at an equivalent volume was substituted for cocaine. After morphine self-injection behaviour stabilized over 10-15 sessions, the second-order schedule of morphine reinforcement was gradually made operative in the following manner.

The basic second-order schedule was a fixed-interval (FI) of fixed-ratio (FR) components (e.g., Goldberg, 1973b). During preliminary training, the first response occurring after 10 min (fixed-

interval of 10 minutes) in the presence of the houselight and masking noise terminated these stimulus conditions and produced simultaneously the red cue light; in the presence of the red light, an intravenous infusion of morphine at a dose of 1 mg/kg was delivered over a period of 3 minutes. The session terminated with the expiry of the 3 min injection; however, the fixed-interval schedule of morphine reinforcement was modified by the inclusion of a limited-hold (Ferster & Skinner, 1957). More specifically, if a monkey did not emit a response within 5 min of the expiry of the fixed-interval, the injection of morphine in the presence of the red light (injection signal) was given automatically i.e. the session was terminated by a non response-contingent infusion of morphine under circumstances in which the animal failed to produce the injection by a response within 5 min of the expiry of the fixed-interval.

Each response that occurred during the fixed-interval of 10 min (FI 10 min LH 5 min schedule of morphine reinforcement) turned off the houselight and masking noise, simultaneously producing the red cue-light (the injection signal, S) for a 2-sec presentation, unaccompanied by the injection of morphine. Over a series of consecutive daily sessions, the fixed-ratio (FR 1) schedule governing presentation of the injection signal was increased gradually from 1 to 5 responses (FR 1 - FR 5). During the next 30-40 consecutive sessions, the duration of the fixed-interval was increased by increments of 10 minutes until a fixed-interval duration of 50 minutes was attained. Throughout the development of responding under the fixed-interval of 50 min

with limited-hold of 5 min (FI 50 min LH 5 min schedule of morphine reinforcement) 5 responses (FR 5: injection signal) were required to produce each 2-sec presentation of the injection signal i.e. FI 50 min LH 5 min (FR 5: S). However, during the development of performance under the second-order schedule of drug reinforcement, the dose of morphine was increased from 1 to 2 mg/kg/infusion for three monkeys (195, 230 and 233) and from 1 to 3 mg/kg/infusion for the remaining animals (202 and 226). Throughout the experiments, the schedule incorporated the limited-hold of 5 min i.e. after expiry of the fixed-interval, each monkey was required to emit a fixed-number of responses (FR 5) within 5 min in order to produce the infusion of morphine. If the animal did not complete the ratio-requirement within the limited-hold, the infusion was delivered independently of the monkey's behaviour, ensuring that each daily session was terminated by the intravenous infusion of morphine accompanied by the injection signal (S).

Once each monkey was responding satisfactorily under the fixed-interval 50 min LH 5 min (FR 5: S) schedule of drug reinforcement the FR response requirement was raised gradually to FR 10 for monkeys 202 and 226 and to FR 30 for monkeys 195, 230 and 233. After stabilization of responding in each animal, the following drug experiments were conducted.

Drug Pretreatment Experiments

Experiment 1: Effects of morphine pretreatment on drug-seeking behaviour.

Five monkeys (195, 202, 226, 230, 233) were used to assess the effects of morphine sulphate at doses of 1.0, 3.0, and 5.6 mg/kg i.m. on morphine-seeking behaviour, maintained by second-order schedules of FI 50 min (FR 30: S) or FI 50 min (FR 10: S). Each dose of morphine was given at least twice to each animal on separate occasions; the testing sequence for individual doses was randomized. At least two control sessions intervened between drug test sessions; of which one was preceded by a control (saline) injection.

Experiment 2: Combined effects of morphine and naloxone pretreatments.

Four monkeys (195, 202, 226, 230) participated in this series of experiments. First the effects of naloxone pretreatment at a dose of 0.1 mg/kg i.m. on morphine-seeking behaviour was assessed. Then naloxone (0.1 mg/kg i.m.) was given in conjunction with morphine at doses of 1.0, 3.0, and 5.6 mg/kg i.m. to assess the ability of naloxone to reverse morphine-induced suppression of responding. Each dose of morphine was given in combination with 0.1 mg/kg i.m. of naloxone, at least twice to each animal on separate occasions; the testing sequence of individual combinations of morphine and naloxone was random. As with the previous series of experimental manipulations, drug test sessions were followed by not less than two control sessions of which one, chosen at random, was preceded by a trial injection of saline.

Experiment 3: Effects of the stereoisomers of pentazocine and cyclazocine on morphine-seeking behaviour.

Four monkeys (195, 202, 226, 230) were used to assess the effects of the stereoisomers of pentazocine on morphine-seeking behaviour at doses of 0.10, 1.0, and 10.0 mg/kg i.m. Each dose of both isomers was given at least twice to each animal on separate occasions 5 min prior to the sessions, the testing sequence for individual doses was randomized. As with the previous drug manipulations, at least two control sessions intervened between drug sessions; a control (vehicle) injection was given on one of these days chosen at random.

Three monkeys (195, 230, 233) were used to evaluate the pretreatment effects of the stereoisomers of cyclazocine on morphine-seeking behaviour maintained by the second-order schedule FI 50 min (FR 30: S). The doses of cyclazocine tested were 0.01, 0.10, and 1.0 mg/kg i.m. Each dose of both isomers was given at least twice to each animal on separate occasions, the dose sequence was randomized. At least two control sessions intervened between drug pretreatment sessions, a control (vehicle) injection was given on one of these days, chosen at random.

Experiment 4: Effects of the stereoisomers of cyclazocine and pentazocine upon morphine-seeking behaviour when combined with morphine pretreatment.

Four monkeys (195, 202, 226, 230) were used to evaluate the effects of 0.1 mg/kg of the isomers of pentazocine given in conjunction with morphine at doses of 1.0, 3.0 and 5.6 mg/kg i.m. upon morphine-seeking

behaviour. Each dose of morphine was given in combination with 0.1 mg/kg i.m. of both d- and l-pentazocine on at least two separate occasions to each animal. Two monkeys (195 and 230) were used to assess the effects of 0.1 mg/kg i.m. of d- and l-cyclazocine when when combined with morphine at doses of 1.0, 3.0 and 5.6 mg/kg i.m. upon responding. Each dose of morphine was given in conjunction with 0.1 mg/kg i.m. of both d- and l-cyclazocine, at least twice to each animal on separate occasions. The testing sequence of individual combinations of morphine and the isomers of the benzomorphan antagonists was random. Drug test sessions were separated by at least two control sessions; one of these control sessions chosen at random was preceded by two pretreatment injections (saline and vehicle).

It should be noted here that the monkey designated 233, participated only in Experiment 1. Due to frequent catheter failures, he was withdrawn from further experimentation.

CHAPTER III

RESULTS

Control Performance:

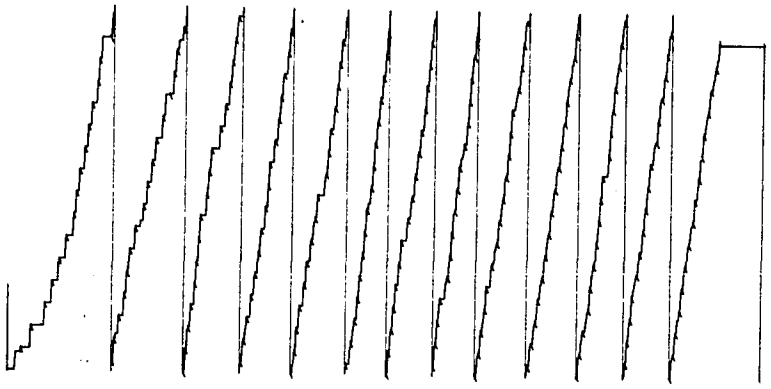
The development of behavioural baselines prior to testing required between 2 to 3 months for each animal. Performance was considered to be stable when the standard error of the mean was less than 10 percent of the value of the standard error of the overall response rate of the previous 10 sessions.

Cumulative-response records, representative of performances during saline control sessions under the second-order schedules are shown in Figures 1 and 2. Panels A, B and C in Figure 1, represent control performance under the second-order FI 50 min (FR 30: S) schedule of morphine reinforcement (2 mg/kg i.v.) for monkeys 195, 230 and 233 respectively. Panels A and B in Figure 2 show control performance for monkeys 202 and 226 under the second-order FI 50 min (FR 10: S) schedule of morphine reinforcement (3 mg/kg i.v.). Each record shows the characteristic pattern of responding engendered by both the FR and FI component schedules. These records also reveal, however, that these schedules engender different overall rates of responding between individual monkeys, though from day-to-day each animal responded consistently in the same manner. When control rates of responding were averaged for individual monkeys under the FI 50 min (FR 30: S) schedule of morphine reinforcement (2 mg/kg i.v.) over 10

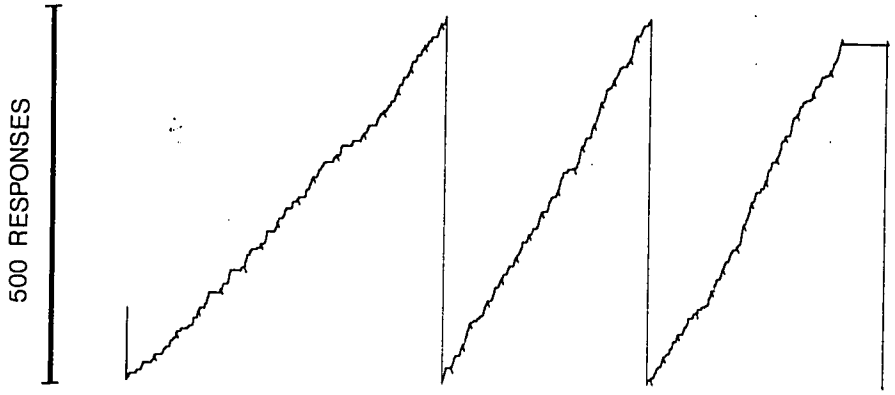
Figure 1

Representative cumulative-response records during saline control sessions under a second-order FI 50 min (FR 30: S) schedule reinforced by 2 mg/kg of morphine. These records for three monkeys demonstrate the individual differences in response rates engendered by the same schedule and reinforcement parameters. Record A refers to monkey 195 (2.08 responses/second), record B to monkey 230 (0.45 responses/second) and record C to monkey 233 (0.17 responses/second). Abscissae, time; ordinates, cumulative number of responses. Each record represents a comple 50-minute session. Short diagonal strokes on the cumulative records indicate 2-sec presentation of the injection signal (S) following the FR 30 requirement. The horizontal tracing by the response pen denotes the 3-min morphine infusion (3 mg/kg) in the presence of the injection signal.

A. MONKEY 195



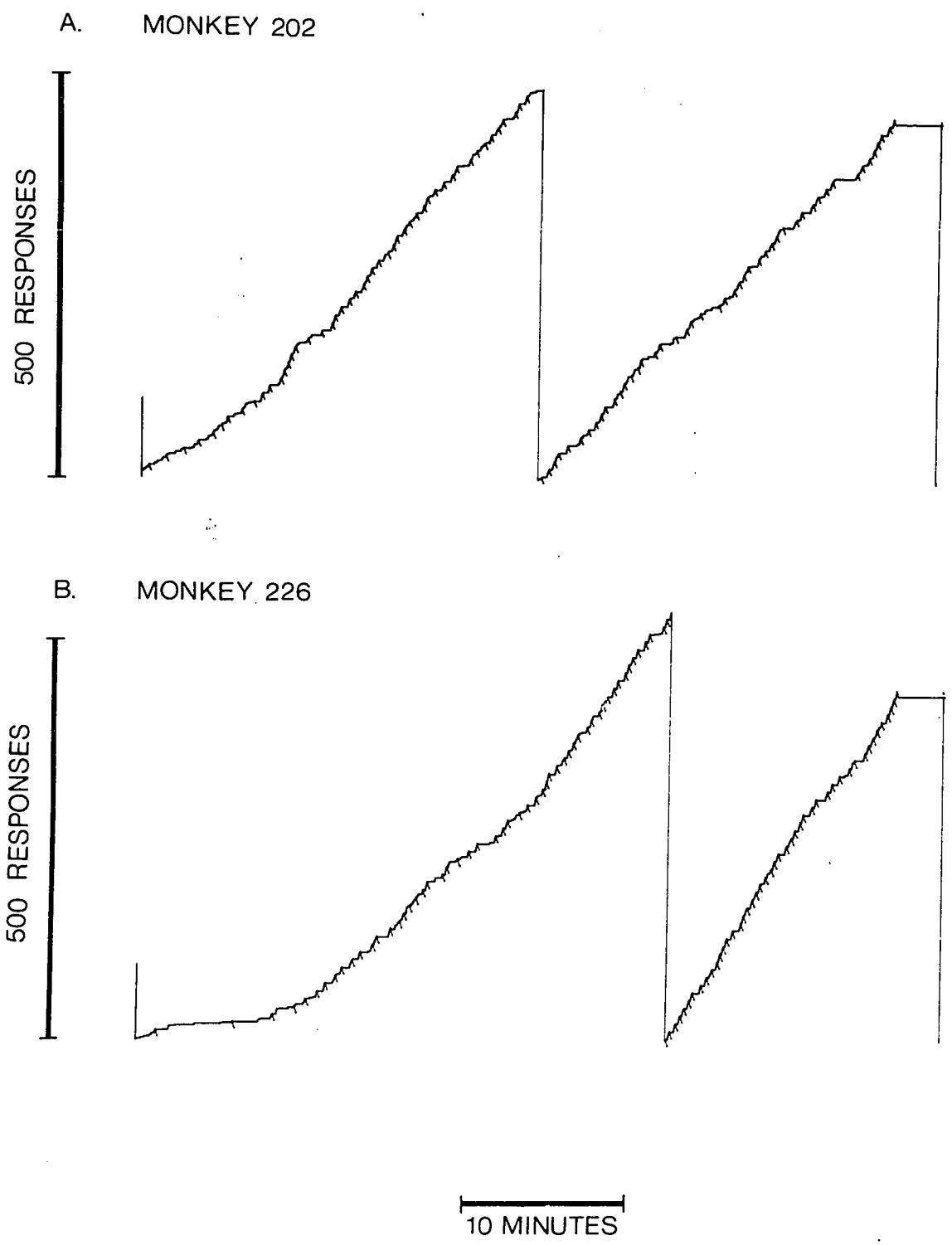
B. MONKEY 230



C. MONKEY 233

Figure 2

Representative cumulative-response records during saline control sessions under a second order FI 50 min (FR 10: S) schedule reinforced by 3 mg/kg or morphine. Record A refers to Monkey 202 (6.34 responses/second) and record B to monkey 226 (0.34 responses/second). Cumulative responses are measured along the abscissae; time along the ordinate axes. Downward deflections of the response pen indicate presentation of the 2-sec injection signal (S), following completion of the FR 10 requirement. The horizontal tracing by the response pen at the termination of the 50-min fixed-interval denotes the 3-min morphine infusion (3 mg/kg) in the presence of the injection signal.


A.
MONKEY 202
500 RESPONSES
B.
MONKEY 226
500 RESPONSES
10 MINUTES

consecutive sessions, overall response rates equalled 2.08 responses/sec (Monkey 195), 0.45 responses/second (Monkey 230), and 0.17 responses/sec (Monkey 233). Two monkeys working under the second-order schedule FI 50 min (FR 10: S) of morphine reinforcement (3 mg/kg i.v.) responded at overall rates of 0.34 responses/sec (Monkey 202) and 0.35 responses/sec (Monkey 226) over an equal number of control sessions. Since the parameters of the schedule and the morphine reinforcement dose were identical in the animals with the highest (Monkey 195: 2.08 resp/sec) and the lowest (Monkey 233: 0.17 resp/sec) overall response rates, variability in performance between animals can be attributed to individual differences, that is, the requirements of the schedule and the dose of morphine acting as the consequent event to maintain responding account only in part for the overall rates of responding adopted by individual monkeys under control conditions.

As discussed in Chapter I FI (FR: S) second-order schedules engender patterns of responding characteristic of both component schedules. The fixed-interval pattern of responding assumes a characteristic form known as the scallop. This scallop, first described by Skinner (1938), is an "upward concavity of the cumulative record of individual intervals" (Dews, 1970, p. 43), representing general positive acceleration through the interval. This trend can be observed in Figures 1 and 2. Dews (1970) states that the rate of

responding in the terminal segment of the interval is asymptotic and "occasionally, the rate may fall in the terminal segment of the interval" (p. 43). In the present second-order schedules, FI 50 min (FR 30: S) and FI 50 min (FR 10: S), the fixed-interval is of fifty minutes duration. The histograms in Figure 3 demonstrate explicitly the overall pattern of fixed-interval responding when sessions are partitioned into five 10 minute periods. The decrease in the rate of response in the terminal 10 minute segments (designated 41-50) is apparent in four of the five histograms. The fifth histogram, that of monkey 230, shows an increase in the rate of responding in the terminal segment of the interval.

Experiment 1: Morphine suppression of drug-seeking behaviour.

In these experiments, the first series of manipulations involved assessment of the extent to which graded doses of morphine, given preceding individual sessions, would act to suppress morphine-seeking behaviour. Table 1 summarizes the results obtained when each monkey received an intramuscular injection of morphine 5 minutes preceding individual sessions at doses of 1, 3, and 5.6 mg/kg. Table 2 contains these results expressed as percent deviation from control rates of responding based upon 10 consecutive sessions, observed prior to assessment of the effect of morphine pretreatment.

From Table 2, it is evident that morphine pretreatment at a dose of 1 mg/kg in the case of Monkey 195 in an 80.1 percent reduction in responding, at 3 mg/kg, responding was decreased by 83.7 percent; and at 5.6 mg/kg, responding was further reduced by 91.8 percent

Figure 3

Histograms for five monkeys (M195, M230, M233, M202 and M226) plot mean response rate for five consecutive 10-min periods (0-10 through 41-50) in the 50-minute intervals. Each 10 min period for the individual monkeys is based on a minimum of five control sessions. Positive acceleration characteristic of fixed-interval responding is seen for each monkey; decrease in rate of responding in the terminal segment of the interval is seen in four instances. The 3 histograms on the left refer to the second-order schedule FI 50-min (FR 30: S); those on the right refer to the second-order schedule FI 50 min (FR 10: S).

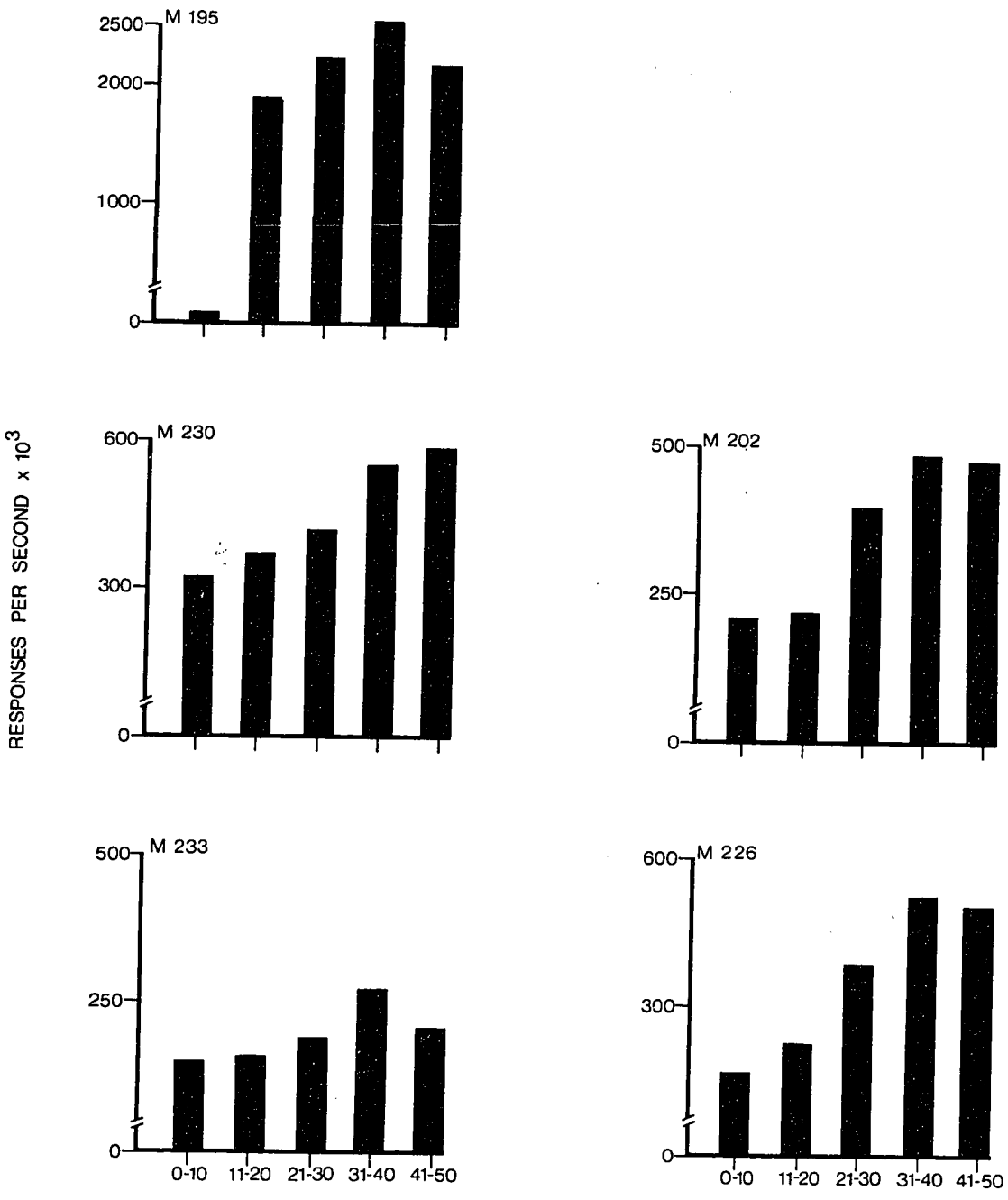

M 195
2500
2000
1000
0
M 230
600
300
0
M 202
500
250
0
M 233
500
250
0
0-10
11-20
21-30
31-40
41-50
M 226
600
300
0
0-10
11-20
21-30
31-40
41-50
RESPONSES PER SECOND x 10^3
CONSECUTIVE 10-MINUTE PERIODS

Table 1

Rates of Responding Following Graded Doses of Morphine Pretreatment

Monkey	Control Rate (resp/sec)	Morphine Pretreatment Dose (mg/kg) 1.0	3.0	5.6
195	2.08 †	0.37 0.46	0.33 0.35	0.28 0.06*
230	0.45	0.10 0.25	0.04* 0.05*	0.002* 0.01*
233	0.17	0 * 0.002*	0 * 0.0006*	0 * 0 *
202	0.34	0.03 0.01*	0.01 0.003*	0.002* 0.002*
226	0.35	0.21 0.28	0.04* 0.02	0.004* 0.0003*

† Figures given are responses/second.

* Indicates session was terminated with a non-contingent injection during the 5-minute limited hold.

Table 2

Summary of Effects of Morphine Pretreatment on Rates of Responding - Expressed as Percent Deviation from Control Rates

Monkey	Morphine Pretreatment Dose (mg/kg)		
	1.0	3.0	5.6
195	80.1†	83.7	91.8
230	61.1	90.0	98.7
233	99.4	99.8	100
202	94.1	98.2	99.4
226	30.0	91.4	98.8

† All figures are percentages below individual control rates of responding and are based on the values presented in Table 1.

in comparison with control performance. Suppression of responding in monkey 230 was 61.1% of control performance at 1 mg/kg morphine pretreatment; 90.0 percent at 3 mg/kg; and 98.7 percent at 5.6 mg/kg. The greatest suppression of responding was shown by Monkey 233, with 99.4, 99.8, and 100% deviation from overall control rate at the 1, 3 and 5.6 mg/kg doses of morphine pretreatments respectively. Monkey 202 demonstrated 94.1 percent reduction in responding compared with control performance when pretreated with 1 mg/kg of morphine; 98.2 percent reduction in responding at 3 mg/kg; and a 99.4 percent decrease from control rate at 5.6 mg/kg of morphine. Finally, Monkey 226 showed a 30.0 percent decrease in responding at 1 mg/kg of morphine; 91.9 percent reduction at 3 mg/kg; and responding was suppressed by 98.8 percent at the 5.6 mg/kg dose. It is clearly evident therefore, that despite individual differences in baseline rates of responding under control conditions, morphine pretreatment, particularly at the longest dose studied, caused a substantial diminution of responding in each animal.

The effects of morphine pretreatment in suppressing drug-seeking behaviour are clearly exemplified in Figures 4-8 in which cumulative response records for individual sessions preceded by morphine pretreatment (5.6 mg/kg) are shown in comparison with a representative control record for each animal.

Figure 4

Representative cumulative-response records for individual sessions A and B obtained from monkey 195. Record A is a representative cumulative response record of a saline control session (response rate-2.02 res/sec). Record B is a representative cumulative response record following 5.6 mg/kg morphine pretreatment (response rate - 0.28 res/sec). Each record refers to a complete session. The cumulative-response pen is displaced in a downward direction to denote the 2-sec presentation of the injection signal (S) after the requisite thirty responses of the FI 50 min (FR 30: S) schedule were emitted. The horizontal tracing by the cumulative-response pen denotes the 3-min morphine infusion (2 mg/kg) in the presence of the injection signal at the expiry of the 50-min fixed-interval.

MONKEY 195

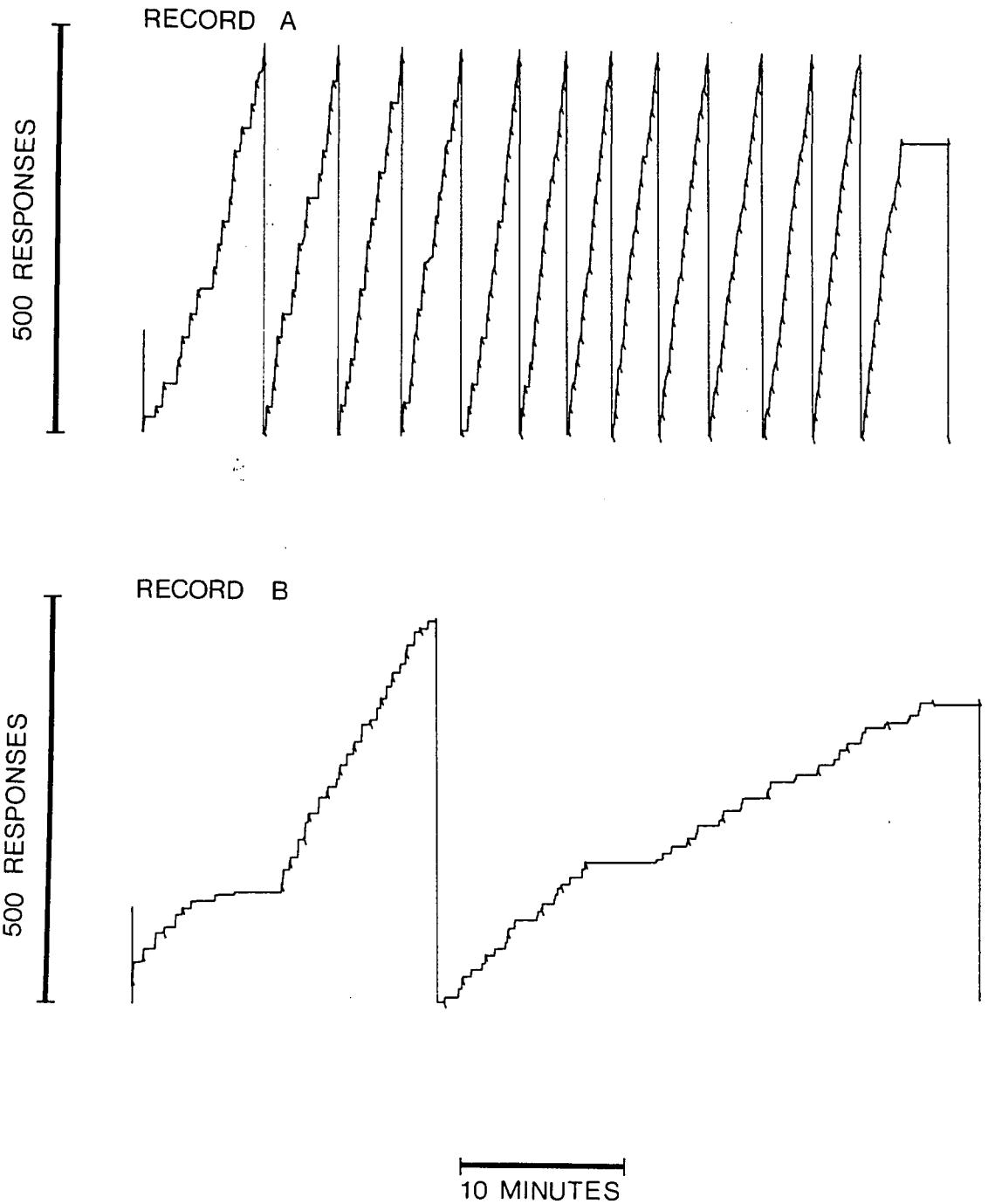


Figure 5

Representative cumulative-response records for individual sessions A and B obtained from monkey 230. Record A is a representative cumulative response record of a saline control session (response rate - 0.42 res/sec). Record B is a representative cumulative response recording following 5.6 mg/kg morphine pretreatment (response rate - 0.01 res/sec). Each record refers to a complete session. The cumulative-response pen is displaced in a downward direction to denote the 2-sec presentation of the injection signal (S) after the requisite 30 responses of the FI 50 min (FR 30: S) schedule were emitted. The horizontal tracing by the response pen denotes the 3-min morphine infusion (2 mg/kg) in the presence of the injection signal at the expiry of the 50-min fixed-interval. The infusion in Record B was given non-contingently after the 5-min limited-hold (LH 5 min) elapsed.

MONKEY 230

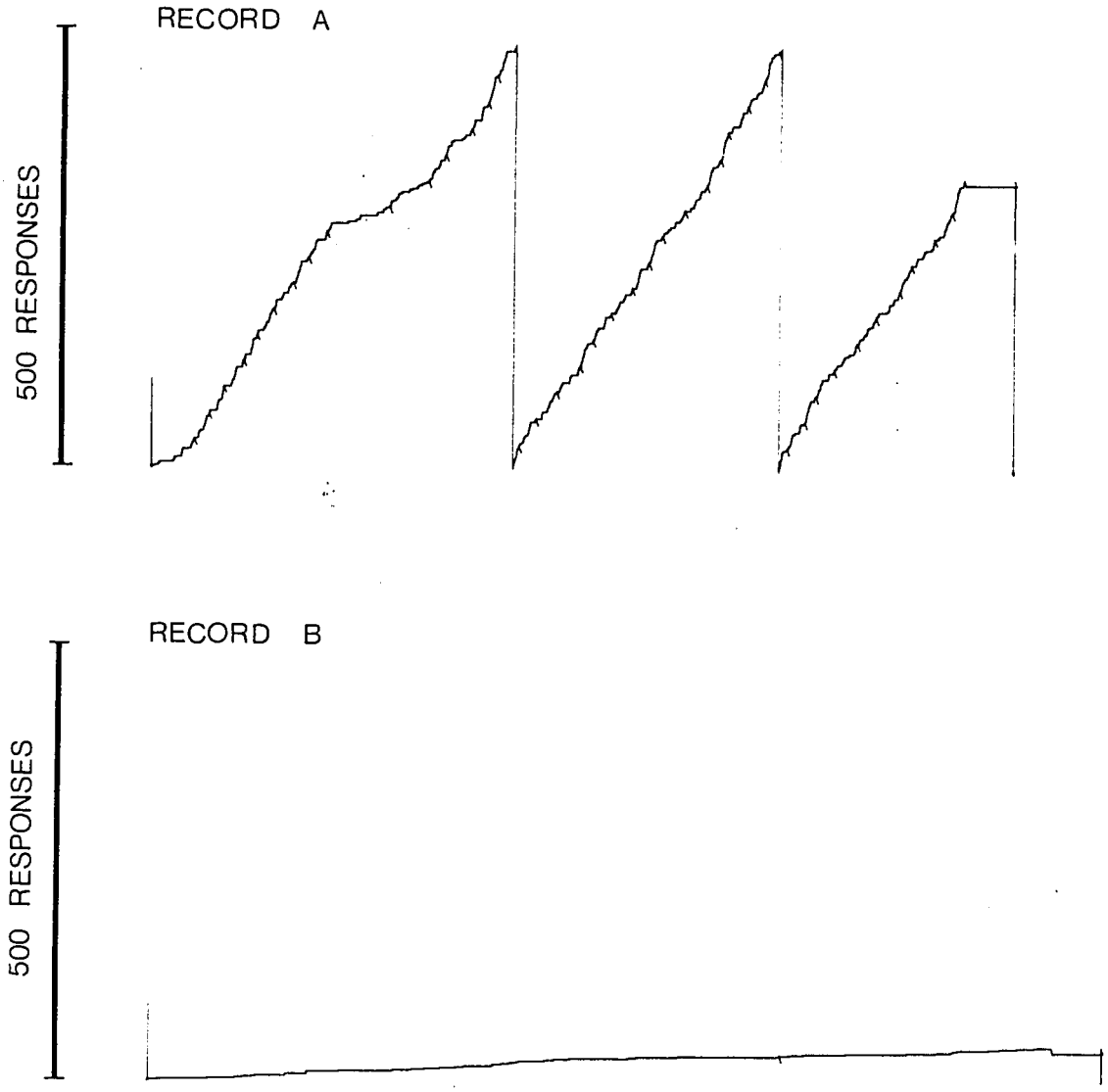


Figure 6

Representative cumulative-response records for individual sessions A and B obtained from monkey 233. Record A is a representative cumulative-response record of a saline control session (response rate: 0.19 res/sec). Record B is a representative cumulative-response recording following 5.6 mg/kg i.m. morphine pretreatment (response rate: zero). Each record refers to a complete session. The cumulative response pen in Record A is displaced in a downward direction to indicate the 2-sec presentation of the injection signal (S) after the requisite 30 responses of the FI 50 min (FR 30: S) schedule were emitted. The horizontal tracing by the response pen denotes the 3-min morphine (2 mg/kg i.v.) infusion in the presence of the injection signal at the expiry of the 50-min fixed-interval. The infusion in Record B was given non-contingently after the 5-min limited-hold (LH 5 min) elapsed.

MONKEY 233

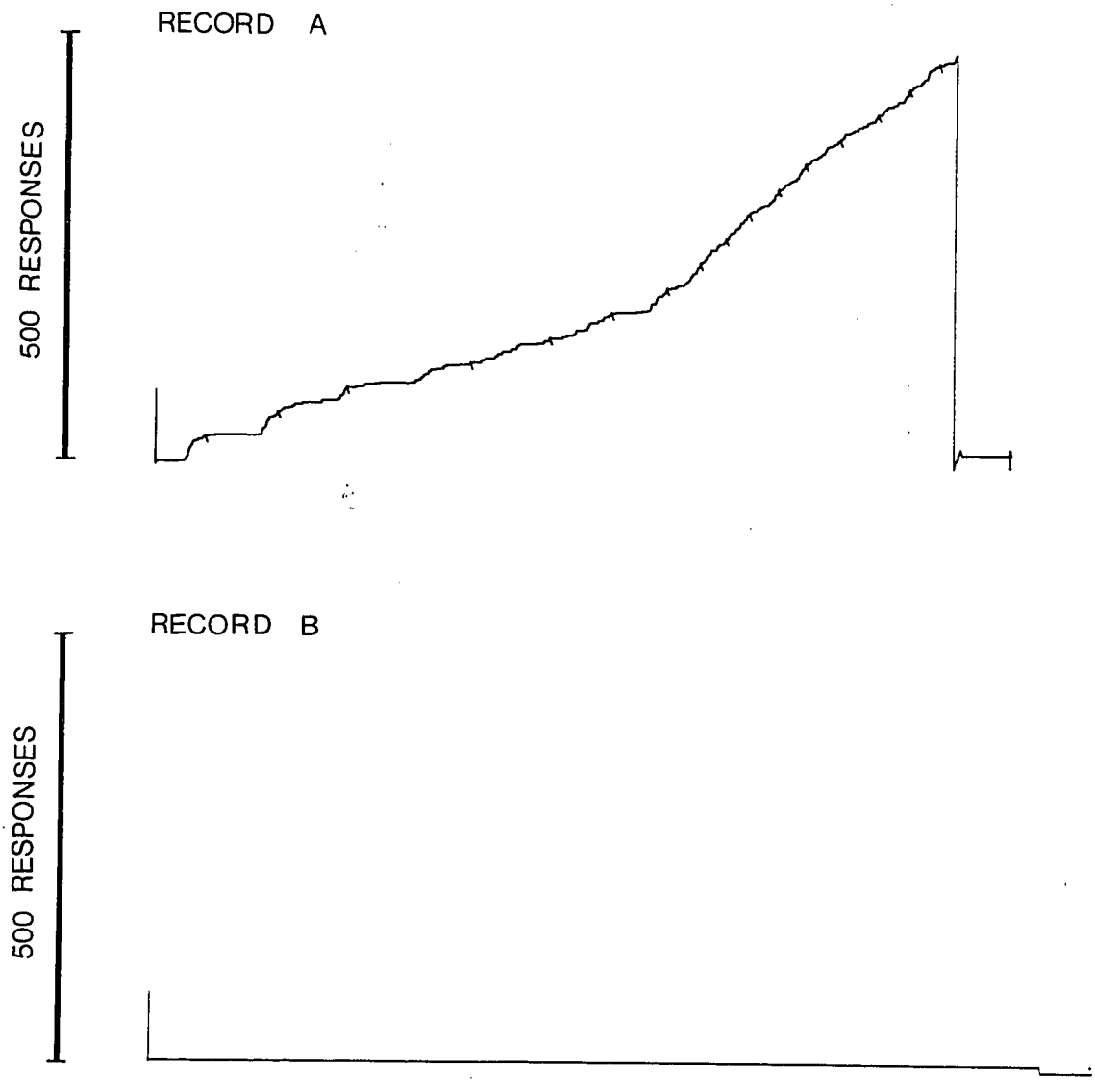
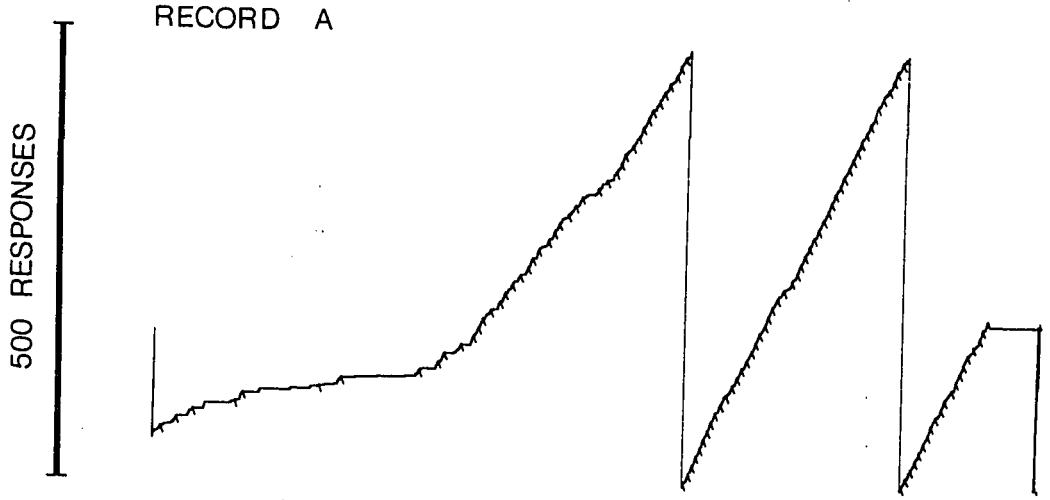


Figure 7

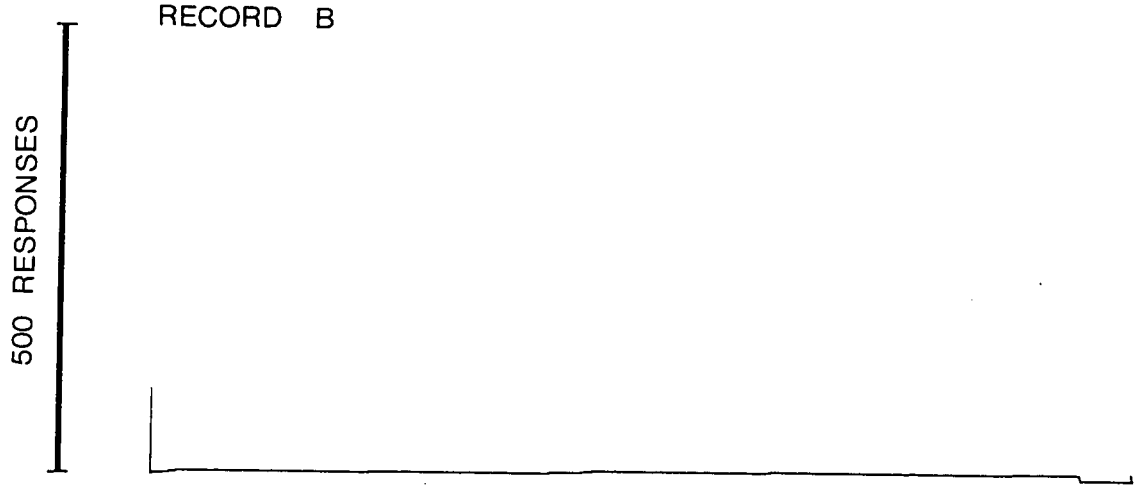
Representative cumulative-response records for individual sessions A and B obtained from monkey 202. Record A is a representative cumulative response record of a saline control session (response rate: 0.35 res/sec). Record B is a representative cumulative response recording following 5.6 mg/kg i.m. morphine pretreatment (response rate: 0.0002 res/sec). Each record refers to a complete session. The response pen in Record A is displaced in a downward direction to indicate the 2-sec presentation of the injection signal (S) after the requisite 10 responses of the FI 50 min (FR 10: S) schedule were emitted. The horizontal tracing by the response pen denotes the 3-min morphine (3 mg/kg i.v.) infusion in the presence of the injection signal at the expiry of the 50-min fixed interval. The infusion in Record B was given non-contingently after the 5-min limited-hold (LH 5 min) elapsed.

MONKEY 202

RECORD A



RECORD B

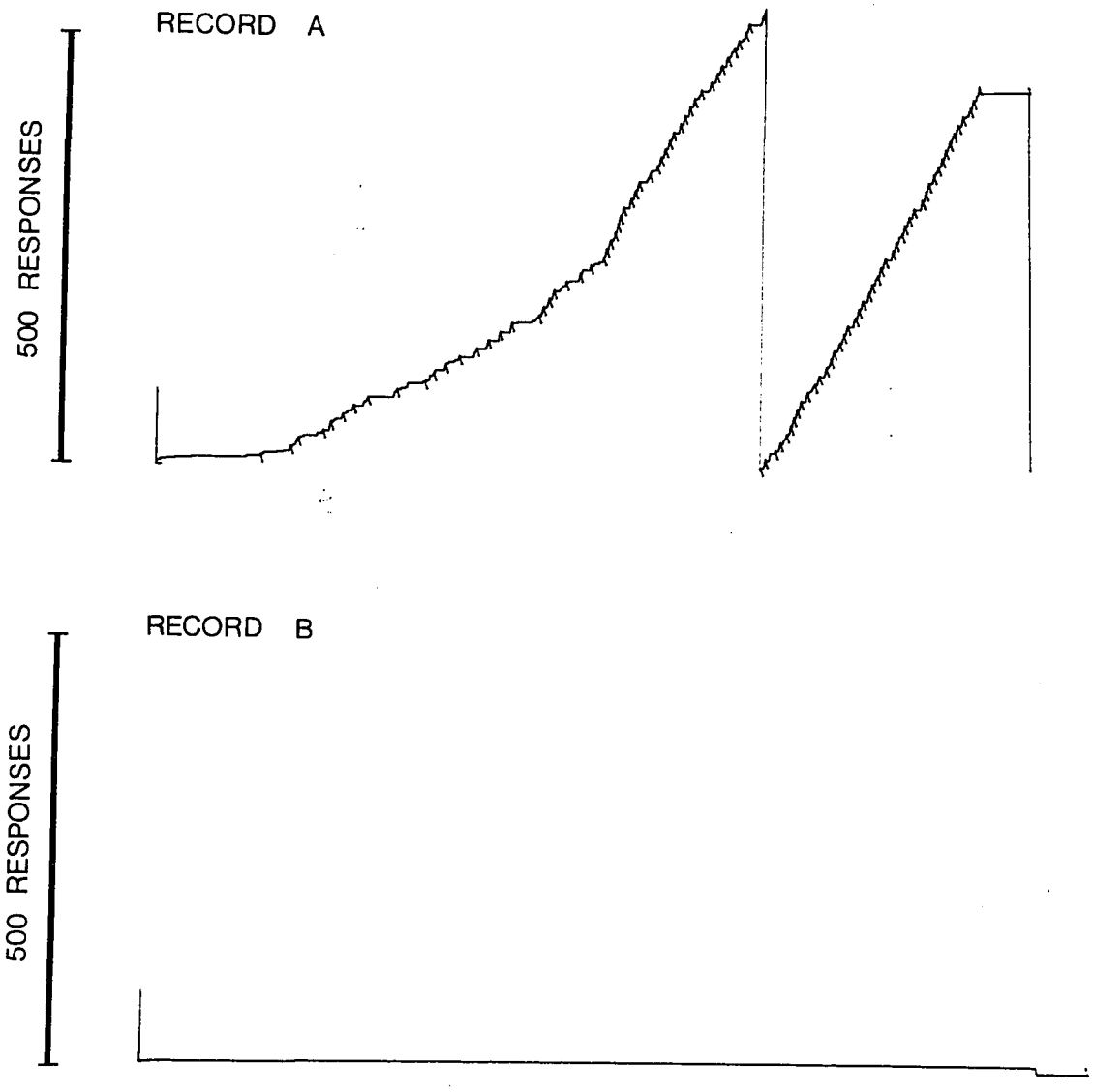


10 MINUTES

Figure 8

Representative cumulative-response records for individual sessions A and B obtained from monkey 226. Record A is a representative cumulative response record of a saline control session (response rate: 0.35 res/sec). Record B is a representative cumulative response recording following 5.6 mg/kg i.m. morphine pretreatment (response rate: 0.003 res/sec). Each record refers to a complete session. The response pen in Record A is displaced in a downward direction to indicate the 2-sec presentation of the injection signal (S) after the requisite 10 responses of the FI 50-min (FR 10: S) schedule were emitted. The horizontal tracing by the response pen denotes the 3-min morphine (3 mg/kg i.v.) infusion in the presence of the injection signal at the expiry of the 50-min fixed-interval. The infusion in Record B was given non-contingently after the 5-min limited-hold (LH 5 min) elapsed.

MONKEY 226



Experiment 2: Effects of naloxone on responding suppressed by morphine pretreatment.

In the second series of experimental manipulations naloxone was administered alone and in combination with graded doses of morphine. Naloxone at a dose of 0.1 mg/kg was first administered intramuscularly to 4 animals prior to individual sessions to assess the effect on drug-seeking behaviour. Comparison of panels A and B in Figure 9 with control records A and B in Figure 1, and comparison of panels A and B in Figure 10 with control panels A and B in Figure 2, reveals the effect of naloxone (0.1 mg/kg) when administered alone 5 minutes prior to individual sessions. The experimental record of Monkey 195 shows a slight decrease in rate of responding compared to the overall control rate (1.76 resp/sec vs. 2.08 resp/sec). Similarly, the record of Monkey 202 demonstrates a rate decrease when pretreated with naloxone (0.24 resp/sec vs. 0.34 resp/sec). Rate decreasing effects of naloxone pretreatment have previously been observed (e.g., Downs & Woods, 1976). Comparison of naloxone pretreatment records to the control records of Monkeys 230 and 226 reveals minimal effects on rates of responding when naloxone was given prior to the sessions. The results of naloxone pretreatment are summarized in Table 3.

Naloxone (0.1 mg/kg) was subsequently given in conjunction with the graded doses of morphine (1, 3 and 5.6 mg/kg) 5 minutes preceding

Figure 9

Representative cumulative-response records for individual experimental sessions following naloxone (0.1 mg/kg i.m.) pretreatment. Record A refers to monkey 195 (rate of response: 84.6% of control rate); and B refers to monkey 230 (rate of response: 93.3% of control rate). Comparisons can be made with control records shown in Figure 1, records A and B for monkeys 195 and 230 respectively. Each record refers to a complete session. The response pen is displaced in a downward direction to indicate the 2-sec presentation of the injection signal (S) after the requisite 30 responses of the FI 50-min (FR 30: S) schedule were emitted. The horizontal tracing by the response pen denotes the 3-min morphine (2 mg/kg i.v.) infusion in the presence of the injection signal at the expiry of the 50-min fixed-interval.

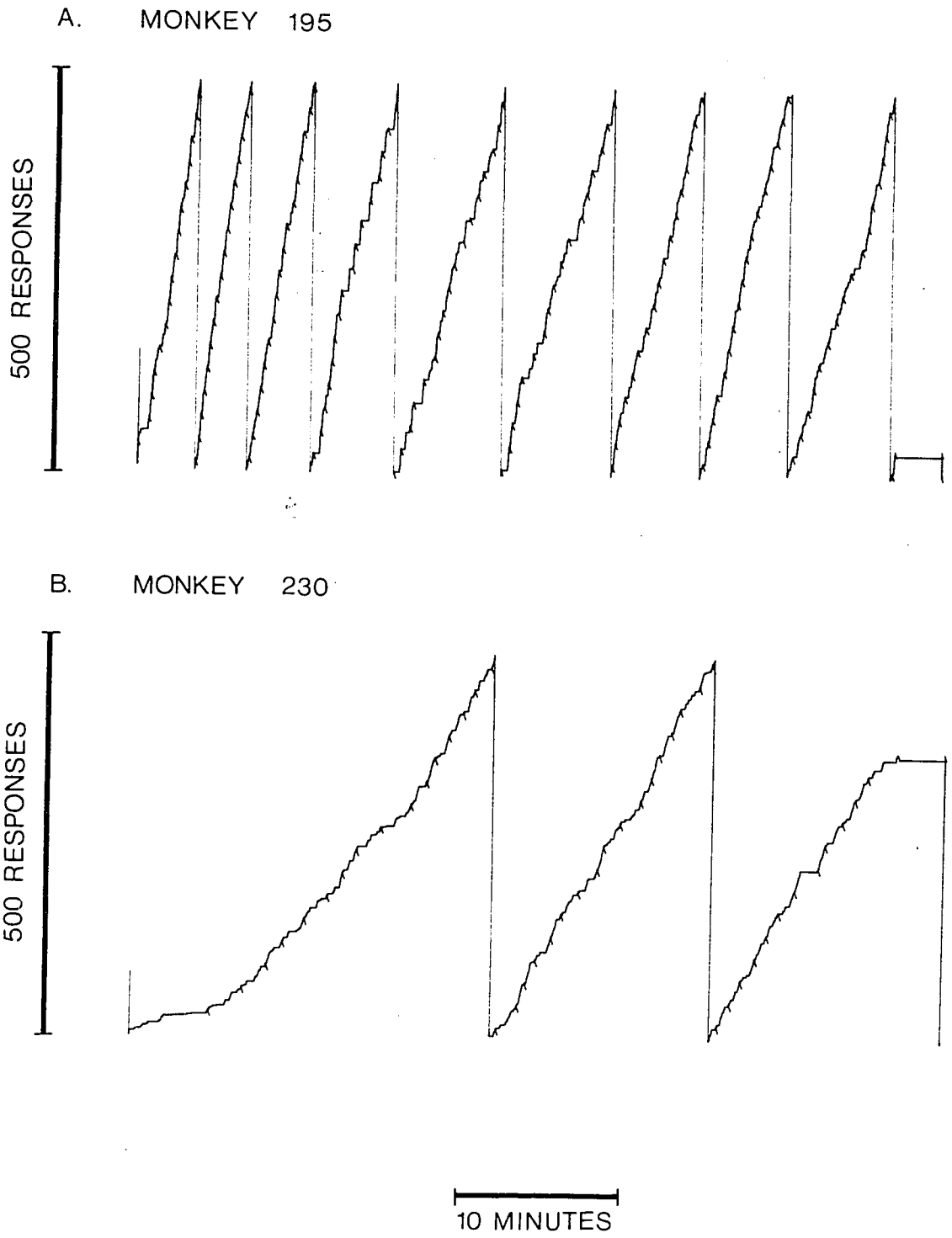

A. MONKEY 195
500 RESPONSES
B. MONKEY 230
500 RESPONSES
10 MINUTES

Figure 10

Representative cumulative-response records for individual experimental sessions following naloxone (0.1 mg/kg i.m.) pretreatment. Record A refers to monkey 202 (rate of response: 68% of control rate); and B refers to monkey 226 (rate of response: 95.2% of control rate). Comparisons can be made with control records shown in Figure 2, records A and B, for monkeys 202 and 226 respectively. Each record refers to an entire session. The response pen is displaced in a downward direction to indicate the 2-sec presentation of the injection signal (S) after the required 10 responses of the FI 50 min (FR 10: S) schedule were emitted. The horizontal tracing by the response pen denotes the 3-min morphine (3 mg/kg i.v.) infusion in the presence of the injection signal at the expiry of the 50-min fixed-interval.

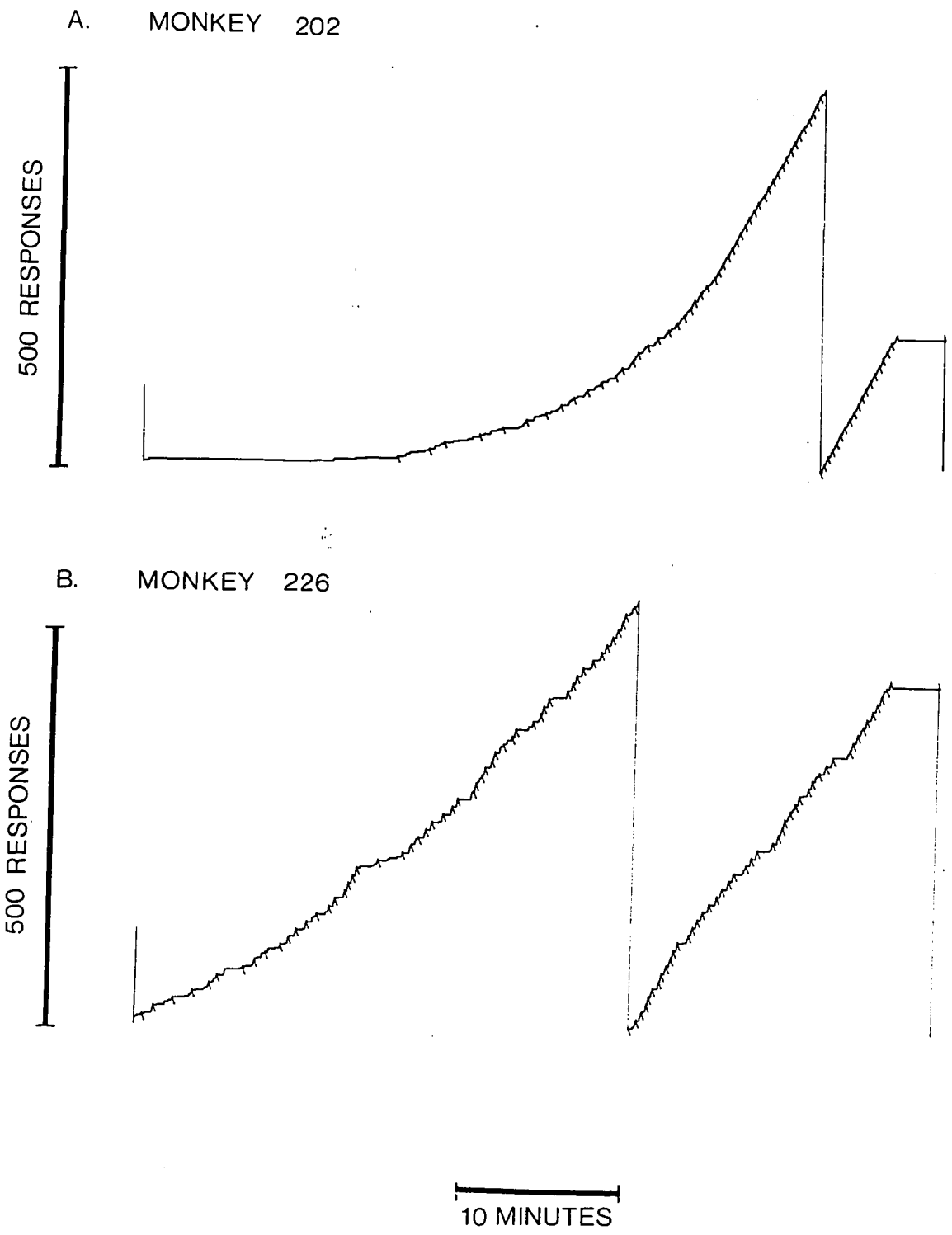

A. MONKEY 202
500 RESPONSES
B. MONKEY 226
500 RESPONSES
10 MINUTES

Table 3

Effects of Naloxone (0.1 mg/kg) Pretreatment on Rates of Responding: Expressed in Terms of Response Rate Per Second and as Percentage Deviation from Individual Control Rates

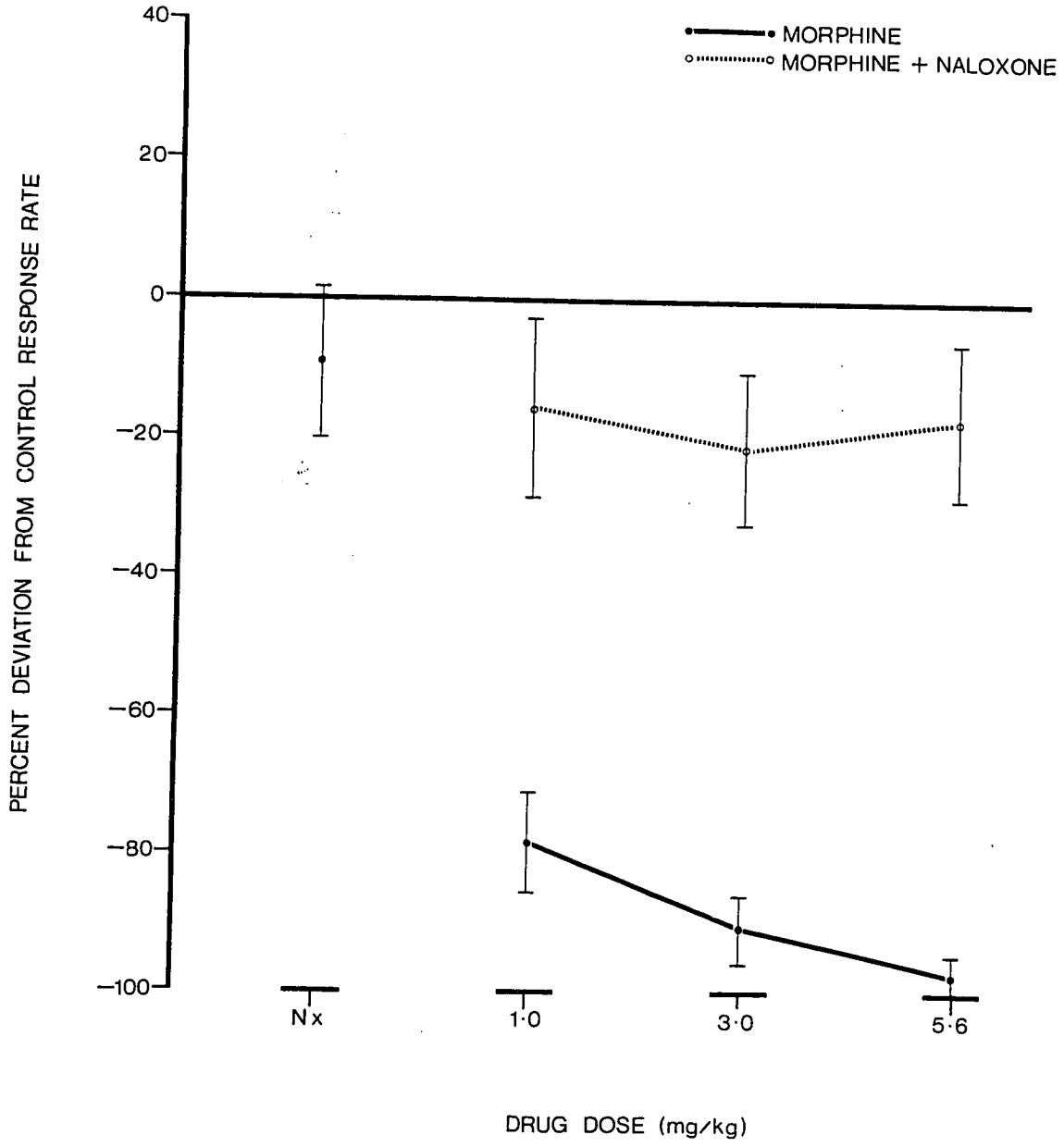
Monkey	Control Rate (r/s)	Naloxone Pretreatment	
		r/s	Percent deviation from control
195	2.08	1.76 1.76	15.4
230	0.45	0.42 0.45	3.3
202	0.34	0.25 0.23	29.4
226	0.35	0.35 0.33	2.9

individual sessions to determine its ability to antagonize the suppressive effects of morphine pretreatment on the rates of responding. On each instance, the dose-effect curve describing the effect of morphine on the rate of responding was shifted to the right when naloxone was administered in combination with the morphine. This effect is demonstrated in Figure 11, in which the mean percent deviations from baseline rates are shown when sessions were preceded by graded doses of morphine individually and in combination with naloxone (0.1 mg/kg). From these dose effect curves, it is apparent that rates of responding are suppressed by morphine pretreatment and rates of responding are significantly increased in the direction of control rates when morphine is given in conjunction with the antagonist naloxone prior to an experimental session. At a morphine pretreatment dose of 1.0 mg/kg, responding was suppressed by 78.4% ± 6.8% when morphine was given alone: suppression of responding was reduced to 16.4% ± 14.2% when given in conjunction with naloxone. When a base of 3.0 mg/kg of morphine was given individually, morphine-seeking behaviour decreased by 90.7% ± 5.4%; when this dose of morphine was combined with naloxone prior to a session, responding decreased by 21.6% ± 11.2%. At the final dose of morphine pretreatment studied here (5.6 mg/kg), responding was suppressed by 97.3% ± 3.2% compared with 18.5% ± 10.8% suppression when combined with naloxone.

The reversal of morphine suppression by naloxone has been reported previously in both morphine-dependent animals (e.g., Downs & Woods,

Figure 11

Graph summarizing the contrasting effects of graded doses of morphine pretreatment upon responding when given alone and in combination with 0.1 mg/kg of naloxone. Percent deviation from control response rates is plotted against the dose of morphine pretreatment. The isolated datum point on the left indicates the mean percent deviation from control rates of responding following 0.1 mg/kg naloxone pretreatment. Naloxone given in conjunction with morphine is indicated by the broken line and open symbols, morphine alone by the solid line and closed symbols. Each datum point is based on a minimum of 8 determinations or two sessions for each of 4 monkeys; each point refers to the mean ± S.E.


MORPHINE
MORPHINE + NALOXONE
PERCENT DEVIATION FROM CONTROL RESPONSE RATE
40
20
0
−20
−40
−60
−80
−100
Nx
1·0
3·0
5·6
DRUG DOSE (mg/kg)

1976; Goldberg, Morse & Goldberg, 1976a; Goldberg, Woods & Schuster, 1971; Sanchez-Ramos & Schuster, 1977; Stretch & Sanchez-Ramos, 1979) and non morphine-dependent animals (e.g., Byrd, 1976; McMillan et al., 1970).

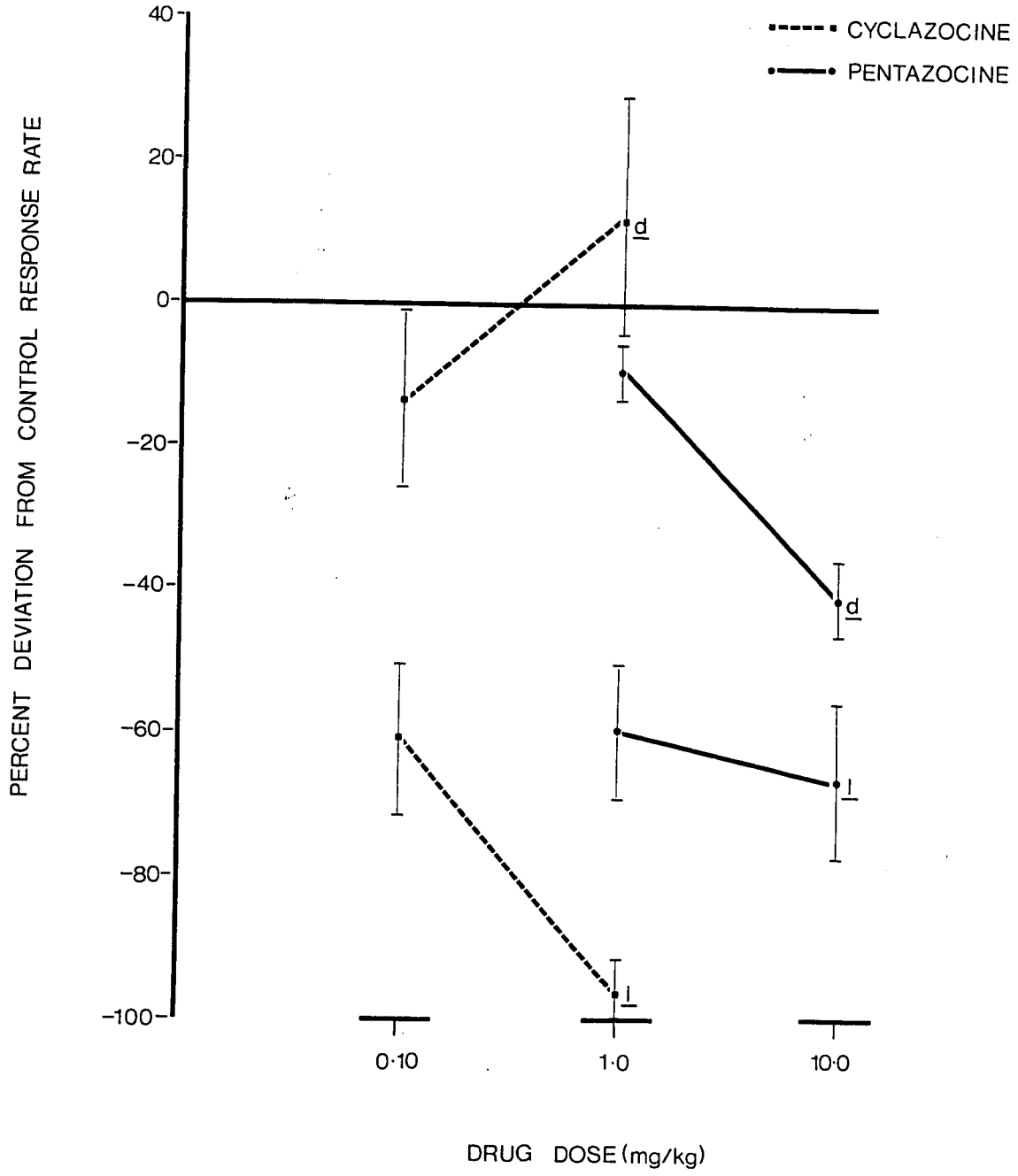
Experiment 3: Effects of the d- and l-isomers of pentazocine and cyclazocine on morphine-seeking behaviour.

In this series, manipulations involved the evaluation of the effects of graded doses of the optical isomers of the two benzomorphan narcotic antagonists, pentazocine and cyclazocine upon morphine-seeking behaviour, when given preceding individual experimental sessions. Figure 12 shows the mean percent deviations from baseline rates when sessions were preceded by graded doses of d- and l-pentazocine and d- and l-cyclazocine. From these dose-effect curves, it is apparent that 0.1 mg/kg of the d-isomer of cyclazocine had a slight rate decreasing effect on responding (-13.4% ± 12.4%) whereas this isomer of cyclazocine at the 1.0 mg/kg dose had a rate-increasing effect (+12.3% ± 16.7%). Both the 0.1 mg/kg and 1.0 mg/kg doses of l-cyclazocine demonstrated a rate-decreasing effect on responding, that is, 60.9% ± 10.8% and 96.3% ± 4.8 respectively.

The results of d-pentazocine pretreatment on baseline rates of responding indicate that at a dose of 1.0 mg/kg, responding was suppressed by 9.7% (± 3.8%). At a dose of 10 mg/kg, d-pentazocine pretreatment resulted in a 41.1% (± 5.5) decrease from baseline conditions. The l-isomer of pentazocine was more effective in

Figure 12

Dose effect curves summarizing the percent deviations from control response rate following pretreatment with graded doses of the optical isomers of pentazocine and cyclazocine. Percent deviation from control response rate is plotted against the dose of antagonist (mg/kg). Cyclazocine is indicated by the broken line, pentazocine by the solid line. d- or l- displayed to the right of each line-graph indicates the relevant isomer. Each datum point is based on a minimum of 6 determinations or two sessions for each of 3 monkeys; each point refers to the means ± S.E.


CYCLAZOCINE
PENTAZOCINE
PERCENT DEVIATION FROM CONTROL RESPONSE RATE
40
20
0
-20
-40
-60
-80
-100
d
d
l
l
0·10
1·0
10·0
DRUG DOSE (mg/kg)

suppressing drug-seeking behaviour at both doses; responding was decreased by 59.8% (± 9.3%) at the 1.0 mg/kg dose and by 66.7% (± 11.2%) at the 10 mg/kg dose. Comparison of the dose-effect curves for l-cyclazocine and l-pentazocine clearly indicates the greater potency of cyclazocine, that is, it has ability to suppress drug-seeking behaviour at a dose of one-tenth that of pentazocine. The pretreatment effects of the 6, 7-benzomorphan narcotic antagonists on schedule-controlled behaviour has previously been reported (e.g., McMillan & Morse, 1967; Holtzman & Jewett, 1972b, 1973; McMillan, 1974; Downs & Woods, 1976; Holtzman, 1976 a, b).

Experiment 4: The effects of the isomers of pentazocine and cyclazocine on responding suppressed by morphine pretreatment.

The final series of these experiments involved the administration of graded pretreatment doses of morphine sulphate in conjunction with the isomers of either pentazocine or cyclazocine. A dose of 0.1 mg/kg of the mixed agonist-antagonist was administered in combination with 1.0 mg/kg, 3.0 mg/kg, or 5.6 mg/kg of morphine intramuscularly 5 minutes prior to the individual sessions to determine the respective capacities to antagonize morphine-induced suppression of morphine-seeking behaviour. The results obtained are shown in Figure 13 and 14. The results of the reference antagonist naloxone (0.1 mg/kg), given in combination with the graded doses of morphine are also shown in each figure for comparison purposes.

Figure 13

Graph summarizing the effect upon response rates of graded doses of morphine given in conjunction with the isomers of 0.1 mg/kg of pentazocine. Percent deviation from control response rates is plotted against the doses of morphine (mg/kg). d-Pentazocine is indicated by the solid line and closed round symbols; l-pentazocine by the heavier broken line and closed square symbols. The dose-effect curve for morphine combined with naloxone (0.1 mg/kg) is shown for comparison purposes and is indicated by the lighter broken line and open symbols. The individual data points on the left of the graph indicate the percent deviation from responding when individual sessions were preceded by 0.1 mg/kg of the isomers of pentazocine or naloxone. Each datum point is based on a minimum of 8 determinations or 2 session for each of 4 monkeys; each point refers to the means ± S.E.

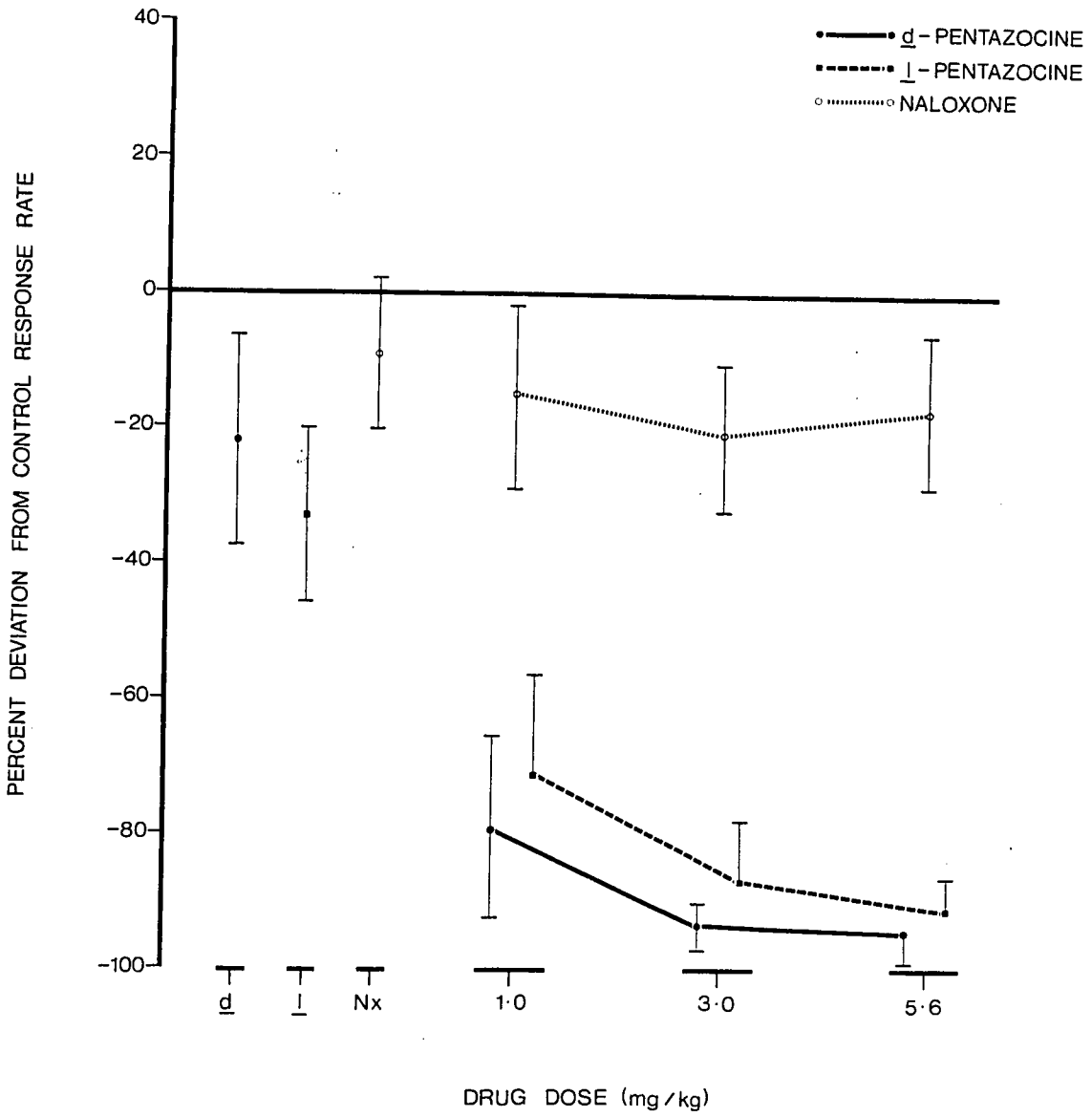
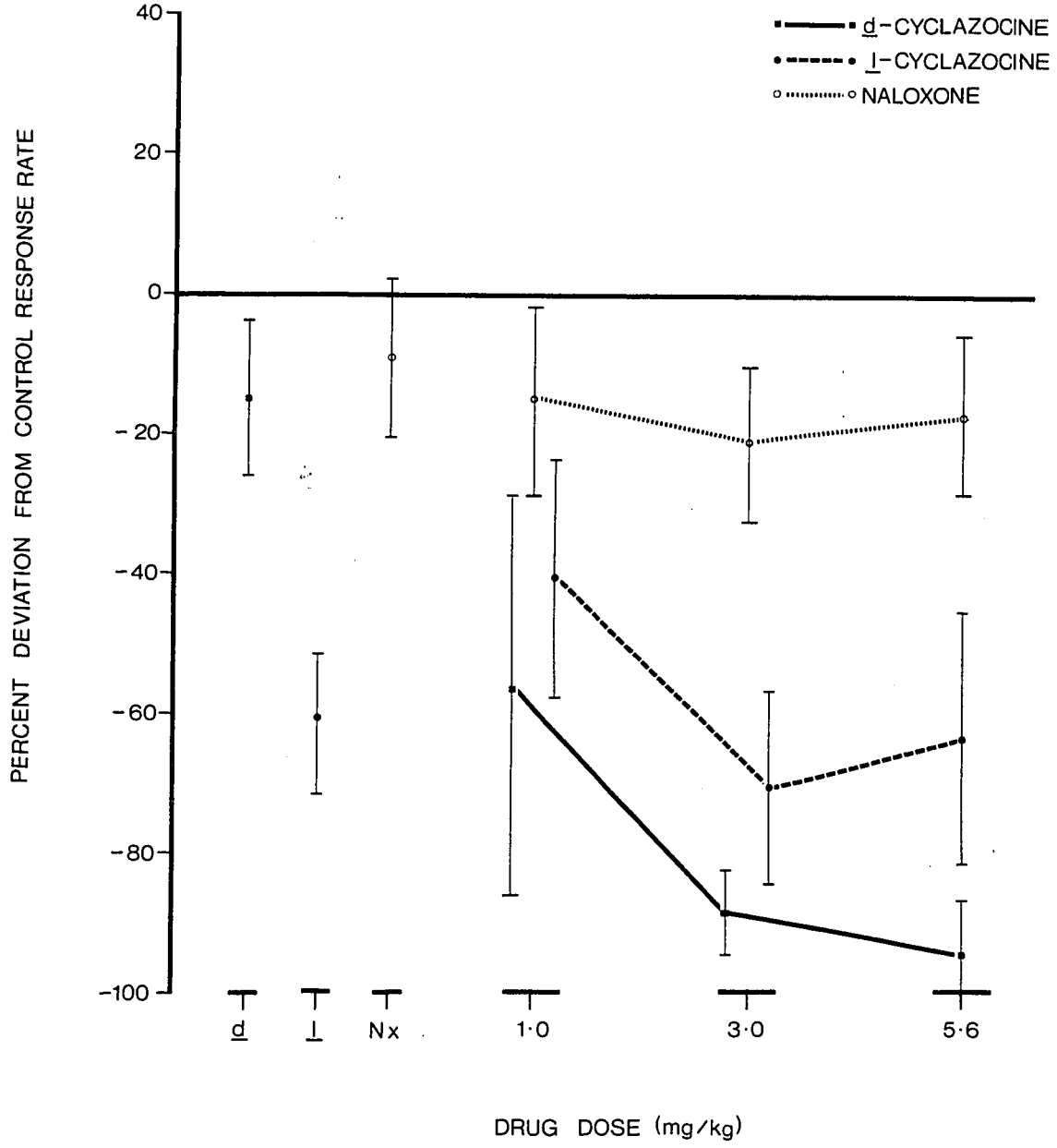

d - PENTAZOCINE
l - PENTAZOCINE
NALOXONE
PERCENT DEVIATION FROM CONTROL RESPONSE RATE
40
20
0
-20
-40
-60
-80
-100
d
l
Nx
1·0
3·0
5·6
DRUG DOSE (mg / kg)

Figure 14

Graph summarizing the effects upon response rates of graded doses of morphine given in conjunction with the isomers of 0.1 mg/kg of cyclazocine. Percent deviation from control response rates is plotted against the dose of morphine (mg/kg). d-Cyclazocine is indicated by the solid line and closed square symbols; l-cyclazocine by the heavier broken line and closed round symbols. The dose-effect curve for morphine combined with naloxone (0.1 mg/kg) is shown for comparison purposes and is indicated by the lighter broken line and the open symbols. The individual data points on the left of the graph indicate the percent deviation from responding when individual session were preceded by the isomers of cyclazocine or naloxone. Each datum point is based on a minimum of 4 determinations or 2 sessions for each of 2 monkeys, each point refers to the means ± S.E.


d-CYCLAZOCINE
l-CYCLAZOCINE
NALOXONE
PERCENT DEVIATION FROM CONTROL RESPONSE RATE
40
20
0
-20
-40
-60
-80
-100
d
l
Nx
1·0
3·0
5·6
DRUG DOSE (mg/kg)

The dose effect curves for the isomers of pentazocine seen in Figure 13 clearly show that both isomers were largely ineffective in reversing the suppressive effects of all morphine pretreatment doses. The l-isomer appeared to be only slightly more effective at each morphine dose. 1.0 mg/kg of morphine given in conjunction with 0.1 mg/kg of l-pentazocine, resulted in responding 71.7% (± 15.5%) below baseline rates: when this dose of morphine was given with 0.1 mg/kg of l-pentazocine, responding was further reduced to 79.3% (± 13.4%) of the baseline rate of responding. Morphine at a dose of 3 mg/kg given with d-pentazocine prior to individual session, resulted in a 93.6% (± 3.5%) decrease in the rate of responding compared with an 87.1% (± 9.1%) decrease when combined with the l-isomer of perntazocine. Combination of 5.6 mg/kg of morphine with 0.1 mg/kg of d-pentazocine resulted in a 94.8% (± 4.3%) suppression of responding, whereas responding was suppressed by 91.1% (±4.9%) when l-pentazocine was given with this morphine dose.

Figure 14 shows the results obtained when the suppressive effect on responding by morphine pretreatment at each of three doses (1, 3 and 5.6 mg/kg) when challenged by the d- and l-isomers of cyclazocine at a dose of 0.1 mg/kg. At the 1.0 mg/kg dose of morphine, responding was reduced below baseline conditions by 56.9% (± 28.2%) in the case of d-cyclazocine and by 40.8% (± 16.9%) when combined with l-cyclazocine. The d-isomer of cyclazocine was largely ineffective in

attenuating the suppression of responding resulting from pretreatment of 3.0 mg/kg and 5.6 mg/kg of morphine (88.8% (± 6.6%) and 94.5% (± 7.9%) reduction respectively), whereas the l-isomer exerted greater antagonistic effects at these doses (70.5% (± 13.7%) and 63.4% (± 18.4%)). As can be clearly seen in both Figures 13 and 14, the isomers of cyclazocine and pentazocine do not antagonize the suppression of morphine pretreatment as effectively as naloxone at the some dose. The ability of the isomers of the mixed agonist-antagoinists, pentazocine and cylcazocine, to reverse the suppressive effects of morphine pretreatment has been reported by McMillan and Harris, 1972.

CHAPTER IV

DISCUSSION AND CONCLUSIONS

The drug-behaviour manipulations reported in this paper were aimed at extending the discrete-trials schedule of morphine-reinforcement (Stretch, 1977b) to that of a second-order schedule of morphine reinforcement. The results of Stretch (1977a, 1977b) indicated that graded-doses of morphine pretreatment suppress drug-taking behaviour but when graded-doses of morphine are given in conjunction with naloxone prior to an experimental session, morphine-induced suppression of responding was antagonized and drug-taking behaviour was reinstated. These results, as mentioned previously, may be at variance with the rationale underlying clinical management programmes advocating conjunctive administration of an agonist and a narcotic antagonist. Several authors (e.g., Fink, 1970; Fink et al., 1973; Nutt & Jasinski, 1973) postulated that the pharmacological actions of the agonist would be antagonized resulting in extinction of physiological dependence and drug-seeking behaviour. The results obtained in these experiments appeared to support those of Stretch (1977a, 1977b) that is, that drug-seeking behaviour is reinstated rather than extinguished following administration of naloxone in combination with morphine. Implications of the results obtained here will be presented in the context of clinical management programmes following discussions of drug pretreatment effects on drug-seeking behaviour maintained by second-order schedules of morphine reinforcement.

Second-order schedules of morphine-reinforcement were utilized in these experiments as they appear to engender responding analogous to drug-seeking behaviour displayed by drug-dependent humans. In addition, second-order schedules of drug-reinforcement circumvent many of the disadvantages of simple schedules of drug-reinforcement. As the responding was maintained throughout the experimental sessions by stimuli associated with drug injections rather than the drug injections themselves, confounding pharmacological effects exerted by the drug such as toxicity, cumulative effects and nonspecific rate-modifying effects were eliminated.

It had previously been reported that responding engendered by second-order schedules was relatively insensitive to the nature of the reinforcer, the magnitude of the reinforcement and the parameters of the schedule (e.g., Goldberg, Morse & Goldberg, 1976b; Sanchez-Ramos & Schuster, 1977). These findings were confirmed by the results obtained here. Examination of the cumulative response records from representative control sessions presented in Figures 1 and 2 indicated that different response rates were engendered in the individual monkeys. However, these differing response rates appeared to be largely independent of the schedule controlling the drug-seeking behaviour and the magnitude of the reinforcement dose of morphine maintaininge the responding. The greatest variability in overall response rates was found between animals working under identical schedule parameters (FI 50 min (FR 30: S)) and morphine reinforcement dose (2 mg/kg i.v.). Intermediate response rates were adopted by animals working under the

second-order schedule (FI 50min (FR 10: S)) and receiving morphine reinforcement of 3 mg/kg i.v. at the end of each session. In all cases, however, response patterns characteristic of both fixed-interval and fixed-ratio component schedules were engendered. These findings are consistent with results reported by Goldberg (1973b), Goldberg et al. (1976b) and Kelleher (1966b).

Rate-suppressive effects were obtained when graded-doses of morphine (1.0, 3.0 and 5.6 mg/kg i.m.) preceded experimental sessions (see Tables 1 and 2). This suppression of operant rates of responding is consistent with the effects of acute morphine administration reported in studies using a multiple FI-FR schedule of food reinforcement in monkeys and pigeons (e.g., Downs & Woods, 1976; Goldberg, et al., 1976a; Holtzman & Villarreal, 1973; McKearney, 1974). Stretch (1977a) also reported overall response rate decreases in a discrete-trials schedule of cocaine self-injection at morphine pretreatment doses of 1-5.6 mg/kg i.m.

The rate-increasing effect of small doses of morphine pretreatment reported by Ford and Balster (1976), Holtzman and Jewett (1972a), McKearney (1974), McMillan and Morse (1967), Thompson et al. (1970) and Woods (1969) were not obtained here regardless of ongoing rates of behaviour and schedule maintaining the behaviours. Utilizing four simple schedules of food-reinforcement, Thompson et al. (1970) reported that a rate-increase was observed on VR and FR schedules of responding but rate-diminution was observed on VI and FI schedules when experimental rats were pretreated with 1.0 mg/kg i.m. of morphine.

Conversely, McMillan and Morse (1967) reported that 1.0 mg/kg of morphine given intramuscularly, increased the rate of key pecking for food reinforcement by pigeons in the FI component of a multiple FI-FR schedule, but this dose of morphine had no effect on the response rate during the FR component. The rate-increasing effects of 1 mg/kg of morphine on the FI component performance of a multiple FI-FR schedule was confirmed by Woods (1969) in rhesus monkeys and pigeons.

Utilizing a DRL schedule of food presentation, Ford and Balster (1976) reported that acute morphine administration had a biphasic effect on response rate. Small doses (1.8 - 5.6 mg/kg i.m.) decreased responding. Although diminution of responding at the larger doses was obtained by Adam-Carrière et al. (1978) using a similar DRL schedule of food-reinforcement, rate-enhancement was not obtained at the smaller doses.

Holtzman and Jewett (1972a) studied the effects of morphine pretreatment on electric-shock avoidance behaviour in rats. It was found that morphine (0.5 - 8 mg/kg i.m.) exerted dose-dependent increases in the rate of avoidance responding over a 10- to 16-fold dose range that exceeded 200% of the control rate in some portions of the experimental sessions.

McKearney (1974, 1975) found that small doses of morphine (0.03-1.0 mg/kg) produced increases in responding under an FI schedule of shock presentation; however, this range of morphine doses only decreased responding under comparable FI schedules of food presentation.

The reasons for these discrepant results on the effects of small morphine pretreatment doses may be due to the type of subjects, the type of schedule, the schedule parameters and the reinforcer maintaining behaviour. In addition, the importance of the baseline rate of ongoing behaviour as a factor determining the behavioural effects of morphine and other drugs has been well documented (Dews, 1958a, 1970; Kelleher & Morse, 1968; McMillan, 1973). From the data obtained here, the two animals with the lowest control rates of responding demonstrated the greatest percentage deviation from control response rates when pretreated with 1.0 mg/kg i.m. of morphine (See Table 2 - data for 202 and 233). These two animals were working under different schedule parameters and differing morphine reinforcement doses. However, at 3.0 and 5.6 mg/kg of morphine response rates for all animals were suppressed by greater than 83%. Examination of Figures 4-8 demonstrates that suppression of rates exceeded 91% in all cases following 5.6 mg/kg i.m. of morphine pretreatment. Therefore, despite individual differences in baseline rates of responding under-control conditions, morphine pretreatment, particularly at the largest dose studied caused a substantial diminition of responding in each animal. Further experimentation utilizing a greater range of morphine pretreatment doses is needed to determine whether doses below 1.0 mg/kg of morphine would 'stimulate' responding under second-order schedules of drug-seeking behaviour. Further experimentation is also needed to determine whether the differences in the behavioural effects of small

doses of morphine depend primarily upon the ongoing rates of responding or the nature of the event maintaining behaviour (e.g., food, electric-shock or stimuli associated with a primary reinforcer).

In contrast to morphine, naloxone, when administered alone, had no systematic effect on second-order schedules of morphine-seeking behaviour (See Table 3 and Figures 9 & 10). Response rates decreased between a mean of 2.9% (Monkey 226) and 29.4% (Monkey 202). The present results are consistent with previous reports on the effect of the small pretreatment dose of naloxone (0.1 mg/kg i.m.), utilized here (Downs & Woods, 1976; Goldberg, 1970; McMillan, 1973) upon behaviour controlled by fixed-ratio and fixed-interval schedules.

The results of the second series of manipulations in experiment 2 in which morphine-induced suppression of responding was reversed when graded-doses of morphine were administered in conjunction with 0.1 mg/kg of naloxone were consistent with previous reports. Naloxone has consistently been found to be an effective antagonist of acute morphine effects upon operant behaviours maintained by either electric-shock or food delivery in rats (Adam-Carrière et al., 1978; Holtzman, 1976a) squirrel monkeys (Byrd, 1976; Goldberg, Morse & Goldberg, 1976a; Holtzman, 1976a; Stretch, 1977a; Stretch & Sanchez-Ramos, 1979) rhesus monkeys (Goldberg, Woods & Schuster, 1971) and pigeons (McMillan, 1974; McMillan et al., 1970). These authors observed that the magnitude of reinstatement of responding which had been suppressed by morphine pretreatment depended upon the dose

of naloxone and upon the amount of morphine given to suppress the operant behaviour. The magnitude of reinstatement of morphine-seeking behaviour in the direction of baseline rates did not appear to be related consistently to the dose of morphine pretreatment, in the present experiments. This difference in comparison with other reported studies may be due to the fact that only one dose of naloxone (0.1 mg/kg i.m.) was given in conjunction with three morphine doses (1.0, 3.0 and 5.6 mg/kg i.m.). Future studies on the effects of naloxone on morphine-induced suppression of morphine-seeking behaviour could utilize broader doses ranges for both drugs.

Unlike naloxone, the isomers of the mixed agonist-antagonist, cyclazocine substantially modified morphine-seeking behaviour controlled by the second-order schedules. One dose of d-cyclazocine (1.0 mg/kg i.m.) increased responding above baseline rates of responding, whereas the smaller dose (0.1 mg/kg i.m.) decreased responding by approximately the same amount. The l-isomers of cyclazocine (0.1 and 1.0 mg/kg i.m.) decreased responding in a dose-dependent manner. These results are generally consistent with previous studies. McMillan and Harris (1972), for instance, compared the effects of the optical isomers of cyclazocine on responding in pigeons maintained by a multiple FI-FR schedule of food reinforcement. In these experiments 1.0 mg/kg i.m. of d-cyclazocine produced a rate increase in both schedule components above baseline rates, whereas the l-isomer was found to decrease responding under both schedule components. They concluded that the l-isomer of cyclazocine were 2 or 3 times

as potent as the d-isomer in decreasing rates of responding under both schedule components, suggesting that most of the rate-decreasing effect of the racemic mixture is a property of the l-isomer. The results obtained here indicated that the l-isomer of cyclazocine was approximately 5-9 times as potent as the d-isomer in decreasing the overall rates of morphine-seeking behaviour maintained by the second-order schedules (See Figure 12).

The larger pretreatment dose of l-cyclazocine (1.0 mg/kg i.m.) suppressed morphine-seeking behaviour by approximately the same extent as 3.0 mg/kg i.m. of morphine. This result is generally consistent with a report by McMillan (1974) which stated that l-cyclazocine was 1.7 times more potent than morphine in decreasing fixed-interval responding by pigeons. The effects of the racemic mixture of cyclazocine have also been found to be equal or greater than the effects of morphine upon schedule-controlled behaviour (McMillan et al., 1970).

As the results obtained here utilizing squirrel monkeys working under second-order schedules of morphine-reinforced behaviour were qualitatively similar to those obtained by McMillan (1974), McMillan and Harris (1972) using pigeons reinforced under a multiple FI-FR schedule of food presentation, further experimentation is required to determine whether these results on the effects of d- and l-cyclazocine are maintained over a greater range of doses. In addition, in studies using the racemic mixture of cyclazocine, small doses of dl-cyclazocine have been found to exert rate-enhancing effects in a dose-dependent

fashion on avoidance responding in rats and squirrel monkeys (Holtzman, 1976a, 1974a; Holtzman & Jewett, 1973) and on DRL responding for food by rats (Adam-Carrière et al., 1978). Whether these divergent results in the effect of small pretreatment doses of dl-cyclazocine are due to the ongoing rates of responding, the nature of the event maintaining the behaviour or whether due to racemic mixture needs further investigation.

Pretreatment with the stereoisomers of pentazocine resulted in dose-dependent decreases in morphine-seeking behaviour in the study. In comparing the effects of the optical isomers of pentazocine on responding in pigeons maintained by a multiple FI-FR schedule of food presentation, McMillan and Harris (1972) obtained somewhat differing results. That is, at the lower dose studied here (1 mg/kg i.m.) they found that the suppressive effect of both isomers on both FI and FR responding was minimal. Although overall rates of responding were decreased by less than 10% following pretreatment with d-pentazocine in this study; responding was suppressed by almost 60% following pretreatment with 1 mg/kg of the l-isomer. At the larger dose(10.0 mg/kg i.m.) studied here however, decreases in the response rates were similar to the suppression of responding found by McMillan and Harris (1972) under both FI and FR schedules of food presentation. The potency of the l-isomer in suppressing responding maintained by the second-order schedules was 2-6 times greater than d-pentazocine. (See Figure 12). This separation of potencies of the d- and l-isomer effects upon responding is compatible with that reported by McMillan

(1974) in which the l-isomer was stated to be at least twice as effective as the d-isomer in decreasing fixed-interval responding in pigeons on a food-reinforcement schedule.

Utilizing the racemic mixture of pentazocine, Downs and Woods (1976) found that responding increased slightly under both FI and FR components of a multiple FI-FR schedule of food reinforcement in pigeons and rhesus monkeys, following injection of 0.32 mg/kg i.m. However, at both doses examined in the current study (1.0 and 10 mg/kg) rates of responding were suppressed substantially under FI and FR components in both the pigeons and the monkeys. The authors estimated that the rhesus monkeys were 2 to 3 times more sensitive than the pigeons to the rate-decreasing effects of dl-pentazocine. The results obtained in this study that appear to be at variance with previous reports may be attributed to the ongoing response rates, the type of subject or the nature of the reinforcing event; further study is needed for clarification.

The comparison of the effects of the isomers of cyclazocine and pentazocine upon operant behaviour as determined by this study appear to be consistent with those found by McMillan (1974) McMillan and Harris (1972). That is there was at least a 10-fold potency difference between the effects of cyclazocine upon morphine-seeking behaviour and the effects of pentazocine despite the differences in individual rates of responding prior to the administration of these drugs; The overall effect on response rates by pretreatment with the stereoisomers of either drug was found to be greater than that of naloxone when given at a dose of 0.1 mg/kg i.m.

The next series of experimental manipulations involved the assessment of the ability of the stereoisomers of cyclazocine and pentazocine to antagonize the suppressive effects of morphine pretreatment. Both isomers of pentazocine (0.1 mg/kg i.m.) were generally ineffective in antagonizing the effects of morphine at all morphine pretreatment doses (1, 3 and 5.6 mg/kg i.m.). These data are presented in Figure 13. These results are congruent with reports studying the antagonistic effects of the isomers of pentazocine on food-reinforced responding in pigeons (McMillan and Harris, 1972) and the antagonistic effects of the racemic mixture of pentazocine or morphine suppressed food-reinforced responding in pigeons and rhesus monkeys (Downs & Woods, 1976; McMillan et al., 1970). These results are also consistent with the ineffective antagonist actions of dl-pentazocine in precipitating abstinence in narcotic-dependent monkeys (Villarreal, 1973) and humans (Jasinski, Martin & Hoeldtke, 1970) as well as counteracting the effects of morphine in the isolated guinea-pig ileum (Kosterlitz & Watt, 1968).

The ability of l-cyclazocine (0.1 mg/kg) to reinstate morphine-suppressed drug-seeking behaviour depended on the pretreatment dose of morphine. The antagonism of morphine-induced suppression by the d-isomer (0.1 mg/kg) was also dose-dependent; the d-isomer was largely ineffective in attenuating the morphine-suppression at the larges doses of morphine (3, 5.6 mg/kg i.m.). At all morphine pretreatment doses l-cyclazocine was more effective than the d-isomer in antagonizing

the effects of morphine (See Figure 14). Both isomers of cyclazocine displayed greater antagonism of morphine suppression than either of the isomers of pentazocine (for comparison see figures 13 and 14). These results are qualitatively similar to previously published results but differ quantitatively in some respects. That is, the observed differences in potency between the d- and l-isomers in terms of their morphine-antagonistic activity are congruent with reports by McMillan (1974); McMillan and Harris (1972). Also the observed differences in the antagonistic activity between cyclazocine and pentazocine are consistent with these authors. However, the relative ineffectiveness of the l-isomer of cyclazocine to reverse morphine-induced suppression of responding is inconsistent with the study by McMillan and Harris (1972). They found that at the dose of the stereoisomers studied here (0.1 mg/kg) the l-isomer was 30 times more effective in reversing the effect of morphine-induced suppression McMillan (1974) also reported that l-cyclazocine was 30 times more potent as a morphine antagonist than d-cyclazocine. In addition McMillan (1974) pointed out that a dose of 0.1 mg/kg of l-cyclazocine will reverse 50% of the rate-decrease produced by 30 mg/kg of morphine on both FI and FR schedules of food reinforced responding in pigeons. Future studies will be necessary to determine if there is a differential interspecies effect of cyclazocine similar to that reported for pentazocine between pigeons and rhesus monkeys (Downs & Woods, 1976; Goldberg et al., 1976b) or whether the schedule and reinforcer

maintaining behaviour can account for these differences. Tolerance to the agonist properties of cyclazocine has been reported in humans (e.g., Martin et al., 1966). These authors found that tolerance did not develop to the antagonist activities of cyclazocine. Further investigations will be needed to determine whether following prolonged morphine reinforcement of 2 to 3 mg/kg per day, cross-tolerance to cyclazocine (including antagonistic activity) develops in squirrel monkeys.

The rank order of potency of the five antagonists to re-instate morphine-seeking behaviour as determined by the results of this study was: naloxone > l-cyclazocine > l-pentazocine > d-cyclazocine > c-pentazocine. This order of potency prevailed for all morphine doses except that d-cyclazocine appeared to reverse morphine-induced suppression more effectively than l-pentazocine at 1 mg/kg of morphine. These results are in general agreement with previous rankings of these drugs (e.g., Blumberg et al., 1965; McMillan, 1974; McMillan et al., 1970) with the exception of the order of l-pentazocine and d-cyclazocine. However, ranking of the antagonist activity of the isomers of these mixed agonist-antagonists has previously been based on either non operant measures or upon schedule-controlled food-reinforced behaviour in the pigeon. The rank order of the antagonists used here remained the same regardless of wide differences in ongoing operant rates, the second-order schedule parameters and the magnitude of morphine reinforcement.

In conclusion, the first hypothesis that responding maintained by stimuli paired with morphine would be suppressed in a dose-dependent manner by morphine pretreatment similar to that obtained in food-reinforced responding and responding for drug reinforcement was confirmed. The second hypothesis that this morphine-induced suppression would be reinstated by concomitant administration of naloxone was also confirmed. The third objective was to assess the relative capacities of the isomers of pentazocine and cyclazocine to effect drug-seeking behaviour when given individually prior to experimental sessions and to further assess their abilities to antagonize the suppressive effects of morphine. The ranking of the effects of the individual antagonists on drug-seeking behaviour was: l-cyclazocine> d-cyclazocine > l-pentazocine > d-pentazocine > naloxone; this was consistent with previous reports. However, the ranking of the antagonistic capabilities of these drugs; naloxone > l-cyclazocine > l-pentazocine > d-cyclazocine > d-pentazocine differed from previous results using non operant procedures or food-reinforced behaviour in pigeons maintained by multiple FI-FR schedules. It was suggested a broader range of doses of the antagonists be used in future studies to determine whether this difference is species-specific or dependent on the schedule and reinforcement maintaining the behaviour.

The results of the present studies confirmed Stretch's (1977a, 1977b) observations that drug-taking behaviour suppressed by morphine pretreatment is reinstated by concomitant delivery of naloxone. This

result could not be extended to the mixed agonist-antagonists as both stereoisomers of cyclazocine and pentazocine were largely ineffective in reinstating morphine-suppressed drug-seeking behaviour. Since clinical tests are being conducted in which an agonist (e.g., methadone) is combined with a drug displaying antagonist properties for purposes of assisting in the clinical management of human heroin dependence, the procedures used in the present experiments may yet afford an efficient preclinical test of the acute effects of such drug combinations upon drug-seeking behaviour.

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