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General Introduction: Control of Drug-Taking Behavior by Schedules of Reinforcement*

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THE essential characteristic of drug dependence is persistent drug-seeking behavior. Although the potential importance of behavioral factors in drug dependence has long been recognized—for example, there have been many attempts to characterize an addictive personality—scientific studies of drug-seeking behavior required the development of suitable methods, especially methods that could be used with laboratory animals. In the last 15 years objective and quantitative techniques, developed by experimental psychologists for behavioral research, have been increasingly applied to the study of pharmacological and behavioral factors involved in drug-seeking behavior. Much of this research has been previously reviewed (5, 12, 34, 41, 42). In this volume, current research on the control of drug-taking behavior is reviewed critically by investigators from several different points of view. The purpose of the present paper is to provide background material that will help the nonspecialist to appreciate the empirical and conceptual issues that are addressed. We will start with a brief historical perspective on experimental studies of drug dependence. In the subsequent sections, we will consider terminology and the behavioral methods and concepts that are especially relevant to the behavioral pharmacology of drug dependence.

Historical Background

The early experimental studies of drug dependence were primarily concerned with morphine as the prototypical dependence-producing drug and with the role of physiological and pharmacological factors in the development of drug dependence. Pharmacological studies in both man and experimental animals revealed a characteristic sequence of events that occurred with repeated administration of morphine. Most of the initially observed physiological effects of a morphine injection diminished and then disappeared as the drug was given several times a day over a period of several weeks, but the original effect could be obtained again by increasing the dose; that is, tolerance developed with chronic administration of morphine. If morphine injections were then stopped, a series of physiological disturbances, notably lacrimation, rhinorrhea, vomiting, diarrhea, and muscle spasms, increased to a peak intensity at about 48 to 72 hr after the last injection and then slowly decreased. This morphine withdrawal syndrome could be reversed rapidly by an injection of morphine or other narcotic analgesics. It was conjectured that a major reason morphine was sought by morphine-dependent individuals was because administration of the drug postponed or terminated the with-

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drawal syndrome. Characteristic signs of withdrawal can also be observed after chronic administration of ethanol or barbiturates. In such cases, it is inferred that a state of physiological dependence has been induced by the chronic administration of the drug.[1]

The first experimental studies of drug-seeking behavior, which were also primarily concerned with morphine, were strongly influenced by the earlier studies that emphasized the importance of physiological dependence. The design of the behavioral studies typically included an initial period of time in which physiological dependence was established by chronic administration of morphine before the behavioral part of the study was begun. For example, in a study of morphine dependence in chimpanzees, Spragg (44) administered morphine (2 mg/kg, s.c.) twice a day for several months until withdrawal signs appeared when injections were delayed. Only then did he begin the experiments which showed that morphine-deprived chimpanzees would open a box containing a morphine-filled syringe more often than a box containing food. Several subsequent studies demonstrated that after physiological dependence had been established in rats or rhesus monkeys, responding that resulted in the administration of morphine could be developed and maintained (47, 50).

The emphasis on the importance of physiological dependence seems to have led many investigators to conclude that it was not only a major but indeed the essential component in drug dependence. Both logic and empirical observations eventually directed attention to other factors. Even with drugs that can induce physiological dependence, the initial drug-taking behavior could not be reasonably attributed to physiological dependence. Moreover, it had been commonly observed that people who were formerly morphine-dependent often relapsed to use of morphine after long drug-free periods when signs and symptoms of physiological dependence were no longer evident. Other drugs such as cocaine, which were compulsively sought by some people, had not been reported to produce physiological dependence in man and were not found to induce tolerance or physiological dependence in dogs or rhesus monkeys (46). Also, rhesus monkeys, which had no drug or experimental history, were studied under conditions in which each lever-pressing response resulted in an intravenous injection of a drug (2). Among the drugs that engendered and subsequently maintained responding were cocaine, *d*-amphetamine, morphine, codeine, pentobarbital, ethanol, and caffeine although there could not have been physiological dependence initially. It was finally shown clearly in several experiments that behavior could be maintained by consequent drug injections in the absence of physiological dependence (*e.g.*, 16a, 39, 56, 57). Even with drugs that can induce physiological dependence, the dependence can only enhance such responding, but cannot be essential for initiating or maintaining responding.

Analysis of Behavior

Several comprehensive accounts of the use of behavioral techniques and principles in behavioral pharmacology have been published (25, 27, 48). In the present section, we will consider some of these methods and concepts as they apply to drug-seeking and drug-taking behavior. Both Pavlovian and operant conditioning will be briefly discussed; it is likely that they are commingled in most instances of drug dependence.

In Pavlovian conditioning, a stimulus that produces a particular response is pre-

[1] We will use *physiological dependence* rather than the more commonly-used *physical dependence* because the measured responses are usually physiological and because the latter term encourages a philosophical dualism by implying that it has a complement such as mental or psychic dependence. Several of the authors in the present volume, while not disagreeing with our point of view, preferred to use physical dependence because it would be more familiar to many readers.

sented just after a stimulus that does not produce the response (neutral stimulus). After a few such paired presentations of the stimuli, the neutral stimulus itself may be followed by a response. For example, an injection of nalorphine results in profuse salivation in a morphine-dependent monkey; if a light is presented just before nalorphine injections, the light itself will come to be followed by salivation. The injection of nalorphine is called the unconditioned stimulus; the light is called the conditioning stimulus; and the salivation is called the conditioned response. If the light is repeatedly presented alone, salivation gradually ceases; this process, called experimental extinction, is typically slower than the original conditioning process.

In operant conditioning, the occurrence of a particular event just after a response increases the subsequent frequency of occurrence of responses of the same kind. For example, an injection of cocaine just after a monkey presses a lever will increase the subsequent frequency of lever-pressing responses. Under these conditions, lever pressing is called an operant; the increase in frequency of the operant is the process of operant conditioning or reinforcement; and the cocaine injection is called a reinforcer. If the response is no longer followed by a reinforcer, its frequency of occurrence will gradually decrease. This process is also called experimental extinction. Since the range of behaviors that can be controlled by operant conditioning is vast, it is a phenomenon of great generality.

Punishment is analogous to reinforcement and refers to the decreased subsequent frequency of responses similar to one that immediately preceded some event; the event is called a punisher; and the presentation of a punisher just after such a response is called punishment. To date, there have been few experiments concerned with whether drug injections can function as punishers (23).

Although reinforcement is a central concept in operant conditioning, terms relating to reinforcement may be used in different ways by different investigators or even by the same investigator at different times. Some events such as food or cocaine can function as reinforcers when they are delivered; others such as electric shock or naloxone can function as reinforcers when they are terminated. Some investigators call an event a positive reinforcer if it can increase responding that precedes its presentation or a negative reinforcer if it can increase responding that precedes its termination. It is often assumed that a positive reinforcer is an inherently pleasant event and that a negative reinforcer is an inherently unpleasant or aversive event, but more and more examples are inconsistent with this assumption (36, 37). Punishment is sometimes defined as the presentation of a negative reinforcer. And although the behavioral effects of presenting and terminating a negative reinforcer are often opposite, there are again numerous important exceptions (36, 37). Other investigators refer to both events simply as reinforcers because the increase in responding indicates the process of reinforcement in both instances and because this more general term does not involve a tacit assumption that the presentation or termination of an event will always have the same effect on behavior.[2]

Drugs and Schedules of Reinforcement

The injection of certain drugs consequent upon some behavior can develop and sustain that behavior. There is, as yet, no coherent account that explains why certain events are reinforcers. Speculation on the nature of reinforcement has not been profitable. For example, many investigators have believed that reinforcers act by

[2] Some investigators make a distinction between *operations* as experimental procedures that are imposed by the environment and *processes* as the behavioral effects of these procedures (1, 11). Although reinforcement is often described as a relation or operation—the presentation of a reinforcer just after a response—it is clear that the operation of reinforcement (or punishment) has a behavioral effect implicit in its meaning (37).

changing motivational states; it has often been surmised that a drug can function as a reinforcer because it produces pleasure or euphoria that leads to craving for the drug. Such interpretations of drug-seeking behavior have not been useful because they are expressed in terms that are undefined scientifically and, so far as they have any meaning, have been inconsistent with what is known about the properties of the diverse types of events that can function as reinforcers. The advantage of considering drug-seeking behavior in terms of reinforcement is not that this explains why drugs can act as reinforcers but rather that drug-seeking behavior can be analyzed functionally in the same way as other operant behavior.

Many of the most interesting characteristics of operant behavior are revealed only when reinforcers are delivered intermittently. The parameters of the sequential and temporal relations between responses and reinforcers are called schedules of reinforcement. One fundamental classification of schedules distinguishes between those that program the occurrence of the reinforcer on the basis of number of responses (ratio schedules) and on the basis of time (interval schedules). Comprehensive accounts of schedules of reinforcement have been published (11, 35, 40). In recent years, research on schedules of reinforcement has begun to provide data on the dynamic properties of drugs as reinforcers. As indicated in the first four sections of the present volume, schedule-controlled patterns of responding provide a meaningful way to compare drugs and other events as reinforcers; moreover, the effectiveness of a drug injection or other consequent event in controlling behavior can often be determined by the way in which it is scheduled.

Drug Injections and Other Events as Reinforcers

Many different types of events have been found to function as reinforcers. Under suitable conditions, for example, events as diverse as the presentation of food and the delivery of an electric shock can function similarly to maintain a characteristic pattern of responding under an interval schedule (26, 27, 30). However, the conditions required for the suitability of each type of event differ markedly. The degree of food deprivation and type of food can be important in the use of food presentation; the experimental history of the animal and the intensity of the electric shocks can be important in the use of electric shocks. Further, food and electric shock would be unlikely to maintain similar patterns of responding under a schedule in which each response produced the consequent event (31). This illustrates the general importance of conditions such as experimental history and type of schedule in determining whether characteristic patterns of responding will be maintained by a consequent event. Of course, knowledge about performances that are characteristic under particular schedules is essential for determining when appropriate conditions have been achieved.

As with other consequent events, drug injections can be used to engender and maintain operant behavior only under certain conditions. Although the dose of drug is of obvious importance, whether or not a particular dose will maintain responding depends upon other conditions such as the experimental history of the subject and the schedule of drug injection. For example, a dose of cocaine that will not maintain responding in a recently trained animal may do so in animals with well developed behavior (14). Also, Schlichting *et al.* (39) found that rates and patterns of responding initially maintained under ratio schedules of *d*-amphetamine injections in rhesus monkeys could differ depending on whether responding had previously been maintained by cocaine, codeine, or pentobarbital injections.

Since drugs that can function as reinforcers also have direct effects on behavior, the level of responding maintained by scheduled drug injections can reflect both of these actions. Several of the papers in the present volume are concerned with

minimizing the direct effects of a drug on behavior being controlled by the same drug as a reinforcer. One approach is to introduce after each injection a stimulus associated with a different condition for a period of time. The new condition is usually a time-out period, and while it prevails responding may be recorded but has no scheduled consequences (11). If the duration of action of the drug is short, the direct effects of each injection on responding during the periods in which the schedule of drug injection is in effect can be minimized by time-out periods of reasonable length (for example, 1 to 15 min), and possible cumulative effects of successive doses of the drug may be prevented. Under these conditions, the control of behavior by scheduled injections of cocaine, for example, has been improved (14, 17). If the duration of action of the drug is long, however, inordinately long time-out periods may severely restrict the time available for studying behavior.

Another approach to minimizing the influence of the direct effects of drugs is to use dependent variables other than rates of responding—for example, relative rates of responding—to measure the effects of drugs as reinforcers. In one study described in the present volume, for example, responding on each of two available levers was maintained under two independent but equal interval schedules of reinforcement that operated concurrently (24). As under single schedules, the average rates of responding on both levers would reflect in part the direct effects of drug injections. However, the relative rates of responding or the relative frequencies of drug injection can be used to estimate the degree of control exerted by each consequent event. This type of approach has been widely used in experimental psychology for studying parameters of reinforcement.

Although these two approaches to controlling the direct effects of drugs lead to the study of different types of experimental variables—the former emphasizes schedules and patterns of responding, for example, whereas the latter emphasizes reinforcement parameters and derived quantitative measures—both approaches give consistent results on the effects of relatively high doses of drugs that can reinforce behavior. Since rates of responding maintained by drug injections without time-out periods characteristically decrease as the dose is increased above some level, some investigators have suggested that drugs may be functioning as punishers at doses above this level. When the severe disruption of behavior produced by the direct effects of high doses is controlled, however, these doses can function effectively as reinforcers of behavior that precedes their injection. None of the evidence supports the notion that high doses function as punishers rather than as reinforcers.

Efficacy of Drugs as Reinforcers

In many studies of reinforcement, there is an explicit or implicit assumption that different consequent events can be ranked according to their reinforcing efficacy. Thus, drugs are assumed to have inherent properties that determine how effectively they will function as reinforcers. This assumption is usually explicit in those studies in which relative rates of responding or relative frequencies of drug injection are measured because the effects of different consequent events are being directly compared. It is still too early to tell whether the various specific methods for determining "preference" or "choice" will yield results that are applicable under other conditions. The assumption usually remains implicit in studies of behavior controlled by schedules of drug injection. Yet many studies have shown that rates and patterns of responding maintained by drug injections can be determined at least as much by factors such as the history of the individual and the schedule of drug injection as by inherent properties of the drug.

The limitation in the studies on efficacy of reinforcement by drugs appears to be their preoccupation with the inherent properties of the drugs. It would probably

be more fruitful to compare drugs on the basis of the range of different conditions under which they function as reinforcers. Thus, one might ask questions such as the following about each drug. What type of experimental history is required? Is physiological dependence important? Under what schedules can characteristic performances be maintained? What other effects occur at doses that control behavior? The answers to such questions should provide a functionally significant basis for comparing these drugs.

Environmental Determinants of Drug-Taking Behavior

The initial development of drug-taking behavior in man is usually attributed to sociological factors operating in conjunction with widespread availability of the drug; however, relatively few experimental studies have been concerned with environmental conditions that might predispose an individual to take drugs. Several papers in the present volume describe the use of an experimental method for developing drug-taking behavior as an adjunct to behavior directly controlled by schedules of reinforcement (9, 28, 33). When water is freely available to an animal exposed to certain schedules of intermittent food presentation, for example, the animal will ingest inordinately large volumes of water in each daily experimental session. This phenomenon, called schedule-induced polydipsia, is intriguing because the animal drinks many times its usual daily intake of water without being subject to any of the usual physiological or behavioral factors discussed under thirst (6–8). Several experimental studies have shown that schedule-induced polydipsia can occur with solutions containing ethanol, barbiturates, or narcotics (10, 29, 32, 38a). This method can be used in several different species to maintain a level of oral drug intake while studying the drug as a reinforcer (*e.g.*, 33) or while establishing physiological dependence (9, 28). Moreover, schedule-induced polydipsia is just one of various adjunctive behaviors that can be induced by various schedules of reinforcement. Thus, drug-taking behavior as adjunctive behavior should be susceptible to modulation by specific types of alterations in the inducing schedule of reinforcement.

After physiological dependence has developed in an individual, several new factors may enter into the control of drug-seeking and drug-taking behavior by scheduled injections of drugs. As noted previously, under these conditions withdrawal signs and symptoms develop if an injection is sufficiently delayed, and termination or postponement of withdrawal signs may contribute to the maintenance of responding that results in drug injections. Some experimental evidence indicates that in morphine-dependent animals responding leading to the injection of morphine increases when the time elapsed since the last morphine injection is made longer and withdrawal signs appear (41). Similarly, when withdrawal is precipitated in a morphine-dependent animal by the injection of a narcotic antagonist, rates of responding maintained by morphine injections can be enhanced (21, 47, 51).

In animals that have been made physiologically dependent on morphine, responding may be maintained that results in termination of the injection of narcotic antagonists or of stimuli that have been associated with their injection (4, 16, 45, 55). The results of several of the studies described in the present volume indicate that rates and patterns of responding controlled by these schedules of termination of drug injections are similar to those controlled by comparable schedules of electric shock termination (4, 45). In animals that have not been made physiologically dependent on morphine, some of the same effects have been observed with relatively high doses of the narcotic antagonists, but these effects have not been consistently obtained in different laboratories (22, 55). The studies of increased responding leading to morphine injections during withdrawal together with the studies of re-

sponding that terminated narcotic antagonist injections indicate that termination or postponement of withdrawal can function as a reinforcer in physiologically dependent animals.

Environmental stimuli that have been repeatedly associated with the withdrawal syndrome can through the process of Pavlovian conditioning come to evoke withdrawal signs (13, 19, 53). Several studies with experimental animals have shown that some withdrawal signs are observed in the presence of stimuli that had been present during the withdrawal syndrome produced by drug deprivation or precipitated by injection of a narcotic antagonist (15, 19, 54). In the present volume, O'Brien has described the conditioning of naloxone-induced withdrawal signs and symptoms in physiologically dependent human subjects (38). Such conditioned withdrawal symptoms might predispose formerly dependent individuals to take drugs again. Although conditioned withdrawal signs have been obtained in experimental animals that are no longer physiologically dependent (20, 53, 54), there is no objective evidence as yet to indicate that such conditions increase drug-seeking behavior.

Environmental stimuli that have been repeatedly associated with drug injections that function as reinforcers may also come to affect behavior that precedes their presentation (41). For example, several investigators have shown that during extinction of responding previously maintained by morphine administration, the frequency of responding will increase when it results in the presentation of stimuli that had been previously associated with injections of morphine (43). Stimuli that come to maintain behavior as a result of their association with drug injections are called conditioned reinforcers. The effects of such stimuli are usually transitory, diminishing over time when drug injections are no longer available.

Under certain schedules, called second-order schedules, responding results in a drug injection only when the animal has completed a sequence of schedule components. If a stimulus that has been associated with drug injections is presented at the completion of each schedule component, patterns of responding characteristic of the component schedule can be controlled by the stimuli over long periods of time with only occasional injections of drug (18). Although stimuli associated with drug injections can control responding under second-order schedules of this type, more evidence is needed to establish clearly the importance of the association between the stimulus and the drug injection.

Drug Abuse

Terms such as drug abuse or drug addiction are used in a general way to refer to aspects of drug-seeking and drug-taking behavior that are highly detrimental to the drug-dependent individual or to society. Most discussions of drug abuse have emphasized pharmacological factors related to particular classes of drugs. Thus, drugs such as the narcotic analgesics, barbiturates, or ethanol have long been considered as drugs that have a high abuse potential because of the possible development of tolerance and physiological dependence. More recently drugs such as amphetamines or cocaine are considered to have abuse potential because they can induce aggressive behavior and even pyschotic behavior. In the present paper we have been more concerned with discussing pharmacological and behavioral factors involved in drug dependence than with the possible adverse consequences of drug dependence.

The present analysis of control of drug-taking behavior by schedules of reinforcement emphasizes the behavioral processes involved in drug dependence that are general processes known also to operate in various situations not involving drugs. These processes are relevant to considerations of drug abuse because they maintain drug-taking behavior and are thereby responsible for the continued exposure of the individual to the effects of the drug. But

this is not the only way in which behavioral processes are relevant. There is much recent evidence that behavior is more controlled by the nature of the prevailing schedule of reinforcement than by the nature of the scheduled events; for example, experimental studies have shown that the responding of monkeys can be maintained by response-produced electric shocks under appropriate schedule conditions (30, 31, 36). Behavior developed by the operation of normal processes can be so powerfully controlled that it is maintained despite consequences that are detrimental to the individual (3). Thus, schedules of reinforcement embody much of what traditionally has been called motivation. One way in which such behavior can be detrimental is in pre-empting other important activities. In drug-dependent people, sequences of drug-seeking behavior—even when maintained by doses of heroin too low to induce physiological dependence—can become a way of life (49, 52, 53).

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