Reports from the Research Laboratories

of the

Department of Psychiatry

University of Minnesota

"Conditioning Factors and

Drug Dependence"

by

TRAVIS THOMPSON and ROY PICKENS

Report Number PR-67-3

Conditioning Factors and Drug Dependence[1]

Travis Thompson and Roy Pickens

August 15, 1967

PR-67-3

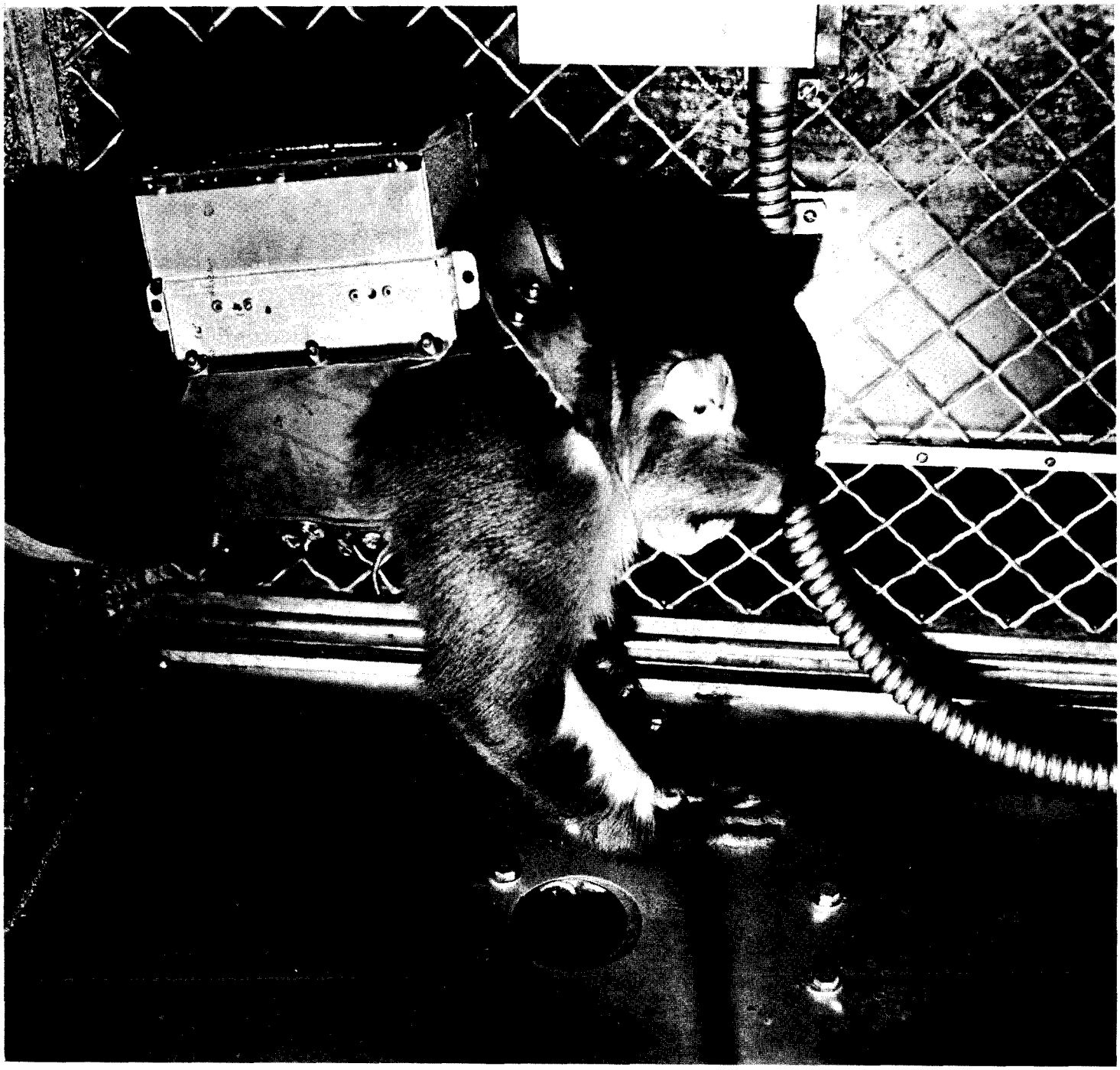
[1] The preparation of this article and part of the work reported herein was supported by Grants No. MH-14112, MH-11135 and MH-08565 from U.S.P.H.S.

Drug addiction[2] has existed for at least 3000 years (Terry, C. E., and Pellens, M., 1928), however the relation between drug dependence and basic learning phenomena has been a relatively recent discovery. Evidence of such a relation was first suggested by clinical observations (Kolb, L., 1939) and animal experiments (Spragg, S. D. S., 1940; Masserman, J. H., and Yum, K. S., 1946), indicating that drugs can have effects similar to those of known reinforcing events in operant conditioning. It was not until the mid-1950's, however, that experimental evidence definitely relating operant conditioning to drug dependence was presented. In general, operant behavior is controlled by its consequences. The specific consequence which strengthens the preceding behavior is called a reinforcer. In 1955 morphine was shown to serve as a reinforcer for physically dependent rats (Headlee, C. P., Coppock, H. W., and Nichols, J. R., 1955), much as food is a reinforcer for a hungry animal.

The fact that drugs can serve as reinforcers for operant responses has been widely confirmed. Procedures which provide animals with the opportunity to inject themselves with drug solutions (such as figure 1) (Davis, J. D., 1966; Popovic, V., and Popovic, P., 1960; Pickens, R., 1967; Slusher, M. A., and Browning, B., 1961; Weeks, J. R., 1962; Davis, W. M., and Nichols, J. R., 1963) or drink (Wikler, A., Martin, W. R., Pescor F. T., and Eades, C. G., 1963; Masserman, J. H., and Yum, K. S., 1946; and Casey, A., 1960), have been exploited for this purpose, and are called

---

[2] A drug dependent organism may be physically dependent, behaviorally dependent and/or may self-administer the drug on which it is dependent. Physical dependence refers to a condition produced by chronic drug administration in which a characteristic syndrome of illness ensues on discontinuing drug administration, while behavioral dependence refers to a comparable state characterized by behavioral disruption on discontinuing drug administration. While human drug addicts (e.g., morphine) exhibit all three features of drug dependence, many drugs are self-administered producing neither physical nor behavioral dependence.



self-administration methods. The largest body of evidence that drug self--administration falls within the framework of operant conditioning is based on opiate self-administration by physically dependent rats (Weeks, J. R., 1962; Weeks, J. R., and Collins, R. J., 1964) and monkeys (Thompson, T., and Schuster, C. R., 1964). More recent studies have shown that drugs from other classes will serve as reinforcers as well (Deneau, G., personal communication; Davis, J. D., and Miller, N. E., 1963; Pickens, R., Meisch, R., and McGuire, L. E., in press; Pickens, R., Harris, W., 1967; Pickens, R., and Thompson, T., in press). Sufficient data are now available to justify a more systematic examination of factors governing the ability of drugs to serve as reinforcers. An understanding of the ways in which these variables function in controlling drug-reinforced behavior is fundamental to understanding basic behavioral mechanisms underlying drug dependence.

If the analysis of drug dependence outlined above possesses verisimilitude, factors known to control acquisition, maintenance, and elimination of other operant responses should also control acquisition, maintenance, and elimination of drug-reinforced responses. Through an understanding of acquisition of behavior reinforced by drug injection, we may come to grasp initial development of drug dependence, through investigating factors influencing maintenance of already learned operant drug-reinforced responses we may have a better understanding of the maintenance of previously established drug dependence, and through studying factors known to contribute to the elimination of operant behavior we may come to understand basic mechanisms controlling the elimination of drug dependence. Finally, through studying the influence of drug dependence on other behaviors it may be possible to understand some of the factors which contribute and are related to the reinforcing effects of drugs.

The present paper systematically explores the possible role of the major classes of factors known to influence other operant responses, as they might relate to drug-reinforced behavior.

Acquisition and Maintenance of Drug Dependence

Antecedent Variables: An array of procedures performed prior to introducing organisms into an experimental situation can influence the acquisition and maintenance of operant responses. Among the most potent factors are the organism's past history and the current motivational conditions. When dealing with drugs as reinforcers an additional antecedant consideration is the pharmacological status of the organism (i.e., the degree of tolerance, the chronicity of drug treatment and the presence of other drugs).

Experience with the reinforcer and the particular mode of its presentation are of importance in initial acquisition. A common procedure used in the laboratory to establish new operant responses is called magazine training. In this method, a hungry animal is given experience with the reinforcing food pellets by repeatedly presenting food non-contingent on his behavior. Training of this sort greatly facilitates subsequent learning of a response which is to be reinforced by food pellets. By the same token, repeated infusion of a potentially reinforcing drug solution, non-contingent on the organism's behavior has the functional status of magazine training. It provides the organism with some experience with the reinforcing drug, and the specific mode of presentation (route of administration). Presumably such magazine training with drugs can markedly influence initial establishment of drug dependence. Hospitalized patients frequently receive drugs in this manner. This experience with potentially reinforcing drugs can provide the basis for subsequent drug dependence (Kolb, L., 1962).

Specific learning histories have been shown to faciliate reacquisition of operant responses reinforced by food, water and shock-avoidance (Keller, F. S., and Schoenfeld, W. N., 1950). The same is true of reinforcing drugs. Rats given a history of intravenous morphine reinforcement, then withdrawn, reacquire the self-administration response far more rapidly than matched subjects receiving the same amount of morphine, but not having learned a response to produce drug infusion (Weeks, J. R., 1967).

Motivational conditions are also of critical importance in conditioning and maintenance of operant behavior. Some minimal level of food deprivation is necessary for food to act as a reinforcer. Once the food--reinforced behavior has been acquired, the level of performance varies directly as a function of food deprivation conditions (Lawson, R., 1960). The role of drug deprivation conditions has been explored in physically dependent rats and monkeys. Monkeys were deprived of morphine for 24 hours producing an approximately tenfold increase in morphine reinforced responding (Thompson, T., and Schuster, C. R., 1964). Chemically-induced morphine deprivation was affected by nalorphine administration. Nalorphine antagonized the effects of morphine, thereby effectively placing the physically dependent organism in a state of deprivation, with morphine reinforced responding increased proportional to the dosage of nalorphine treatment (Weeks, J. R., 1962; Weeks, J. R. and Collins, R. J., 1964; Thompson, T., and Schuster, C. R., 1964).

Another procedure for studying motivational or deprivation conditions consists of "pre-feeding" an animal shortly before a work session in which food will be used as the reinforcer. Generally, diminution in food-reinforced responding covaries with the amount of prefeeding (Skinner, B. F., 1938). Similar experiments have been conducted in which morphine is administered to an animal shortly before the normal

work period was scheduled. An orderly diminution in morphine-reinforced responding was produced, comparable to the results obtained by pre-feeding in a food-reinforcement experiment (Thompson, T., and Schuster, C. R., 1964). Substitution of a related drug (etonitazine) diminished morphine--reinforced responding, supporting the notion that the effective degree of drug deprivation can alter drug-reinforced responding (Weeks, J. R., and Collins, R. J., 1964).

When non-opiates are used as the reinforcing drugs, the role of drug deprivation conditions is open to conjecture. Minimum deprivation intervals between successive drug administrations may be necessary for specific drugs to act as reinforcers. Presumably, the lengths of such deprivation periods will vary as a function of dosage per reinforcement.

One of the distinguishing characteristics of many drugs subject to human abuse is the tendency for development of tolerance on chronic administration. That is, increasing dosages of the drugs are required to produce the same effect. The role of tolerance in drug self-administration is not at all clear. Presumably the degree of tolerance to a given dosage of a drug would determine the range of dosages of a drug that would be reinforcing. As tolerance is developed to progressively higher dosages, the range of dosages which function as reinforcers should shift upward. Prior treatment of subjects with varying dosages of various stimulant (e.g., amphetamines, cocaine), opiates (e.g., morphine) and sedative-hypnotics (e.g., pentobarbital) might alter the ability of those drugs to serve as reinforcers. Tolerance may play quite different roles in various classes of drugs. Thus, tolerance may be more important in determining whether morphine will act as a reinforcer than cocaine. Whether this is the case can only be determined by investigating the effects of prior tolerance with these classes of drugs on their relative

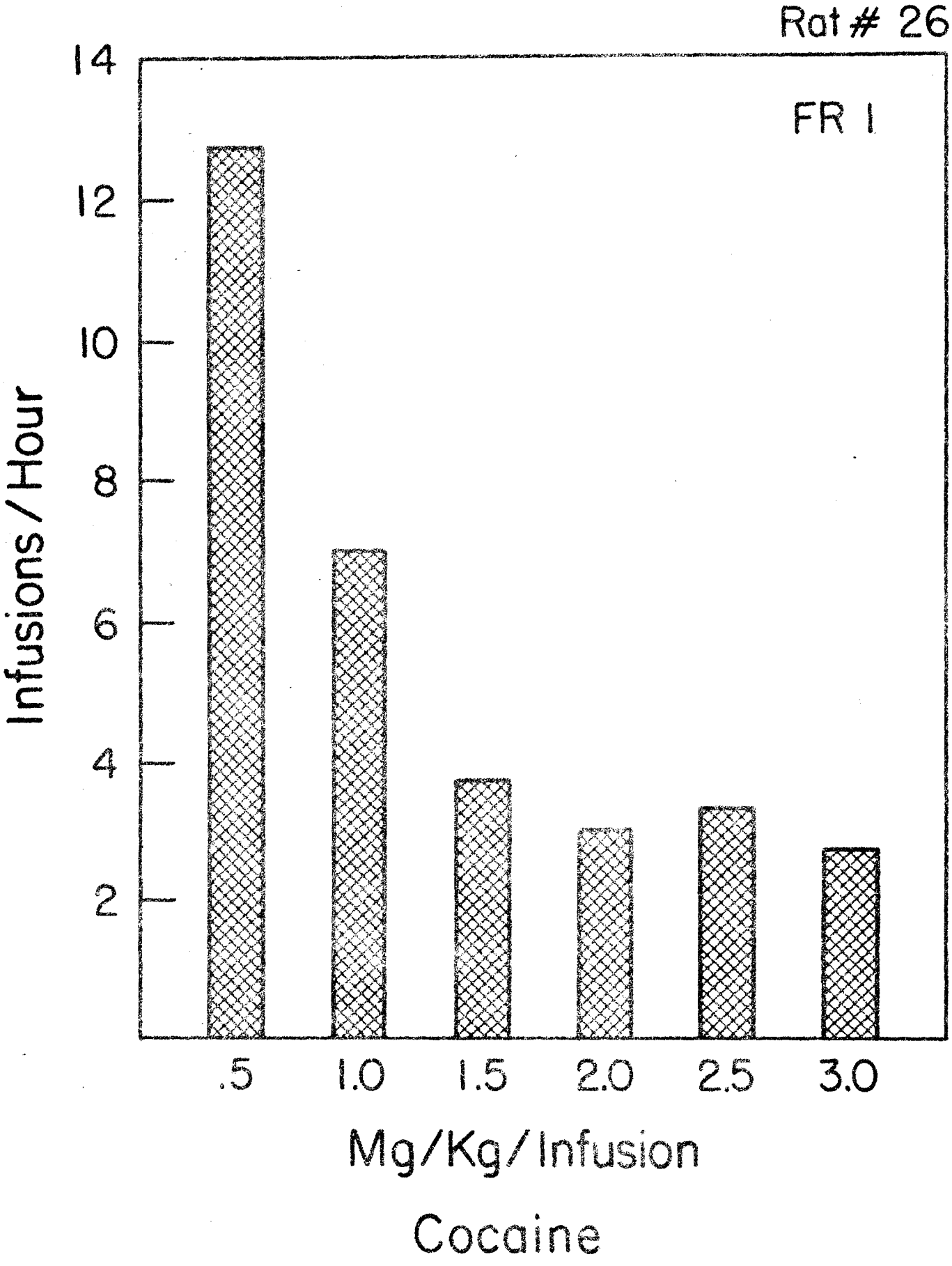
rates of acquisition. There is even suggestions that discontinuation of treatment with relatively high dosages of chlorpromazine induces a withdrawal syndrome (Waller, M. B., and Waller, P. F., 1962), suggesting that considerable tolerance may have developed with the possibility that the drug may be self-administered under those conditions.

The development of tolerance over a short period of treatment is quite a different matter from the effects of chronic treatment with high dosages of a drug. Monkeys self-administering high dosages of cocaine go through "voluntary" periods of abstinence (Deneau, G, personal communication). Long-term treatment with drugs may produce cumulative toxic effects which cannot be anticipated based on more acute preparations. This problem is particularly knotty with stimulant drugs where chronic self-administration has only recently begun to be investigated.

Reinforcement Variables: It is well known that certain substances are more effective as reinforcers than others (Cofer, C. N., and Appley, M. H., 1964). Thus, while food, electrical stimulation of the brain, and a flash of light will all serve as reinforcers, they vary widely in their effectiveness to reinforce and maintain operant behavior (Kish, G. B., 1955; Olds, J., 1958) and are influenced in different degrees by changes in experimental conditions such as satiation and extinction (Brady, J. V., Boren, J. J., Conrad, D., and Sidman, M., 1957; Seward, J. P., Uyeda, A, and Olds, 1959; Crowder, W. F., Morris, J. B., Dyer, W. R., and Robinson, J. V., 1961). There is evidence suggesting that some drugs are more reinforcing than others, as reflected in the clinical observations that heroin has a greater "addiction liability" than morphine, morphine has a greater addiction liability than phenadoxone, etc. (Eddy, N. B., Halback, H., and Braenden, O. J., 1957). Addicts are also known to prefer certain drugs and combinations of drugs to others and will work more actively to obtain them (Ausubel, D. P., 1963).

Inexorably tied to the question of kind of reinforcement is that of amount of reinforcement. A large amount of a normally less-preferred substance may be a more effective reinforcer in maintaining an instrumental response than a small amount of a highly preferred substance (Crespi, L. P., 1942). In general, increases in amount of food and water reinforcement are known to result in increases in level of performance (Kimble, G. A., 1961); however, with other reinforcers (e.g., heat, sucrose), curvilinear relationships have been found between amount of reinforcement and performance (Guttman, J., 1953; Weiss, B., and Laties, V. G., 1961). A curvilinear relationship has been observed between drug dosage (amount of reinforcement) and frequency of self-administration of morphine by animals when the dosage range is less than that necessary to produce observable physical dependence (Schuster, C. R., 1967). At higher dosages and with physically dependent animals, frequency of morphine self-administration is seemingly linearly related to infusion dosage (Weeks, J. R., and Collins, R. J., 1964). With cocaine, a drug which does not produce physical dependence, only a limited range of infusion dosages (0.5 to 3.0 mg/kg) will maintain drug self-administration (as shown in figure 2). Both higher and lower dosages produced ragged performance or a complete cessation of drug self-administration (Pickens, R., and Thompson, T., in press). Comparable effects have not been reported with morphine or other drugs which produce physical dependence (Beach, H. D., 1957; Weeks, J. R., 1962; Deneau, G., personal communication; Thompson, T., and Schuster, C. R., 1964).

Number of reinforcements is also known to influence the strength of an instrumental response. During initial acquisition the more frequently a response is reinforced, the greater the tendency for the response to recur (Lawson, R., 1960). Thus, presumably the more experience an


Rat # 26
FR 1
14
12
10
8
6
4
2
Infusions / Hour
.5
1.0
1.5
2.0
2.5
3.0
Mg/Kg/Infusion
Cocaine

organism has with a reinforcing drug, the greater will be its degree of "dependence" upon it. The importance of this variable in the development of drug dependence is suggested by the commonly heard addict's lament of taking that "one injection too many," although this behavior is undoubtably related to kind and amount of drug reinforcement and to other variables as well.

The time between the occurrence of a response and reinforcement is known to influence instrumental conditioning (Weeks, J. R., 1962; Weeks, J. R., and Collins, R. J., 1964; Thompson, T., and Schuster, C. R., 1964). Responses followed immediately by reinforcement are learned faster than those having a delay before reinforcement (Perin, C. T., 1943). The addiction liability of narcotic drugs is known to be related to the method of their administration. Oral administration with a rather long delay before peak of drug action yields a low addiction liability, while parenteral administration with a relatively rapid peak of drug action produces a much higher addiction liability (Goodman, L. S., and Gilman, A., 1963). While it would thus seem that the intravenous route would always be the favored method of drug administration among addicts, such is not the case. In fact, of the most commonly abused drugs, morphine, heroin, and cocaine are almost always injected intravenously, while pentobarbital and amphetamine are taken orally and marijuana is smoked (Way, E. L., 1965). This apparent discrepancy between theory and fact has not yet been investigated, but it seems likely that at least part of the discrepancy may be related to the forms in which the drugs are readily available and the untoward effects involved in administration of the various compounds (e.g., abscesses formed by pentobarbital in the subcutaneous tissues).

Drugs are rarely freely available to human addicts. More commonly, drugs are available at specified times, and after completion of a specified amount of work (usually expressed in terms of an amount of money earned). Stated in terms of contingencies for reinforcement, one can say the addict is reinforced on some interval schedule[3], following completion of a specified ratio[4] of work. Among the variables most profoundly important in the maintenance of any operant behavior is the schedule of reinforcement (Ferster, C. B., and Skinner, B. F., 1957; Morse, W. H., 1966). It would be very suprising if the schedule of drug reinforcement were not equally important in the maintenance of drug self-administration behavior. Evidence accumulated to date indicates that at least some of the schedules of reinforcement investigated using food and water as reinforcers generate similar patterns of drug-reinforced responding. Generally characteristic fixed-ratio performance[5] using morphine as a reinforcer has been reported, though the temporal characteristics of performance were quite different (Weeks, J. R., 1962; Weeks, J. R., and Collins, R. J., 1964). Variable-interval[6] morphine reinforcement produces a characteristic low steady rate of responding, much as has been observed with other reinforcers (Woods, J., 1967). Across an array of fixed-ratio values, cocaine reinforcement produces characteristic fixed-ratio run,

---

[3] A reinforcement schedule in which the first response after a specified interval following the preceding reinforcement will be reinforced.

[4] A reinforcement schedule in which the first response after a specified number of responses following the preceding response will be reinforced.

[5] A reinforcement schedule in which the first response after a fixed number of responses following the preceding reinforcement will be reinforced.

[6] A reinforcement schedule in which the first response after a specified time interval following the preceding response, will be reinforced, where the interval length varies randomly around a predetermined mean.

alternating with regular pausing (Pickens, R., and Thompson, T., in press). The pause duration is very reliable, but far longer than might be expected with other reinforcers. A chained schedule[7] of morphine reinforcement produced characteristic chained schedule performance (Thompson, T., and Schuster, C. R., 1964).

Stimuli paired with reinforcers gain reinforcing properties of their own. Such conditioned reinforcers are thought to be responsible for maintaining complex sequences of responses both inside and outside the laboratory (Kelleher, R. T., 1966). Repeated pairing of drug administration with other reinforcing stimuli (e.g., food, shock, social stimuli) may cause drugs to be reinforcing in their own right. For example, dogs were infused with acetylcholine, norepinephrine or epinephrine preceding a painful shock. Soon the infusion of the drug alone lead to occurrence of a response which would terminate infusion and avoidance of the painful shock. Thus, not only did the drug infusion act as a warning stimulus, but its removal was reinforcing (Cook, L., Davidson, A., Davis, D. J., and Kelleher, R. T., 1960). Similarly, cats were conditioned to avoid the arm in a T-maze that was associated with infusion of norepinephrine, when injection of that drug had been followed by painful shock (Sharpless, S. K., 1961). The circumstances under which many drugs (e.g., alcohol, marijuana) are taken by humans are social and one might therefore expect these drugs would gain their reinforcing properties, in part, because of pairing with social reinforcement.

---

[7] A reinforcement schedule in which satisfying the contingencies of a first component produces a stimulus, in the presence of which satisfying a second set of contingencies leads to reinforcement. The contingencies in this case were a fixed interval two minute-fixed ratio 25 chain. T. Thompson and C. R. Schuster, Psychopharmacologia 5, 87 (1964).

Not only may drugs gain reinforcing properties when paired with other reinforcing stimuli, but other stimuli which were not initially reinforcing may come to be reinforcing because they are paired with drug infusion. A light paired with drug infusion has been shown to be capable of maintaining responding on discontinuation of morphine reinforcement (Schuster, C. R., and Thompson, T., 1962; Schuster, C. R., 1967). Presumably a great many stimuli associated with drug reinforcement may come to be reinforcing and may be responsible for maintaining much "drug-seeking" behavior, even in the non-physically dependent organism. The role of such conditioned reinforcers in maintaining drug-reinforced behavior is essential to understanding, and ultimately controlling drug dependence.

Current Circumstance: Since not all people taking addicting drugs become drug addicts, it seems obvious that drug dependence is not due to drug action alone. In all likelihood, drugs must act in combination with other factors to become reinforcers, just as food and water are not reinforcers in their own right but become so only when certain conditions prevail (Cofer, C. N., and Appley, M. H., 1964). Little experimental attention, however, has been paid to the role of current circumstances in the development and maintenance of human drug dependence. Perhaps the most important of these factors are the social influences which comprise the organism's immediate stimulus environment. Just as the effects of antecedent conditions and reinforcement variables are not the same for all classes of abused drugs, neither are the environmental factors influencing drug dependence expected to be the same for all drugs. While one type of environment may increase the tendency to self-administer one drug, it may decrease the tendency to self-administer a second drug and have little or no effect on the self-administration of a third. Besides influencing the tendency for drug self-administration, a specific environ-

ment may be the necessary condition for the development of self-administration of certain drugs. For example, amobarbital and alcohol have been shown not to be self-administered in one environment, but actively self--administered under other circumstances (Davis, J. D., and Miller, N. E., 1963; Masserman, J. H., and Yum, K. S., 1946). Clearly, therefore, drug self-administration is dependent at least to some extent on the environment of the organism.

An aversive environment is reported to be a significant factor in the development of human drug addiction (Ausubel, D. P., 1963). It has been hypothesized that drugs serve as reinforcers in such environments by their ability to decrease the effects of aversive stimulation (Davis, J. D., and Miller, N. E., 1963). The influence of sensory deprivation or isolation on behavior also appears to be similar to that of aversive stimulation (Miller, N. E., 1948; Berlyne, D. E., 1955; Welker, W. I., 1956). Consequently, drugs which change sensory input (e.g., analgesics, hypnotics, hallucinogenics, etc.) may become reinforcing under these conditions.

Social factors in the organism's environment are also thought to play a significant role in the development of drug dependence. Indeed, it would seem fair to say that human drug addiction, at least initially, is outstandingly social in character. Social reinforcement contingent on drug taking, reinforcement of imitation (Miller, N. E., and Dollard, J., 1941) and social enhancement of effectiveness of a drug (Lundin, R. W., 1961) might all contribute to the role of social interaction in drug dependence.

The importance of current circumstances in drug dependence is illustrated by a study (Thompson, T., and Ostlund, W., 1965) in which rats were orally addicted, withdrawn, then half were readdicted in the same environment and half in a new environment. Changing the environment significantly diminished the rate of readdiction. Thus, a specific history with drug-reinforced behavior under a given set of conditions

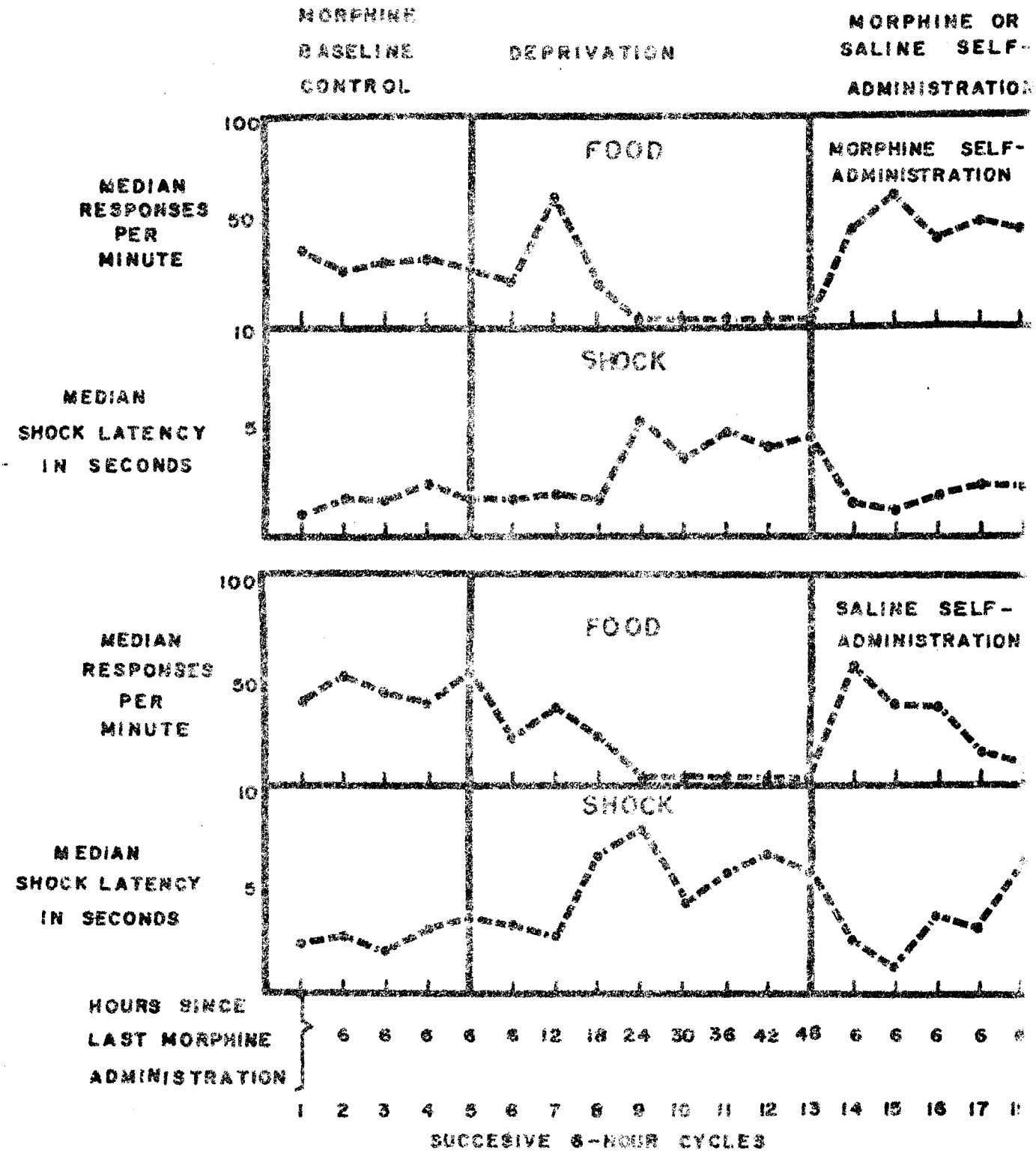
profoundly altered subsequent reacquisition of the previously learned response.

Effects of Drug Dependence on Other Behavior

Clinical evidence suggests that drug dependence has a pervasive influence on the organism's behavior. The nature of this influence depends in part on the type of drug on which the organism is dependent. For example, opiate addiction decreases behavior concerned with the attainment of food, sex, and social stimulation, while barbiturate or alcohol dependence does not (Wikler, A., 1953). Experimental evidence also indicates an interaction between drug self-administration and other behavior in animals. Morphine self-administration and abstinence have been found to interact with food-reinforced and shock-avoidance behaviors in monkeys (Thompson, T., and Schuster, C. R., 1964). Under conditions of morphine abstinence, food-reinforced and shock-avoidance behaviors were disrupted, but recovered again after reinstatement of drug self-administration. Stimuli paired with morphine infusion were also capable of reinstating the disrupted behaviors, though only temporarily (figure 3). No investigation of this sort has been conducted with drugs which are non-narcotics and/or do not produce physical dependence.

Elimination of Drug Dependence

The common methods for eliminating operant responses are punishing the unwanted response, discontinuing reinforcement or satiation with the reinforcer. The traditional treatment for drug addiction, on the other hand, has involved depriving the addict of the drug. This technique is based on the observation that abstinence leads to elimination of physical dependence, which in the case of the opiates and barbituates is associated with diminished frequency of drug self-administration. Experimental investigation of the effectiveness of abstinence in eliminating drug

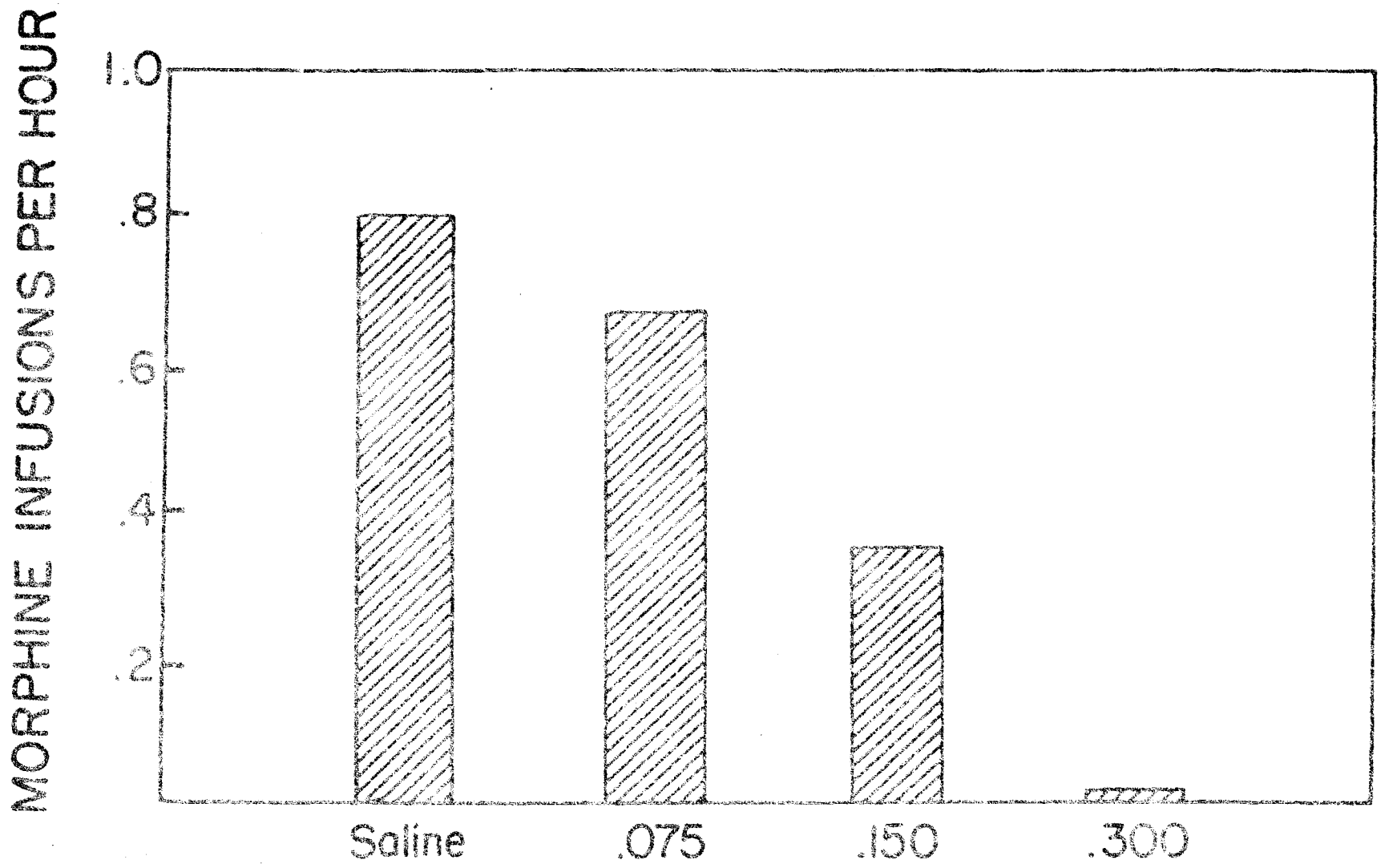

MORPHINE BASELINE CONTROL
DEPRIVATION
MORPHINE OR SALINE SELF-ADMINISTRATION
MEDIAN RESPONSES PER MINUTE
100
50
10
FOOD
MORPHINE SELF-ADMINISTRATION
MEDIAN SHOCK LATENCY IN SECONDS
5
SHOCK
MEDIAN RESPONSES PER MINUTE
100
50
10
FOOD
SALINE SELF-ADMINISTRATION
MEDIAN SHOCK LATENCY IN SECONDS
5
SHOCK
HOURS SINCE LAST MORPHINE ADMINISTRATION
6 6 6 6 6 12 18 24 30 36 42 48 6 6 6 6 6
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
SUCCESIVE 6-HOUR CYCLES

dependence has only recently been initiated. Animals withdrawn and repeatedly given the opportunity to self-administer morphine take the drug with reliability (Weeks, J. R., 1967). Such data suggest that abstinence alone is not a sufficient condition to eliminate drug reinforced responding.

Punishment is perhaps the most commonly used procedure for eliminating unwanted behaviors (Azrin, N. H., and Holz, W. C., 1966). The general procedure consists of presenting some consequence following a response, decreasing the frequency of the response that produced it. For example, if each food-reinforced response produces a brief shock, the food-reinforced response will tend to decrease in frequency. Such aversive stimulation is said to suppress the ongoing food-reinforced response.

Substituting methadone for morphine or heroin in the opiate dependent addict has received increasing attention in the past few years (Dole, V. P., and Nyswander, M., 1965). This procedure is essentially one of satiating the addict so opiates will not function as reinforcers. Satiation has the effect of suppressing the instrumental response which has been maintained by that reinforcer. Methadone has been shown to reduce morphine self-administration in the monkey (see figure 4). This method for controlling drug self-administration is effective as long as the treatment is given.

Behavior is rarely entirely eliminated by punishment or satiation. Instead behavior is temporarily suppressed as long as the contingencies are in effect. If one wants to truly eliminate an instrumental response, it is generally necessary to extinguish it -- that is to allow the response to occur but go unreinforced. By using various extinction procedures it may be possible to effect long-term suppression of subsequent drug-reinforced responding. One approach is to allow the animal to con-


MORPHINE INFUSIONS PER HOUR
1.0
.8
.6
.4
.2
Saline
.075
.150
.300
HOURLY INJECTIONS OF METHADONE
IN MG/KG

tinue responding for the drug but to decrease the dosage per reinforcement. Insufficient reinforcement with drugs such as cocaine, d-amphetamine and methamphetamine (Pickens, R., and Thompson, T., 1967; Pickens, R., Meisch, R., and McGuire, L. E., 1967; Pickens, R., and Harris, W., 1967) indicate that responding ceases rather abruptly and all together if the magnitude of reinforcement decreased to a minimal level. Comparable manipulations with morphine produce prolonged responding, suggesting that the diminished dosage retains potent reinforcing properties.

Finally, if one hopes to eliminate drug-reinforced behavior, it will also be necessary to weaken the effectiveness of stimuli associated with drug administration. The importance of such stimuli in maintaining behavior cannot be overemphasized. For example, it was found that chimpanzees would emit as many as 120,000 responses per food reinforcement, when every 400th response produced a stimulus which had been paired with food. In the absence of these conditioned reinforcers, lever pressing ceased altogether (Findley, J. D., and Brady, J. V., 1964). It seems evident that the extended behavior sequences called "drug seeking" are maintained by-and-large by stimuli paired with drug administration. Elimination of such behavior necessitates no longer presenting stimuli associated with drug administration, much as elimination of lever pressing required discontinuing presentation of the stimulus paired with food.

Summary

Knowledge of the variables controlling a particular operant behavior is a prerequisite to an understanding of the behavioral mechanisms by which a drug influences that behavior (Thompson, T., and Schuster, C. R., 1968). In drug self-administration, the drug can be viewed as one variable in the network of interacting factors controlling the drug-maintained operant. Antecedant conditions, current stimulus circumstances, qualitative and quantitative properties of the reinforcing drug as well as stimuli associated with drug administration, all have the status of "behavioral" variables affecting the drug-reinforced response. In the present paper we have reviewed the roles of each of these classes of factors as they relate to the initial development of drug dependence (acquisition), the maintenance and elimination of drug dependence. Finally, the interactions between drug-reinforced responding and behavior controlled by other reinforcers and contingencies have been examined. The body of evidence indicates that drug self-administration and dependence can be profitably analyzed within this framework, leading to insights into basic mechanisms underlying drug dependence as well as suggesting other avenues of approach to the many unanswered questions.

Footnotes

Ausubel, D. P. Drug addictions: Physiological, psychological, and sociological aspects. New York: Random House, 1963.

Azrin, N. H., and Holz, W. C. Punishment. In Honig, W. H. (Ed.) Operant behavior: Areas of research and application. New York: Appleton-Century-Crofts, 1966.

Beach, H. D. Morphine addiction in rats. Canad. J. Psychol., 1957, 11, 104-112.

Berlyne, D. E. The arousal and satiation of perceptual curiosity in the rat. J. comp. physiol. Psychol., 1955, 48, 238-246.

Brady, J. V., Boren, J. J., Conrad, D., and Sidman, M. The effect of food and water deprivation upon intracranial self-stimulation. J. comp. physiol. Psychol., 1957, 50, 134-137.

Casey, A. The effects of stress on consumption of alcohol and reserpine. Quart. J. Stud. Alchol., 1960, 21, 208-216.

Cofer, C. N., and Appley, M. H. Motivation: Theory and research. New York: John Wiley and Sons, 1964.

Cook, L., Davidson, A., Davis, D. J., and Kelleher, R. T. Epinephrine, norepinephrine, and acetylcholine as conditioned stimuli for avoidance behavior. Science, 1960, 131, 990-991.

Crespi, L. P. Quantitative variation of incentive and performance in the white rat. Am. J. Psychol., 1942, 55, 467-517.

Crowder, W. F., Morris, J. B., Dyer, W. R., and Robinson, J. V. Resistance to extinction and number of weak-light reinforcements. J. Psychol., 1961, 51, 361-364.

Davis, J. D. A method for chronic intravenous infusion in freely moving rats. J. exp. Anal. Behav., 1966, 9, 385-387.

Davis, J. D., and Miller, N. E. Fear and pain: Their effect on self--injection of amobarbital sodium by rats. Science, 1963, 141, 1286-1287.

Davis, W. M., and Nichols, J. R. A technique for self-injection of drugs in the study of reinforcement. J. exp. Anal. Behav., 1963, 6, 233-235.

Dole, V. P., and Nyswander, M. A medical treatment of diacetylmorphine (heroin)addiction. J. Am. Med. Ass., 1965, 195, 646-650.

Eddy, N. B., Halback, H., and Braenden, O. J. Synthetic substances with morphine-like effects. Bull. Wld. Hlth. Org., 1957, 17, 569-863.

Ferster, C. B., and Skinner, B. F. Schedules of reinforcement. New York: Appleton-Century-Crofts, 1957.

Findley, J. D., and Brady, J. V. Facilitation of large ratio performance by use of conditioned reinforcement. J. exp. Anal. Behav., 1965, 8, 125-129.

Goodman, L. S., and Gilman, A. The pharmacological basis of therapeutics. New York: Macmillan, 1963.

Guttman, N. Operant conditioning, extinction, and periodic reinforcement in relation to concentration of sucrose used as a reinforcing agent. J. exp. Psychol., 1953, 46, 213-224.

Headlee, C. P., Coppock, H. W., and Nichols, J. R. Apparatus and technique involved in a laboratory method of detecting the addictiveness of drugs. J. Amer. Pharm. Ass. (Sci. ed.) 1955, 44, 229-231.

Kelleher, R. T. Chaining and conditioned reinforcement. In W. H. Honig (Ed.) Operant behavior: Areas of research and application. New York: Appleton-Century-Crofts, 1966. pp. 160-212.

Keller, F. S., and Schoenfeld, W. N. Principles of psychology. New York: Appleton-Century-Crofts, 1950.

Kimble, G. A. Hilgard and Marquis' conditioning and learning. New York: Appleton-Century-Crofts, 1961.

Kish, G. B. Learning when the onset of illumination is used as reinforcing stimulus. J. comp. physiol. Psychol., 1955, 48, 261-264.

Kolb, L. Drug addiction as a public health problem. Sci. Monthly, 1939, 48, 391.

Kolb, L. Drug addiction: A medical problem. Springfield, Illinois: Thomas, 1962.

Lawson, R. Learning and behavior. New York: Macmillan, 1960.

Lundin, R. W. Personality: An experimental approach. New York: Macmillan, 1961.

Masserman, J. H., and Yum, K. S. An analysis of the influence of alcohol on experimental neurosis in cats. Psychosom. Med., 1946, 8, 36-52.

Miller, N. E. Studies of fear as an acquirable drive. I. Fear as motivation and fear-reduction as reinforcement in the learning of new responses. J. exp. Psychol., 1948, 38, 89-101.

Miller, N. E., and Dollard, J. Social learning and imitation. New Haven: Yale University Press, 1941.

Morse, W. H. Intermittent reinforcement. In W. H. Honig (Ed.) Operant behavior: Areas of research and application. New York: Appleton--Century-Crofts, 1966. pp. 52-108.

Olds, J. Satiation effects in self-stimulation of the brain. J. comp. physiol. Psychol., 1958, 51, 675-678.

Perin, C. T. A quantitative investigation of the delay-of-reinforcement gradient. J. exp. Psychol., 1943, 32, 37-51.

Pickens, R. A device for chronic intravenous injection of drugs in unrestrained rats. Rpts. Res. Lab., Dept. of Psychiatry, Univer. of Minnesota, No. PR-67-2, April, 1967.

Pickens, R., and Harris, W. C. Self-administration of d-amphetamine by rats. Psychopharmacologia, in press.

Pickens, R., Meisch, R., and McGuire, L. E. Methamphetamine reinforcement in rats. Psychon. Sci., 1967, 8, 371-372.

Pickens, R., and Thompson, T. Cocaine-reinforced behavior in rats: Effects of reinforcement mganitude and fixed-ratio size. J. Pharm. exp. Ther., in press.

Popovic, V., and Popovic, P. Permanent cannulation of aorta and vena cava in rats and ground squirrels. J. appl. Physiol., 1960, 15, 727.

Schuster, C. R. Classically conditioned morphine withdrawal and influence of morphine on effects of other reinforcers. Paper presented at Midwest. Psychol. Ass., Chicago, 1967.

Schuster, C. R., and Thompson, T. I. Self-administration of morphine in physically dependent Rhesus monkeys. Lab. Psychopharm., Univer. of Maryland, Tech. Rpt. No. 62-29, 1962.

Seward, J. P., Uyeda, A., and Olds, J. Resistance to extinction following cranial self-stimulation. J. comp. physiol. Psychol., 1959, 52, 294-299.

Sharpless, S. K. Effects of intravenous injection of epinephrine and norepinephrine in a choice situation. J. comp. physiol. Psychol., 1961, 54, 103-108.

Skinner, B. F. The behavior of organisms. New York: Appleton--Century-Crofts, 1938.

Slusher, M. A., and Browning, B. Morphine inhibition of plasma corticosteroid levels in chronic venous-catheterized rats. Am. J. Physiol., 1961, 200, 1032.

Spragg, S. D. S. Morphine addiction in chimpanzees. Comp. Psychol. Monogr., 1940, 15, No. 7.

Terry, C. E., and Pellens, M. The opium problem. New York: Bureau of Social Hygiene, 1928.

Thompson, T., and Ostlund, W. Susceptibility to readdiction as a function of the addiction and withdrawal environment. J. comp. physiol. Psychol., 1965, 59, 388-392.

Thompson, T., and Schuster, C. R. Morphine self-administration, food--reinforced and avoidance behaviors in Rhesus monkeys. Psychopharmacologia, 1964, 5, 87-94.

Thompson, T., and Schuster, C. R. Behavioral pharmacology. Englewood, N. J.: Prentice-Hall, 1968.

Waller, M. B., and Waller, P. F. Effects of chlorpromazine on appetitive and aversive components of a multiple schedule. J. exp. Anal. Behav., 1962, 5, 259-264.

Way, E. L. Control and treatment of drug addiction in Hong Kong. In Wilner, D. M., and Kassebaum, G. G. (Eds.) Narcotics. New York: McGraw-Hill, 1965.

Weeks, J. R. Experimental morphine addiction: Method for automatic intravenous injections in unrestrained rats. Science, 1962, 138, 143-144.

Weeks, J. Self-administration of opiates by rats. Paper presented at Midwestern Psychological Association, Chicago, May 5, 1967.

Weeks, J. R., and Collins, R. J. Factors affecting voluntary morphine intake in self-maintained addicted rats. Psychopharmacologia, 1964, 6, 267-279.

Weiss, B., and Laties, V. G. Behavioral thermoregulation. Science, 1961, 133, 1338-1344.

Welker, W. I. Variability of play and exploration in chimpanzees. J. comp. physiol. Psychol., 1956, 49, 181-185.

Wikler, A. Opiate addiction. Psychological and neurophysiological aspects in relation to clinical problems. Springfield, Illinois: Thomas, 1953.

Wikler, A., Martin, W. R., Pescor, F. T., and Eades, C. G. Factors regulating oral consumption of an opioid (etonitazene) by morphine--addicted rats. Psychopharmacologia, 1963, 5, 55-78.

Woods, J. Parametric studies of morphine self-administration by monkeys. Paper presented at Midwest. Psychol. Ass., Chicago, 1967.

Figure Legends

Figure 1. A system permitting intravenous drug self-administration by unrestrained Rhesus monkeys. The leather vest supports a back-pack containing a radio receiver and battery-operated infusion pump. The monkey presses a lever activating a nearby transmitter, which sends a signal to a receiver located inside the back-pack. When the receiver is operated the pump infuses drug solution into the internal jugular vein via a chronically indwelling catheter.

Figure 2. Effects of magnitude of intravenous cocaine reinforcement on rate of responding by a rat. There is an inverse relation between dosage per infusion and response rate from 0.5 to 3.0 mg/kg/infusion, and a mean hourly intake of 7.3 mg/kg/hour. At higher or lower dosages, responding becomes erratic and ceases altogether (Pickens, R., and Thompson, T., in press).

Figure 3. The disruptive effect of morphine abstinence on food and shock avoidance behaviors in the Rhesus monkey. A monkey self-administering 1 mg/kg of morphine every six hours, also worked for food pellets and avoided a painful electric shock. The upper graph shows food and avoidance behaviors under conditions of morphine self-administration, 48 hours without the opportunity to self-administer morphine, followed by a return to morphine self-administration baseline. During morphine deprivation, both food-reinforced and shock-avoidance behaviors deteriorated. The lower graph shows a replication in which saline was substituted for morphine and a light which had been paired with morphine was presented following each response, after the 48 hour abstinence period. Note the temporary return of food and shock avoidance behaviors (Thompson, T., and Schuster, C. R., 1964).

Figure 4. Effects of methadone treatment of morphine self-administration by monkeys. The frequency of 0.15 mg/kg intravenous morphine self--administrations over a six-hour period was reduced by hourly intramuscular injections of methadone (Pickens, R., and Thompson, T., unpublished data).