SELF ADMINISTRATION OF AND BEHAVIORAL DEPENDENCE ON DRUGS[1]

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INTRODUCTION

Man has self-administered chemical substances since before recorded history [Lewin (1)]. When an individual self-administers an illicit or a legal drug in amounts which society considers excessive or inappropriate, the terms "drug abuse" and "addiction" have frequently been applied. Objective investigation of drug self-administration has been hampered by the a priori moral implications inherent in these terms. It has become increasingly clear that a scientific understanding of drug dependence must be based on more purely descriptive concepts divested of such moral evaluations. Since 1929 it has been recognized that the biological factors involved in drug dependence can be studied in infra-human organisms [Tatum, Seevers & Collins (2)]. It has, however, only recently been accepted that the behavioral aspects of drug dependence can be studied in infra-human organisms. In addition to the obvious advantage of greater experimental control, the use of infra-human organisms has another more subtle advantage. The investigator using infra-human organisms is less likely to invoke untestable mentalistic constructs as the factors generating the self-administration of drugs.

We believe that the literature regarding the behavioral aspects of drug dependence can most profitably be interpreted within the framework of operant conditioning principles. The fundamental principle underlying operant conditioning is that certain aspects of behavior are controlled by their consequences. Past occurrence of certain behavioral consequences controls the future frequency of recurrence or pattern of behavior or both which produced those consequences. Behavior controlled by its consequences is termed operant behavior and the controlling consequences are reinforcers. A drug serving as a controlling consequence for the operant behavior leading to its administration is therefore defined as a reinforcer. The principal goal of the experimental analysis of the behavioral aspects of drug dependence is to determine the biological and environmental variables which modify a drug's reinforcing efficacy, that is, the extent to which a drug is self-administered.

The purpose of this review is to examine the classes of variables which have been demonstrated to affect the self-administration of drugs.

[1] The survey of literature pertaining to this review was concluded in June 1968.

TECHNOLOGY FOR STUDYING DRUG-SELF-ADMINISTRATION

The development of techniques permitting experimental animals to self-administer drugs has provided a major impetus to research on the behavioral aspects of drug dependence. The principal developments in drug-self-administration technology have taken place since 1955 [Headlee, Coppock & Nichols (3)]; however, this type of drug administration has its conceptual roots in early investigations on alcohol consumption by animals [Masserman & Yum (4)]. Self-administration methods are distinguishable on the basis of the route of administration: (*a*) oral, (*b*) inhalation, (*c*) intraperitoneal, (*d*) intracerebral, and (*e*) intravenous.

Few studies have involved inhalation, intraperitoneal, and intracerebral injection methods. Jarvik (5) published the only experimental report of inhalation self-administration by animals. Puffing one of two tubes (one providing tobacco smoke mixture, the other containing heated air) was used to assess the reinforcing properties of tobacco smoke for monkeys. Headlee, Coppock & Nichols (3) were not only the first to demonstrate clearly that drug administration could act as a reinforcing consequence for animals, but have been the only investigators to use an intraperitoneal route of self-administration. In their study, restrained rats were conditioned to turn their heads laterally, interrupting a beam of light falling on a photo-electric cell, thus starting an infusion pump. The pump infused a morphine solution through a hypodermic needle inserted through the body wall directly into the peritoneal cavity. A detailed description of a later version of this method has been given by Davis & Nichols (6). Intracerebral self-administration of drug solutions was first reported by Olds & Olds (7) using pipettes chronically implanted in the lateral hypothalamus. Initial observations suggested that rats would self-administer iproniazid at significantly higher rates than equal volumes of a Ringer's solution; however, subsequent studies showed that these effects were attributable to the relatively large volumes injected (1 mm^3) and the pH of the solutions (about 3.5) [Olds (8)]. Myers (9) reported on a system for chronic intracerebral drug self-infusion.

In most research on drug self-administration the oral or intravenous routes have been used. In oral self-administration methods, animals are given a choice of several solutions, one an active drug, and the others tap water, sucrose, or quinine. Further, they may be induced to drink drug solutions adjunctively or to obtain other reinforcers. The "preference" methods often involve prior parenteral administration to establish physical dependence [Nichols, Headlee & Coppock (10), Wikler et al. (11)], or the imposition of a procedure assumed by the experimenter to be stressful [Masserman & Yum (4), Kamano & Arp (12)], though it has recently been shown that rats can be trained to drink morphine solutions without pretreatment or apparent environmental stress [Kumar, Steinberg & Stolerman (13)]. The relative tendency to ingest the drug and control solutions is subsequently assessed. As with all such "preference" methods the

palatability of the solution is inextricably tied to any reinforcing properties the drug might have. For example, even when the drug solution and quinine are matched initially for aversiveness, it cannot be assumed that animals adapt at the same rate to the suppressive effects of the solutions on drinking. When two or more solutions are presented concurrently there is also the problem of "position habit," i.e. the animal will tend to ingest the solution in one tube more frequently than another regardless of its contents. Further, the drinking tubes themselves may vary in their characteristics, thus giving rise to a preference. It is therefore necessary to alternate not only the position of the test solutions, but the dispensing bottle as well. Failure to include such a control may cause animals to cease taking a drug simply by changing the position of the drug tube, which might be misinterpreted as a "cure" [Gillespie & Lucas (14)]. A further confounding factor is that it is nearly always necessary to deprive animals of water for 24 to 72 hr before beginning an oral preference test because little fluid will be consumed at lower deprivation states. Hence, the degree of water deprivation plays an important role in the initial establishment of drug dependence.

A further disadvantage of the oral route of administration is the variability in time and amount of the drug absorbed. It is well established that reinforcers are maximally effective when the delay between the response being conditioned and the time of reinforcement is minimal. The time delay between the drinking response and the occurrence of the pharmacological effect of the drug may retard conditioning. A further limitation of drinking tube methods is that no information is provided regarding the distribution of drug intake over time.

Finally, the two-bottle method of determining preference may yield different results than a situation allowing the animal a wider variety of choices. For example, Lester & Greenberg (15) found that preference for an ethanol solution disappeared when rats were offered a third choice of a sweetened solution. The problems this could cause in the interpretation of preference experiments are well illustrated by the finding that ethanol preference induced by endocrine stressors disappeared when a sugar solution was offered in a third drinking tube [Zarrow, Aduss & Denison (16)]. Myers (17) provides a fuller discussion of the problems involved in oral preference testing.

The primary advantages of oral preference testing methods are that they are relatively inexpensive (little special equipment is involved, other than graduated drinking bottles), and large numbers of animals can be tested simultaneously.

Oral self-administration of drugs via adjunctive drinking is based on a phenomenon observed by Falk (18). Rats [Falk (18)] and monkeys [Schuster & Woods (19)] trained on intermittent schedules of food reinforcement develop patterns of drinking excessive fluid volumes during the experimental period, though they are not fluid deprived. The primary factors influencing schedule-induced polydipsia are the specific food reinforcement schedule values, and the nature of the reinforcement [Falk (18,

20)]. Lester (21) exploited this phenomenon by training rats on a variable interval schedule of food reinforcement with a 5.6 per cent alcohol solution available in a drinking tube. Rats ingested alcohol at a rate significantly above that which was ingested in the absence of the schedule of food reinforcement or if food was delivered at the same frequency but without lever pressing. In replicating Lester's study, Senter & Sinclair (22) tested subsequent consumption of alcohol and found no greater preference for the drug solution in animals with previous polydipsic training. Meisch & Pickens (23) conditioned rats on a variable interval 1-min schedule of food reinforcement. Rather than allowing free access to the drug solution, the fluid was made available contingent on a response on a second lever. Falk (24) has previously used this method to assess motivational properties of water under these conditions. Alcohol and pentobarbital sodium solutions were made available, and measures of lever pressing and fluid ingestion were recorded. Rats reliably pressed the second lever for access to the drug solutions. Reinforcing effects of drug solutions can be demonstrated by continued responding for drug solutions relative to tap water following discontinuation of food reinforcement, or an increased fluid ingestion, or both, when a drug solution is substituted for water. This technique also makes it possible to assess concurrently the effects of drug ingestion on the food-reinforced baseline.

A second procedure for inducing animals to drink drug solutions has been reported by Harris, Claghorn & Schoolar (25). Rats were initially tested for their preference between water and chlordiazepoxide, meprobamate, lysergic acid diethylamide (LSD), nicotinic acid, and quinine. Quinine was added to all drugs to control for taste. In all instances the rats preferred tap water, drinking only 1 to 2 cc of the drug solution daily. This preference for tap water remained even after a 30 day period in which only the drug solution was available. In the final phase (25 days) of the experiment the rats were trained to lick the drug bottle tube in order to obtain food reinforcement. The volume received in this period was approximately half that consumed in the 30 days of forced drug intake. Subsequent preference testing revealed that following the association of ingestion of the drug solution with food reinforcement, the animals drank significant quantities of chlordiazepoxide, meprobamate, and nicotinic acid. These investigators interpret this as showing that the drug solution had acquired conditioned reinforcing properties by virtue of its association with food reinforcement. This effect was not obtained with LSD or quinine.

Procedures for chronic venous and arterial catheterization have been widely used in physiological and pharmacological research. [Weeks (26)]. The significant development for studies of drug dependence was the arrangement for an animal to control the operation of an infusion pump connected with the indwelling chronic venous catheter. The first report of intravenous self-administration in rats was presented by Weeks (27). Yanagita, Deneau, & Seevers (28) and Schuster & Thompson (29) described chronic intravenous self-administration methods for Rhesus monkeys.

Weeks' initial method was applied to study self-administration of morphine (27, 30), and his combination polyethylene-silicone rubber venous catheter has been described separately [Weeks & Davis (31)]. Other systems for rats have been described by Davis (32) and Pickens (33).

Schuster & Thompson (29) used a chronic polyethylene catheter and motorpowered syringe-driver to study morphine self-administration in restrained monkeys. Yanagita, Deneau & Seevers (28) developed a partial restraint system for studying drug self-administration by monkeys. The device involved a stainless-steel tubular frame, custom fit to each animal, which was connected to the rear corner of a cage via an elbow-hinged catheter-protecting arm. Pickens, Hauck & Bloom (34) developed a similar partial restraint and catheter protection system involving a leather vest and flexible vinyl covered conduit. Methods for drug self-administration in unrestrained monkeys have been reported by Thompson & Pickens (35). In this method monkeys are fitted with a leather vest and an aluminum backpack. The back-pack contains a radio receiver and miniature infusion pump. A signal from a remote transmitter is used to activate the infusion pump. By using receivers tuned to different frequencies, several animals can live in a common experimental space and independently or concurrently self-administer drugs.

VARIABLES INFLUENCING THE SELF-ADMINISTRATION OF DRUGS

In this section, studies designed to determine the pharmacological, organismic, and environmental variables affecting drug self-administration are reviewed. It is impossible at this point in the development of this research to specify how these variables interact or how they affect the self-administration of different classes of drugs. However, this review may help to stimulate research by pointing out the deficiencies in our knowledge.

Pharmacological Variables

Pharmacological compounds shown to be reinforcers.—Just as food, electrical stimulation of subcortical brain structures, and the opportunity to engage in sexual behavior all have different reinforcing properties, one might expect different drugs to have different reinforcing effects. The earliest evidence suggesting that drugs might serve as reinforcers was Spragg's (36) report that physically-dependent chimpanzees would engage in behavior which led to the experimenter's administration of morphine. Though sustained self-administration was not part of this study, the data suggested that morphine administration maintained the drug-directed behavior. Beach (37) made a similar observation in rats using a T-maze. The first study demonstrating that morphine served as a reinforcer in rats was by Headlee, Coppock & Nichols (3). Further morphine self-administration studies have been conducted by Weeks (27, 30), Schuster & Thompson (29), and Yanagita, Deneau & Seevers (28). Subsequent reports by Weeks & Collins (38), Thompson & Schuster (39), Collins & Weeks (40),

Thompson & Pickens (35), Woods & Schuster (41), have confirmed that morphine, over a considerable dosage range, can act as a reinforcer.

Deneau (43) reported comparative studies of self-administration by the Rhesus monkey of several drugs commonly self-administered by humans, including the opioid methadone. Collins & Weeks (40) studied the relative reinforcing properties of intravenously administered codeine, dihydromorphinone, and methadone in rats, using a fixed-ratio 10 schedule of reinforcement. Wikler et al. (11) have reported oral self-administration of the opioid, etonitazine, by rats.

Barbiturates have been shown to be self-administered by rats under conditions of intermittent unavoidable shocks. Amobarbital [Davis & Miller (44)] and hexobarbital [Davis, Lulenski & Miller (45)] were self-administered under these conditions. Deneau (43) has shown that pentobarbital and phenobarbital are self-administered by naive Rhesus monkeys. Kamano & Arp (46) reported that rats would drink a weak chlordiazepoxide solution; however, it was not clear whether the drug was serving as a reinforcer. The oral ingestion of ethyl alcohol has been demonstrated to be a reinforcer for a lever-pressing operant in rats [Myers (47), Mello & Mendelson (48)]. The intravenous infusion of ethyl alcohol has been reported to act as a reinforcer for a lever-pressing operant in Rhesus monkeys [Yanagita, Deneau & Seevers (28)].

The reinforcing effects of stimulant drugs have also been investigated. Yanagita, Deneau & Seevers (28) reported that cocaine was self-administered by monkeys. Similar findings have been reported by Pickens & Thompson (49, 50), Pickens (51), Woods & Schuster (41), and Wilson & Schuster (52), both in rats and monkeys. Methamphetamine has been found to be an effective reinforcer in rats [Pickens, Meisch & McGuire (53); Pickens, Meisch & Dougherty (54); Pickens (51)]. *d*-Amphetamine is self-administered by monkeys [Deneau (43)] and rats [Pickens & Thompson (49), Pickens & Harris (55), Pickens (51)]. Nicotine is self-administered intravenously [Deneau & Inoki (56)] and inhaled as tobacco smoke [Jarvik (5)] monkeys. The drug, SPA (1–2 diphenyl 1-dimethyl-amino ethane hydrochloride), which is of considerable concern in Japan because of human abuse, is also self-administered by the monkey [Estrada, Villarreal & Schuster (57), Woods & Schuster (41), and Wilson & Schuster (52)]. Hitomi & Schuster (58) have shown that Rhesus monkeys will self-administer phenmetrazine, methylphenidate, and pipradrol but not pemoline under the same experimental conditions.

Thus, rats and monkeys have been shown to self-administer representative compounds from several of the major classes of drugs that are illicitly self-administered by man: opioids (morphine, methadone, codeine, dihydromorphinone, etonitazine), barbiturates and related drugs (amobarbital, hexobarbital, pentobarbital, phenobarbital, chlordiazepoxide, ethyl alcohol), stimulants (cocaine, methamphetamine, *d*-amphetamine, nicotine, SPA, phenmetrazine, methylphenidate, pipradrol). Under similar experimental conditions, monkeys will not self-administer nalorphine, chlorpromazine, mesca-

line [Deneau, Yanagita & Seevers (59)], or pemoline [Hitomi & Schuster (58)].

Magnitude of drug reinforcement (dosage per infusion).—The effectiveness of reinforcers in maintaining behavior is dependent not only on the kind but also the amount. It is known that both the initial acquisition and subsequent maintenance of behavior varies with the magnitude of reinforcement. The relationship between rate of responding and reinforcement magnitude varies with the reinforcer. Several investigators have explored the role of drug reinforcement magnitude in maintaining conditioned operants. Weeks (30), Weeks & Collins (39), and Collins & Weeks (40) found that the rate of morphine-reinforced lever-pressing on low ratio schedules was inversely related to dosage, in the range of 3.2 to 10.0 mg/kg per infusion. Woods & Schuster (41), using Rhesus monkeys, have found that response rate on a variable-interval schedule varies in an inverted "U" shaped manner with morphine reinforcement magnitude in the range 10 to 1000 μg/kg per infusion.

A number of investigators have examined the oral ingestion of alcohol as a function of concentration. Myers & Carey (60) described a method for determining a preference threshold for alcohol relative to water. In this procedure rats pressed one lever for alcohol or another for water. The number of lever responses for water and alcohol were recorded when different concentrations of alcohol were tested in successive sessions. This method allows the determination of the concentration of alcohol which is discriminable from water (in rats about 3 to 4 per cent) as well as the maximum preference threshold, which is defined as the concentration at which the alcohol-intake curve crosses the water-intake curve. Myers (17) discusses the advantage of this procedure relative to the use of single concentrations of alcohol for a determination of changes in alcohol preference.

Deneau & Inoki (56) reported an inverse relationship between the number of intravenous nicotine self-infusions by Rhesus monkeys and dosages per infusion. Pickens & Thompson (49, 50), Pickens & Harris (55), and Pickens, Meisch & McGuire (53), found there is an inverse relation between response rate and reinforcement magnitude across all self-administered dosages of methamphetamine, *d*-amphetamine and cocaine. Similar relations have been found using monkeys and the stimulants SPA and cocaine [Woods & Schuster (41), Wilson & Schuster (52)]; phenmetrazine, pipradrol, and methylphenidate [Hitomi & Schuster (58)].

One of the striking features of cocaine self-administration is the marked regularity of inter self-administration intervals. Pickens & Thompson (49) showed that the regular pausing following cocaine self-administration on fixed-ratio schedules was related to both the value of the schedule and the amount of drug infused. Infusing equal amounts of drug following fixed-ratio food-reinforced responding produces comparable pausing to that during drug-reinforced responding.

It would be desirable to compare the relations between magnitude of reinforcement and overall response rate across classes of drugs. Unfortu-

nately, procedures have not been conducted in which identical behavioral baselines were established using a stimulant (e.g., cocaine) and a narcotic analgesic (e.g., morphine). Until this has been done, direct quantitative comparisons are not meaningful.

Drug interaction.—A state of morphine deprivation can be induced in physically dependent animals by administration of the antagonist N-allylnormorphine which causes acute signs and symptoms of withdrawal [Woods (61)]. Weeks (30) found that 4 mg/kg intraperitoneally administered to rats self-administering morphine on a fixed-ratio 10 schedule produced increases in response rate comparable to those associated with morphine abstinence. Thompson & Schuster (39) reported that 1.0 mg/kg intravenously of nalorphine 45 min prior to the opportunity to self-administer 1.0 mg/kg intravenously of morphine produced an increase in the rate of responding in a fixed-interval-fixed-ratio chained schedule of morphine reinforcement. Goldberg, Woods & Schuster (62) reported that monkeys conditioned to self-administer morphine intravenously increased in response rate when pretreated with low dosages of nalorphine (0.1 to 1.0 mg/kg). At higher dosages, however, the animals showed a dose-related depression in response rate for morphine reinforcement.

In addition to controlling motivational conditions by drug deprivation, the degree of deprivation can be manipulated by pretreating the animal with graded amounts of the agent used as the reinforcer. Thompson & Schuster (39) pretreated physically-dependent monkeys with 1.0, 2.0, or 3.0 mg/kg of morphine 45 min before periods when the animals were scheduled to self-administer 1.0 mg/kg of morphine. The length of time required to complete the morphine-reinforced fixed-ratio 25 varied directly with the pretreatment dosage. Thompson (63) also found that hourly intramuscular injections of the opioid, methadone, suppressed morphine-reinforced responding by monkeys. Dole & Nyswander (64) have used the suppressing effect of methadone on morphine and heroin self-administration in human patients. Etonitazine introduced into the drinking water of rats [Weeks (65)] or continuously infused intravenously [Weeks & Collins (38)] suppressed morphine-reinforced lever-pressing. Continuous morphine infusions at rates of 0.5 to 1.0 mg/kg per hr suppressed morphine self-administration in most of the rats, and continuous infusions of codeine and meperidine were approximately equally effective. Dexoxadrol, a clinically effective nonopioid analgesic was found ineffective in suppressing morphine self-administration, as was the opioid, dextrometrophon, which has minimal abuse liability in humans [Collins & Weeks (66)].

Recently attention has been given to interactions of self-administration of stimulant drugs with treatment by the same or other compounds. Pickens & Thompson (50) found that when rats self-administering 1.0 mg/kg of cocaine intravenously were given the same frequency of injections noncontingent on lever-pressing, responding ceased. Pickens, Meisch & Dougherty (54) examined effects of intraperitoneal administration of methamphetamine, alpha-methyl-paratyrosine (AMPT) and L-DOPA on methampheta-

mine self-administration. Both methamphetamine and AMPT suppressed the frequency of methamphetamine self-administration, but L-DOPA had no effect in the range of 20 to 160 mg/kg i.p. At low doses, AMPT produces a temporary increase in the rate of methamphetamine self-administration. It would be tempting but premature at this time to speculate concerning the biochemical mechanisms underlying these behavioral effects. Wilson & Schuster (52) studied the effects of chlorpromazine, trifluoperazine, pentobarbital, morphine, phenoxybenzamine, and phentolamine on intravenous self-administration of cocaine and SPA by monkeys. Chlorpromazine produces suppression of both cocaine and SPA self-administration at high dosages (4.0 to 8.0 mg/kg) but caused rate increase at lower dosages. Trifluoperazine, another phenothiazine derivative, has differential effects on cocaine self-administration increasing up to 200 μg/kg and SPA self-administration decreasing at dosages above 5.0 μg/kg. There is an inverse relation between pentobarbital dosages and SPA and cocaine self-administration at dosages of 10 to 30 mg/kg and morphine over the range of 0.5 to 8.0 mg/kg. Phenoxybenzamine and phentolamine have little or no effect on SPA and cocaine self-administration. The effects of chlorpromazine and trifluoperazine pretreatment in monkeys self-administering cocaine are significant for several reasons. First, these drugs produce a dose-related depression in lever-pressing rate for other reinforcers (e.g., food, water, shock avoidance). The increased lever-pressing rate for cocaine following administration of these phenothiazines appears to be uniquely related to the nature of this reinforcer. If it is assumed that chlorpromazine and trifluoperazine are partially antagonizing the reinforcing effects of cocaine then these results would be expected. The results of pretreatment with morphine and pentobarbital demonstrate that increased intake of SPA and cocaine seen with phenothiazines is not a general property of drugs producing CNS depression. The failure of phentolamine and phenoxybenzamine to alter the intake of cocaine and SPA indicates that the effects observed with the phenothiazines are not based upon their peripheral alpha-adrenergic blocking properties.

The effects of a variety of drugs and hormones have been studied to determine their effects upon alcohol self-administration. This work has been adequately reviewed by Mardones (67) and, more recently, by Lester (68). Therefore we will review this literature only selectively.

Iida (69) has confirmed previous findings relating the experimental production of liver cirrhosis in mice to increased self-administration of alcohol. This effect on alcohol consumption was reversed as long as vitamin C injections were continued. Pretreatment of mice with other hepatotoxic agents (allyl formate and DL-ethionine) failed to produce any increase in alcohol consumption. These findings led Iida to conclude that although liver damage per se was not associated with an increase in alcohol consumption, some action on specific enzymes was involved.

Myers (9, 70) injected alcohol into the lateral ventricles of cats over a period of 10 days, varying the concentration and volume injected. Subse-

quently, the relative preference for an alcohol versus tap water solution was tested. Preference for alcohol solutions increased directly as a function of dosage of previous intraventricular injection.

Schlesinger, Kakihana & Bennett (71) have shown that tetraethylthiuram-disulfide (antabuse) causes a significant decrement in alcohol ingestion in several strains of mice varying in their propensity to drink alcohol, while water intake was unaffected.

Organismic Variables

It is obvious that humans exhibit marked individual differences in their propensity to become dependent upon drugs. It is unknown whether such individual differences are attributable to a genetic predisposition to drug dependence. Further the incidence of drug dependence in man has been shown to vary as a function of sex as well as age. The purpose of the present section is to review the studies relating these organismic variables to the self-administration of drugs.

Genetic variables.—Williams (72) has proposed a genetic basis for alcoholism based on the conception that inherited nutritional deficiencies may enhance the reinforcing properties of alcohol. Animals maintained on a marginal diet develop an appetite for alcohol which declines if various vitamins are added to the diet. The interpretation of these experiments is complicated by the fact that vitamin deficiencies can cause a decrease in food intake which in turn may increase alcohol consumption. Thus, the increased alcohol consumption may be attributable to the animals' caloric deficiency. This interpretation is supported by the fact that the increased preference for alcohol in nutritionally deficient animals is abolished if a sucrose solution is offered in addition to alcohol and water [Lester & Greenberg (15); Mardones et al. (73)].

Evidence for a genetic predisposition for alcohol consumption has been shown for rats [Myers (74)] as well as various strains of mice [McClearn & Rodgers (75)]. Several interesting biochemical differences have been shown to correlate with the propensity of various strains of mice to ingest alcohol. Strain differences in alcohol preference have been shown to parallel the overall activity of liver alcohol dehydrogenase in *in vitro* studies [Rodgers et al. (76); McClearn et al. (77)]. Unfortunately, *in vivo* studies of the metabolism of alcohol by these strains of mice have failed to demonstrate a comparable correlation between rate of alcohol metabolism and alcohol preference [Rodgers & McClearn (78); Schlesinger (79); Bennett & Herbert (80)]. Further, Rodgers & McClearn (81) have more recently reported that strains of mice which show a preference for alcohol over water show an even greater preference for a sucrose solution.

Another interesting correlation has been shown between accumulation of acetaldehyde following the injection of alcohol into high-preference strains of mice (C 57 BL) and mice which avoid alcohol ingestion (DBA/2). The DBA/2 strain show significantly greater acetaldehyde levels one hour

after alcohol administration than the C 57 BL mice. The known aversive properties of acetaldehyde suggest that the accumulation of this metabolic breakdown product of alcohol may account for the aversiveness of alcohol in the DBA/2 strain [Schlesinger, Kakihana & Bennett (71)].

A recent report by Nichols & Hsiao (82) has shown that rats can be selectively bred for their ability to be conditioned to drink a morphine solution. Inbreeding of the more "susceptible" rats from an unselected population produced "susceptible" offspring. In addition, the inbreeding "resistant" rats produced "resistant" offspring. Further inbreeding increased the strain differences in successive generations. Cross-fostering studies ruled out differences in maternal care as a variable. Of further interest is the fact that the susceptible and resistant rats in the F-3 generation also showed a significant difference in their alcohol intake in preference tests conducted 14 days after being conditioned to drink alcohol. The morphine "susceptible" strain drank twice as much alcohol as the animals bred for "resistance" to drinking morphine. Nichols (83) has shown that these strain differences are uncorrelated with emotionality as measured by the Hall open-field test. There is a positive correlation, however, between maze learning ability and "susceptibility" to conditioned morphine ingestion. The meaning of this correlation, however, is obscure.

Sex.—At present the sex of the experimental animal has been studied only in reference to alcohol self-administration. Sex has been reported to be unrelated to alcohol preference in Sprague-Dawley rats [Mardones (67); Zarrow, Aduss & Denison (16)] and various strains of mice [Kakihana & McClearn (84); McClearn & Rodgers (75); Mirone (85)]. In contrast, a tendency for male rats [Clay (86)] and mice to consume more alcohol has been noticed. This difference is even more marked when the females are in heat. The findings of Aschkenasy-Lelu (87) indicate that this is probably related to the suppressant effects of estrogens on alcohol intake. This effect of estrogen is not specific to alcohol ingestion, however, since ingestion of saline or sucrose solutions is as well suppressed.

Rodgers (88) has shown a direct correlation between liver size and alcohol consumption of C 57 BL/Crgl mice during pregnancy and while nursing ten-day-old litters.

As Lester (68) pointed out, "it would be hazardous (and simplistic) to conclude that the male:female ratio of human alcoholism is in any way related to differences in estrogen levels."

Age.—The reports relating age to the ingestion of alcohol indicate species differences as a function of this variable. In mice of BALB/c strain, alcohol preference is greater at 4 weeks of age than at 16 weeks [Kakihana & McClearn (84)]. In contrast, Wallgren & Forsander (89) found than in rats alcohol preference increased as a function of age.

Nichols (90) reported that conditioned morphine ingestion declines as a function of the age of the rats. The significance of these findings concerning changes in the self-administration of drugs as a function of age await a more precise specification of the correlated physiological changes.

Environmental Variables

Antecedent conditions.—Certain classes of drugs, notably the opioids, sedative-hypnotics, and alcohol can produce physical dependence in organisms which receive the drug chronically. Physical dependence is inferred from the occurrence of a characteristic set of signs and symptoms when drug administration is abruptly terminated. This set of signs and symptoms is called the withdrawal syndrome. The role of physical dependence in relationship to opioids as reinforcers has been extensively studied and has been reviewed recently by Schuster & Villarreal (91). There are two aspects to this problem. First, is physical dependence a necessary antecedent condition for these drugs to act as reinforcers, and second, does the development of physical dependence influence the reinforcing efficacy of a drug?

In most experiments in which opioids are used as reinforcers the subjects are made physically dependent by forced administration prior to the opportunity to self-administer the drug. Using this procedure it is impossible to discern whether an animal self-administers the drug in order to escape from the withdrawal syndrome or because the drug possesses positive reinforcing properties. Several lines of evidence suggest that morphine possesses positive reinforcing properties independent of its ability to ameliorate the withdrawal syndrome. Deneau, Yanagita, & Seevers (59) have shown that the majority of naive Rhesus monkeys will initiate lever-pressing for an intravenous injection of morphine, pentobarbital or alcohol. More recently Woods & Schuster (41) have demonstrated that Rhesus monkeys will initiate lever-pressing for intravenously-administered morphine at dosages as low as 10 μg/kg. At this low dosage the monkeys failed to show any signs of physical dependence when saline was substituted for morphine.

A variety of experiments have shown, however, that once physical dependence develops, the reinforcing efficacy of a drug is amplified. That is, physically-dependent animals are differentially disposed to self-administer a drug as a function of the time since the last drug administration. Weeks (30) conditioned rats to press a lever for 3.2 or 10 mg/kg of morphine intravenously. During a 3-hr abstinence period the hourly rate increased from a mean of 3.21 at 3.2 mg/kg and 1.56 at 10 mg/kg to 21.83. Using a far longer deprivation period, Davis & Nichols (92) found that rats immediately placed in an oral preference situation following a period of morphine treatment ingested larger quantities of morphine than animals which were deprived of morphine for 4 days before being placed in the oral preference situation. Thompson & Schuster (39) trained monkeys to self-administer morphine intravenously (1 mg/kg Q.I.D.) and then deprived the animals of the opportunity to self-administer for 24 hr. Using a chained schedule of morphine reinforcement it was found that rates increased approximately tenfold during the fixed-interval component, and the length of time to complete 25 responses on a fixed-ratio schedule decreased as well. Rats previously made physically dependent on morphine were deprived of the drug 7, 7 to 24, or 24 to 48 hr and tested for preference between tap

water and the synthetic opioid, etonitazine [Wikler et al. (11)]. The quantity of etonitazine consumed varied directly with the number of hours of morphine deprivation. Thus, while physical dependence is not a necessary antecedent condition for drugs to act as reinforcers, the reinforcing efficacy of a drug is amplified during withdrawal in physically-dependent organisms.

Current environmental circumstances.—Environmental conditions are clearly important determinants of the effectiveness of any reinforcer, and we have no reason to suspect drug-reinforced behavior is any different. Among the first demonstrations of the importance of environmental conditions in drug self-administration was Masserman & Yum's (4) study of alcohol ingestion under "conflict" contingencies. Cats were presented with a blast of air as they approached a food dish. The animals, in addition to avoiding the food dish, showed a number of behavioral changes judged to be "neurotic." Cats given 1 g/kg of alcohol during training did not develop these reactions and administration of this dosage of alcohol to a "neurotic" cat diminished its "phobic aversion." These animals subsequently showed a preference for food or milk which contained alcohol.

Clark & Polish (93) reported that the consumption of ethyl alcohol by Rhesus monkeys increased when these animals were placed on a shock-avoidance schedule. Subsequent work by Mello & Mendelson (94) demonstrated that shock-avoidance schedules elicited an abrupt increase in alcohol consumption in a monkey which freely selected alcohol prior to conditioning. The avoidance schedule had no demonstrable effect on alcohol consumption for a monkey that had previously refused alcohol in a free choice situation. The increased alcohol consumption associated with the avoidance schedule continued for 6 weeks following the termination of avoidance conditioning. The level of alcohol intake associated with the avoidance schedule, however, did not differ significantly from levels achieved by control monkeys after 4 to 7 months in a free-choice situation. Thus, the avoidance conditioning produced a more rapid increase in alcohol consumption but not a significantly greater level of consumption. Of interest is the fact that none of the monkeys showed any withdrawal signs when drug availability was abruptly terminated.

Davis & Miller (44) presented rats with painful footshock on an intermittent schedule and observed the frequency of lever pressing which produced intravenous infusions of amobarbital (1.5 mg/kg). Paired animals were also provided with the opportunity to self-administer amobarbital but received no shocks. Over the first three daily tests, shocked rats self-administered amobarbital while controls did not. In a later study, Davis, Lulenski & Miller (45) replicated this effect, and in addition found hexobarbital would be self-administered under the same conditions. Whether these barbiturates are effective reinforcers in the rat only under conditions of fear or pain, must wait for a demonstration that a nonaversive stimulus presented on the same schedule is ineffective. Further, as previously stated, Deneau, Yanagita & Seevers (59) have shown that barbiturates are effective

reinforcers in the monkey in the absence of any programmed aversive contingencies.

Another study designed to assess the role of current conditions failed to find any facilitative effect of painful shock on oral ingestion of chlordiazepoxide [Kamano & Arp (46)]. Rats were trained to avoid a painful shock in a shuttle box or presented with unavoidable shocks, and relative preference for chlordiazepoxide versus tap water solution was compared. Under normal "nonstress" conditions the volume of drug solution consumed relative to the total fluid volume was consistently higher than under avoidance conditions or unavoidable shock.

In addition to inducing nondependent rats to self-administer drugs, the similarity of environmental conditions during self-administration to those in which the behavior was originally established appears to be of importance. Thompson & Ostlund (95) made rats physically dependent on morphine using an oral administration procedure similar to that described by Nichols, Headlee & Coppock (10). For 30 days of morphine deprivation half of the rats were moved to a different room and placed in new cages and half were left in original cages. Half of each group remained in the same cage in which withdrawal had been experienced and half were moved to the other set of cages during the readdiction phase. Over 3 weeks oral preference tests were run to assess relative disposition to ingest morphine solutions. Animals returned to the same environments in which original drug administration had occurred ingested significantly larger amounts of morphine and animals placed in an environment different from that in which withdrawal had occurred ingested relatively greater amounts of morphine. In other words, the tendency to self-administer the drug is greater if the environment is the same as that in which the original drug-taking had occurred. Conversely, placing the animal in the situation where withdrawal has occurred decreases the probability of self-administration. These findings have interesting parallels in Vaillant's (96) follow-up study of morphine and heroin addicts. Addicts abstinent at the end of 12 years tended to have undergone withdrawal in their home environment. In addition, many of those that were abstinent lived in different environments from that in which the original drug dependence had developed.

Schedules of drug reinforcement.—The specific patterning of behavior and its persistence are dependent to a large degree on the schedule of reinforcement [Skinner (97), Ferster & Skinner (98), Morse (99)]. Thus, one might expect that the specific pattern of drug-taking behavior and its persistence would depend on the schedule of reinforcement. Most studies have involved continuous reinforcement, i.e., each response produced an injection of drug. However, a number of investigators have begun to examine intermittent schedules of drug reinforcement, though almost exclusively fixed-ratio schedules. Weeks (30), Weeks & Collins (38, 100), and Collins & Weeks (66, 101) have studied fixed-ratio schedules of morphine, dihydromorphinone and codeine reinforcement. In several cases only one value of ratio schedule was used and dosage per infusion varied; however, in other

studies, ratios were varied. Pickens (51), Pickens & Thompson (49, 50), Pickens & Harris (55), and Pickens, Meisch & McGuire (53) have explored fixed-ratio schedules using stimulant drug reinforcement. These investigators have varied ratios (FR 1 to 80) over a range of dosages of cocaine, *d*-amphetamine and methamphetamine. In the case of stimulant drugs, a characteristic pattern of responding develops with runs of responses at very high rates followed by long periods without responding. These "pauses" are related both to the value of the ratio schedule and the magnitude of drug reinforcement. Overall response rate varies directly with the size of the ratio, over a considerable range of ratios. Morphine-reinforced ratio performance is also characterized by runs of responses at high rates, but the interinfusion interval tends to be more variable [Collins & Weeks (40)].

The only other simple intermittent schedule of drug reinforcement reported is a variable-interval schedule. Woods & Schuster (41) have explored morphine self-administration by monkeys over a range of doses and found that a very characteristic constant low rate is generated. The monkeys' response-rates for morphine were consistently lower than their response-rates for food reinforcement.

Two studies have been reported involving more complex schedules. Thompson & Schuster (39) used a fixed-interval-fixed-ratio chained schedule of intravenous morphine reinforcement with monkeys. The behavior developed some characteristics of chained schedules commonly observed using other reinforcers. Recent investigations of highly complex multioperant sequences in which morphine is the terminal reinforcer have been described by Thompson & Pickens (35). In this case monkeys performed a chain of heterogeneous responses beginning with standing on a platform scale, followed by opening and closing a door to a compartment in which morphine is infused, cooperating with another monkey in holding a switch closed, and finally, operating a lever on a fixed-ratio schedule for intravenous morphine. This schedule is well maintained, with pausing during the early components varying with the terminal ratio requirement.

Stimuli paired with drug administration.—Behavior is maintained, not only by the terminal reinforcer following a response sequence, but by stimuli preceding the terminal reinforcer, as well. Such conditioned reinforcers are powerful influences in controlling sustained behaviors where long periods elapse between successive terminal reinforcers (Kelleher & Gollub (102); Kelleher (103)]. Attempts to study the role of conditioned reinforcers in maintaining drug-reinforced behavior have been limited. Schuster & Thompson (29) reported an apparent conditioned reinforcing effect of a light which had been presented during intravenous morphine infusion. The light and morphine infusion had been presented four times daily, following completion of fixed-interval fixed-ratio chained schedule. McGuire (42) attempted to establish a flashing light as a reinforcer by pairing it once daily with a morphine infusion. The light-drug administration pairings were not contingent on the animal's behavior, and took place over a 15-day period.

Using the number of responses on a single extinction test as the primary measure of a conditioned reinforcer effect, McGuire failed to find a significant difference between animals experiencing pairings, and controls. Schuster & Woods (104) examined 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-hr extinction tests were run, 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 consequence.

Stimuli paired with morphine administration also came to influence the disruptive effects of morphine withdrawal on other behaviors [Thompson & Schuster (39)]. Monkeys were conditioned on a complex multiple reinforcement schedule to obtain food and avoid shocks. In addition, the animals self-administered 1 mg/kg of morphine every 6 hr. During a period when the opportunity to self-administer morphine was removed, the food-reinforced and shock-avoidance behaviors progressively deteriorated. A single morphine self-administration reinstated these behaviors. 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 behaviors. Thus, the ameliorative effects of morphine had become conditioned to the light paired with morphine infusion.

Wikler (105) suggested that withdrawal symptoms may become conditioned, and might influence the subsequent disposition to take drugs. The fact that certain withdrawal symptoms can be conditioned now seems clear, however, it is not evident what role this might play in self-administration. Wikler & Pescor (106) placed rats in an environment in which they had previously experienced withdrawal, 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. Goldberg & Schuster (107) demonstrated that a stimulus paired with nalorphine infusion in physically-dependent monkeys, elicits withdrawal symptoms. Monkeys working for food on a fixed-ratio schedule were presented with a 5-min tone followed by an infusion of nalorphine. After several sessions of pairings, the onset of the tone was followed by complete suppression of the operant responding. In addition, signs of acute withdrawal distress, including salivation and vomiting occurred during the tone.

Behavioral dependence.—Behavioral dependence always accompanies physical dependence, in that discontinuation of chronic drug treatment produces behavioral as well as physiological disruptions. Thompson & Schuster (39) found that food-reinforced and shock-avoidance behaviors were disrupted during withdrawal (after about 18 hr) and were reinstated when morphine was administered. Djahanguiri, Richelle & Fontaine (108) re-

ported disruptive effects of morphine withdrawal on food-reinforced fixed-interval performance by cats. After 6 weeks of daily subcutaneous morphine (0.2 mg/kg) one out of three cats showed total suppression of the operant. Seven more weeks of drug administration, followed by cessation of treatment, produced complete disruption of operant performance in the remaining two animals.

Behavioral dependence without physical dependence has been reported with *d*-amphetamine and chlorpromazine. Schuster, Dockens & Woods (109) investigated the effects of chronic administration of *d*-amphetamine in rats trained on a shock-avoidance schedule. Before beginning drug administration, the number of shocks received were relatively high because of the animals' low response rates. Under the influence of *d*-amphetamine, response rates increased and the number of shocks diminished. On discontinuing drug treatment, rather than continuing at the improved level of performance (which was more effective in meeting the environmental contingencies) behavior reverted to its previous level. Waller (110) conditioned dogs on a fixed-interval schedule of food reinforcement, and administered chlorpromazine orally for 15 days. Following discontinuation of drug treatment, disruption of the fixed-interval responding ensued, characterized by long pauses and extremely low rates.

Unfortunately, there are no reports dealing with the relationship of behavioral dependence to the self-administration of a drug. This is an extremely important area of research which should receive the attention of investigators in the near future.

GENERAL DISCUSSION

The importance of animal research using self-administration techniques is based largely on the assumption that its findings will have relevance to the social problems of drug abuse in man. The fact that many of the drugs commonly abused by man are self-administered by experimental animals lends credence to this assumption. The ultimate value of this research lies in the degree to which a new drug's abuse potential in man can be predicted and the insights gained into the basic mechanisms underlying the self-administration of drugs.

It would be simplistic to assume that drugs can be divided into two distinct categories; those that will be self-administered and those that will not. Clearly a wide variety of physiological and behavioral variables alter a drug's ability to act as a reinforcer. There is no experimental justification for assuming that all relevant variables will act alike for all classes of drugs. The diversity of pharmacological actions exhibited by the spectrum of drugs which are self-administered suggests the contrary. It would therefore be hazardous to conclude that because an animal fails to self-administer a drug under one set of conditions that it may not be self-administered under another set of contingencies. However, from a practical viewpoint, drugs with the highest abuse potential are those which have properties leading to their self-administration under a wide variety of conditions. The

problem is to determine experimentally the biological and environmental variables controlling the relative tendencies for drugs to be self-administered, the resulting patterns of drug self-administration, and the behavioral and physiological consequences of chronic self-administration.

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